An update on immunotherapy for food allergy

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Current Opinion in Allergy and Clinical Immunology 2010, 10:587–593

Purpose of review

Recent investigation has resulted in significant advances toward definitive therapeutic options for food allergy. In this review, we will explore novel immunotherapeutic interventions for the active treatment of food allergy.

Recent findings

Because the injection route for allergen immunotherapy to foods has been associated with an unacceptable risk of severe anaphylactic reactions, use of mucosally targeted therapeutic strategies is of significant interest for food allergy. Allergen-specific immunotherapeutic approaches such as oral, sublingual, epicutaneous, and peptide immunotherapy have demonstrated efficacy in increasing threshold dose and inducing immunologic changes associated with both desensitization and oral tolerance in animal and human trials. More global immunomodulatory strategies, such as Traditional Chinese Medicine and anti-IgE therapy have been shown to effectively target the allergic response, and clinical trials are ongoing to determine the efficacy and safety in human food allergy.

Summary

The advent of therapies that target the mucosal immune response to promote oral tolerance have shown great promise in the treatment of food hypersensitivity. However, there is still significant risk of adverse reactions associated with these therapeutic strategies and further study is needed to carefully advance these therapeutic modalities toward general clinical implementation.

Keywords

food allergy, immunotherapy, oral tolerance, T-regulatory cells

Curr Opin Allergy Clin Immunol 10:587–593

1528-4050

Introduction

The development of novel therapeutic modalities targeting the mucosal immune response has shown great promise in providing a definitive therapy for food allergy. Because food allergy is likely a multifactorial disorder with both genetic and environmental influences, development of primary prevention strategies has been frustrating and at times counter-productive, making development of a definitive therapeutic option a high priority. In this review, we will examine the relationship between food hypersensitivity and oral tolerance and explore novel therapeutic approaches to modulate the food allergic response.

Food hypersensitivity and oral tolerance

A diagnosis of food allergy is challenging for affected patients and families not only due to the medical implications, but also due to psychosocial and economic stressors. The standard of care for immediate food hypersensitivity currently includes dietary allergen restriction and ready access to emergency medications in case of accidental exposure; however, there are presently no widely available, active therapeutic options for food allergic patients. Because of the need for stringent dietary restrictions, difficulty comprehending food labels [1,2], the continual threat of accidental ingestions [3], and the risk of severe or fatal reactions [4,5], a diagnosis of food allergy results in significant anxiety, psychosocial stress, economic burden, and reduced health-related quality of life [6–11].

Investigators are continually working to delineate the precise immunologic, genetic, and environmental factors that promote food allergy. The current evidence indicates that food allergy is the consequence of either a failure to establish oral tolerance or an interruption of existing tolerance, resulting in dysregulated T-helper type 2 (Th2) responses and immediate hypersensitivity reactions upon antigen re-exposure. As such, aberrant regulatory T-cell (Treg) induction appears to be a key element in the development of food allergy [12–15].

The prevalence of food allergy continues to escalate in developed countries; current estimates suggest an overall prevalence of 4% in the United States [16••]. Both peanut and tree nut allergies have increased by two-fold to three-fold over the past decade [17,18•], whereas the prevalence of peanut allergy has tripled in the United Kingdom [19,20]. Attempts to avert the development of food allergy through primary prevention strategies such as early dietary allergen restriction and modified timing of complementary 'solid' food introduction to infants have proven to be frustrating and possibly counter-productive. For example, approximately a decade ago, both the United Kingdom Committee on Toxicity (COT) and the American Academy of Pediatrics (AAP) recommended early dietary restriction of peanuts to avoid sensitization [21,22]. However, subsequent data suggested that early consumption of food proteins and subsequent oral tolerance induction in infants and toddlers may be a key element of preventing the development of food allergies [23,24]. Children in countries who have peanut snacks that are safe for infants have relatively low rates of peanut allergies [23]. Additionally, despite earlier introduction of peanut protein into the diet, Jewish children in Israel had a 10-fold lower prevalence of peanut allergy compared with children of similar genetic background in the United Kingdom [24]. A randomized controlled trial (Learning Early About Peanut Allergy (LEAP) Study) is underway in the United Kingdom to compare the efficacy of early peanut protein consumption vs. peanut avoidance in preventing peanut allergy. Studies have shown that neither the diversity, nor the timing of introduction of complementary foods had any association with development of eczema [25], and delayed introduction of complementary foods did not protect from asthma or atopic disease [26]. The most recent AAP recommendations for high-risk infants do not endorse restriction of maternal diet during pregnancy and lactation or restriction of allergenic foods in infants after 4–6 months of age [27]. European guidelines suggest similar dietary recommendations [28].

Novel therapeutic interventions targeting food hypersensitivity

Both allergen-specific therapies that harness mucosal tolerance to abrogate the allergic response and more generalized immunomodulatory approaches are under investigation in animal and human models. The goals of these therapies are generally to induce some combination of desensitization and/or tolerance. Desensitization is defined as a change in threshold dose of ingested food allergen necessary to cause allergic symptoms; this state is dependent on ongoing antigen exposure. Mechanistic markers of desensitization include increased IgG4 and reduced IgE, as well as decreased activation and release of inflammatory mediators by mast cells and basophils. In contrast, tolerance is the induction of long-term immunologic changes associated with the ability to ingest a food without symptoms and without ongoing therapy. Mechanisms of tolerance induction include active modulation of the immune response to promote regulatory T-cell development and immunologic skewing away from a Th2 response (Table 1).

Table 1 Comparison of immunologic changes in food allergy vs. allergen-specific immunotherapy

	Food allergy	Effective immunotherapy
Serum IgE	↑	↓
Serum IgG4	-/↓	↑
Th2 cytokine production	↑	↓
Mast cell/basophil reactivity	↑	↓
Regulatory T-cell activation	↓	↑

Alternative approaches to traditional injection immunotherapy

Allergen immunotherapy via the injection route has been utilized successfully for the treatment of allergic rhinoconjunctivitis and venom hypersensitivity for decades [29]. Despite its efficacy in treating allergic rhinoconjunctivitis and venom hypersensitivity, the 'traditional' approach to allergen immunotherapy via the subcutaneous route is impractical and unsafe for treatment of food allergy due to an unacceptably high rate of anaphylactic reactions [30,31]. At present, multiple therapeutic alternatives to subcutaneous injection therapy are being investigated for treatment of food allergy (Table 2) [32–36,37••,38•,39,40•,41•,42–45,46•,47••,48,49,50•,51,52•,53].

Traditional Chinese Medicine

Most investigators have utilized an allergen-specific approach to target food allergy. However, an innovative approach with potential for the treatment of food allergy utilizes Traditional Chinese Medicine, thus providing an approach that is not allergen specific. In mouse models, Food Allergy Herbal Formula (FAHF-2) has been shown to promote tolerance and protection from anaphylaxis [51,52•,54]. Human clinical trials are just beginning and hold promise for future clinical efficacy.

Humanized monoclonal anti-IgE therapy

Omalizumab, a recombinant, humanized, monoclonal anti-IgE antibody has been utilized effectively in concert with rush immunotherapy for allergic rhinitis [55] and as an adjunctive therapy to minimize systemic immunotherapy reactions in patients with allergic asthma [56]. Anti-IgE therapy (TNX-901) was previously demonstrated to significantly increase the threshold peanut protein dose at oral food challenge from 178 to 2805 mg affording treated individuals with potential protection from accidental peanut ingestions [53]. Clinical trials are in progress evaluating both anti-IgE monotherapy for food allergy,

Table 2 Summary of selected immunomodulatory therapies for food allergy

Therapy	Model	Allergen	Route of administration	Clinical response	Immunologic effects
Allergen-specific therapies					
Oral immunotherapy	Human	Milk [32–36,37••,38•], egg [39], peanut [40•,41•], fish [32], other [32]	Oral	Clinical desensitization, ↑ threshold dose	↓/= specific IgE, ↓ PST reactivity, ↓ basophil activation, ↑ IgG4, ↑ FOXP3$^+$ T cells, down regulation of apoptosis genes, *trials ongoing*[a]
Sublingual immunotherapy	Human	Hazelnut [42,43], kiwi [44,45], milk, peanut	Sublingual	Clinical desensitization, ↑ threshold dose	↑ IgG4, ↑ IL-10, ↓ PST reactivity, *Trials ongoing*[a]
Epicutaneous immunotherapy	Mouse	Peanut [46•], egg [46•], aeroallergens [46•]	Epicutaneous	↓ Airway hyper responsiveness	↑ IgG2a, ↓ IgE/IgG2a ratio
	Human	Milk [47••]	Epicutaneous	Trend toward ↑ cumulative tolerated dose	No increase in IgE noted during 3 months of treatment, *Trials ongoing*[a]
Peptide immunotherapy	Mouse	Peanut [48,49], egg [50•]	Rectal, subcutaneous	Protection from anaphylaxis	↑ IFNγ, ↑ IGFβ, ↓ Th2 cytokines
	Human	Peanut	Rectal	*Trials ongoing*[a]	*Trials ongoing*[a]
Allergen nonspecific therapies					
Traditional Chinese Medicine (FAHF-2)	Mouse	Peanut [51,52•]	Oral	Protection from anaphylaxis	↓ Peanut-specific IgE, ↑ IgG2a levels, ↓ Th2 cytokines, ↑ IFNγ by CD8$^+$ T cells
	Human		Oral	Phase I trials	Trials ongoing[a]
Monoclonal anti-IgE	Human	Peanut [53], milk	Subcutaneous	↑ Threshold dose	Trials ongoing[a]

[a] http://www.clinicaltrials.gov.

as well as use of omalizumab as an adjunct to oral immunotherapy (OIT).

Peptide immunotherapy

In mouse models, rectal immunization with mutated peanut protein allergens has been shown to protect mice from anaphylaxis [48,49]. Peptide immunotherapy has also been utilized with the immunodominant epitopes of OVA [50•]. Mice treated with subcutaneous injections of peptides were protected from anaphylaxis upon OVA challenge, in addition to exhibiting decreased serum histamine levels, decreased OVA-specific IgE, reduced Th2 cytokines and increased IFNγ. Additionally, animals that received peptide immunotherapy showed significantly higher levels of mRNA transcripts for Foxp3 and TGFβ in the intestine, suggesting modification of the local mucosal immune response in the target tissue. Studies using a similar approach are currently in early human trials.

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) has been utilized for treatment of allergic rhinitis in humans [57••] and in mouse models of inhalant and food allergy [46•]. Animal and ex-vivo skin models suggest that EPIT targets Langerhans cells and dermal dendritic cells to modulate the immune response [58]. A recent pilot study [47••] of EPIT in milk allergic children suggested that this therapy was overall well tolerated and did not result in sensitization. Clear clinical efficacy was not demonstrated in this study, likely due to the short treatment period of only 3 months, but trends toward improvement were noted in the active treatment group. It is notable that immunotherapy using this delivery system on intact skin did not result in sensitization. Phase I human trials are in progress in Europe and the United States.

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) has shown broad efficacy for treatment of inhalant allergies. SLIT employs a liquid concentrate administered under the tongue that is given in small, increasing doses of antigen in a controlled setting usually during an initial dose coupled with home dosing to reach a maximum tolerated maintenance dose of allergen. In clinical trials, treatment is followed by an oral food challenge with antigen or placebo to determine efficacy.

Investigators have utilized SLIT for treatment of hazelnut allergy [42,43] and in a single case for treatment of life-threatening kiwi allergy [44,45]. Trials are currently in progress evaluating the efficacy of SLIT for other food allergens including peanut and milk.

Oral immunotherapy and specific oral tolerance induction

Investigation of OIT as a therapeutic modality has yielded promising results for a variety of food allergies.

OIT appears to be effective in inducing desensitization in most patients, as well as oral tolerance in a subset of patients with food allergy. OIT generally involves the use of a powdered food protein given orally, often in a vehicle food. The usual approach to OIT involves an initial dosage escalation phase followed by observed build-up dosing to daily maintenance therapy. Therapeutic effect is evaluated by food challenge at standard points in the treatment protocol.

Investigators have utilized a standardized OIT protocol for treatment of food allergies including, most commonly, milk, egg, and fish, and described successful desensitization in 77% of treated patients [32]. Other studies utilized specific oral tolerance induction therapy to desensitize children with IgE-mediated milk hypersensitivity [33–36].

Buchanan *et al*. [39] utilized a 24-month egg OIT protocol to desensitize egg allergic children; in the seven patients who completed the 24-month protocol, four of seven passed a double-blind, placebo-controlled food challenge to 10 g of egg at the conclusion of the therapy, and all patients tolerated significantly higher doses of egg protein than noted at entry into the study. A subsequent report [59] indicated that two of 21 patients enrolled in this ongoing protocol were unable to achieve the maintenance egg protein dose due to frequent and unacceptable therapy-associated adverse reactions, highlighting that this therapy is not ready for broad implementation into routine clinical practice settings. Ongoing clinical trials continue to examine the safety, efficacy, and mechanism of egg OIT.

Another study [60•] suggested that consumption of heated egg in egg-allergic individuals may have an immunomodulatory therapeutic effect. Patients with IgE-mediated egg allergy underwent physician-supervised oral food challenges to extensively heated egg (e.g. muffin or waffle). Patients tolerating heated egg protein challenge integrated heated egg into their diets. Continued consumption of heated egg protein in the diet was associated with decreased skin test size, reduced egg-specific IgE levels, and increased IgG4 levels.

In a recent randomized, double-blind, placebo-controlled cow's milk OIT trial [37••], investigators treated 19 children with cow's milk allergy. Treatment with OIT was associated with increased median milk threshold dose inducing allergic symptoms during oral food challenge (40 mg → 5140 mg OIT vs. 40 mg → 40 mg placebo). No significant difference in milk-specific IgE levels was detected in the treated vs. untreated groups; however, milk-specific IgG4 was significantly increased. This cohort was subsequently monitored during an open label portion of the study to evaluate the continued safety of milk OIT and the patients' ability to tolerate gradual home dose escalation [38•]. Six of 13 patients undergoing follow-up food challenge tolerated the maximum cumulative dose of 16 000 mg (16 oz) of cow's milk protein without any adverse reaction. The other seven participants tolerated doses ranging from 3000 to 16 000 mg, with associated clinical symptoms including oral pruritus, abdominal pain, sneezing, cough, and urticaria. Significant decreases in end-point titration skin prick testing and milk-specific IgE and significant increases in milk-specific IgG4 were detected following OIT.

Oral immunotherapy in peanut allergic patients

Preliminary trials of OIT in pediatric patients with peanut allergy have yielded encouraging results regarding the safety and efficacy of this therapy. Our group utilized an OIT protocol to treat children with peanut allergy and evaluate both clinical efficacy and immunologic changes in treated patients [40•]. Twenty-nine children completed the protocol and 27 of 29 (93%) ingested the maximal amount (5 g) of peanut protein during oral challenge while receiving OIT, supporting the role of OIT in effective clinical desensitization. Another group reported similar clinical effectiveness in four patients who received OIT using a similar protocol [41•]. In our cohort, clinical effectiveness was correlated with reduced titrated skin prick test reactivity and decreased basophil activation [40•]. Treated patients demonstrated initial increases in peanut-specific IgE which subsequently decreased by 12 and 18 months on therapy, whereas peanut-specific IgG4 increased significantly throughout the study. Additionally, a 1.5-fold increase in $FOXP3^+$ Tregs was noted in peanut stimulated cells at 6 and 12 months of therapy. T-cell microarray data revealed down-regulation of genes in apoptotic pathways in patients while on OIT. A related study [61•] examined the safety of OIT throughout all phases of treatment. Allergic reactions occurred most frequently on the initial escalation day with the majority of patients requiring some form of treatment. The likelihood of allergic reactions decreased significantly during the build-up and home dosing phases; however, two patients received epinephrine on one occasion each during home dosing. Further examination of adverse reactions during home dosing associated increased risk of reaction with concurrent illness, physical exertion following dose administration, dosing during menses, poorly controlled asthma, and timing of dosing following food ingestion [62•].

A newly published study [63••] employed a peanut OIT protocol that included a 7-day rush OIT treatment phase, followed by a long-term build-up protocol with bi-weekly dose increases up to 0.5 g of peanut protein, and a subsequent 8-week maintenance phase. Twenty-three patients underwent the rush OIT protocol, with 22/23 continuing the long-term treatment protocol. The

median threshold dose eliciting symptoms after rush OIT was 0.15 g, whereas, after long-term treatment the median tolerated dose was 1 g. From a safety standpoint, the authors reported that 2.6% of the total 6137 doses elicited mild to moderate symptoms, whereas 1.3% of doses resulted in pulmonary obstruction; OIT was discontinued in four patients. Immunologic changes while on OIT included significant increases in peanut-specific IgG4, and significant decreases in Th2 cytokine production by peripheral blood mononuclear cells (PBMCs).

Although clinical safety and mechanistic evaluation are of utmost priority when designing clinical food allergy trials, recent data suggest psychological factors that influence enrollment should be considered. DunnGalvin *et al.* [64•] evaluated the factors that influence parental decision to enroll a child in a potentially risky therapeutic trial, reporting that parents of children with food allergy who elected to enroll in immunotherapy trials perceived a significantly higher likelihood of their child having a severe reaction or dying if a food was ingested [odds ratio (OR) = 6.753 (3.451–9.728) $P = 0.001$]. Participation in immunotherapy trials could be predicted with 90% accuracy using this model. These data suggest that the design of future immunotherapy trials for food allergy should focus not only on stringent clinical safety regulations, efficacy, and mechanistic evaluation, but should also consider psychological factors that influence enrollment and employ strategies to eliminate unintentional coercion, and possibly selection bias, when enrolling potentially high-risk families.

Conclusion

Advances in our understanding of the immunologic mechanisms underlying food allergy and of the elegant complexities of the mucosal immune response have resulted in substantial progress toward definitive therapeutic options for food allergic individuals. Current therapeutic strategies are focused on harnessing oral tolerance to modulate the allergic response using antigen-specific modalities, while others, such as Traditional Chinese Medicine and monoclonal anti-IgE therapy utilize a more global immunomodulatory approach. Clinical trials are ongoing to address these issues through the NIH Consortium of Food Allergy Research (CoFAR) and others with trial details available at www.clinicaltrials.gov. The current advances have brought us into an exciting era with regard to food allergy therapy. We are on the cusp of definitive therapeutic options, providing hope and optimism for food allergic patients and families. However, it should be noted that these approaches have significant associated risk and at present should only be conducted by experienced investigators in clinical trials centers. Ongoing studies will carefully move toward broader clinical application in the future.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 606).

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