Published in final edited form as:

Immunotherapy. 2010 May 1; 2(3): 329–338. doi:10.2217/imt.10.15.

Immunotherapy in food allergy

Toral Kamdar¹ and Paul J Bryce^{†,1}

¹Division of Allergy-Immunology, Feinberg School of Medicine, Northwestern University, 240 E Huron, M315 Chicago, IL 60610, USA

Abstract

Food allergies are caused by immune responses to food proteins and represent a breakdown of oral tolerance. They can range from mild pruritis to life-threatening anaphylaxis. The only current consensus for treatment is food avoidance, which is fraught with compliance issues. For this reason, there has been recent interest in immunotherapy, which may induce desensitization and possibly even tolerance. Through these effects, immunotherapy may decrease the potential for adverse serious reactions with accidental ingestions while potentially leading to an overall health benefit. In this review, we discuss the mechanisms of food allergy and give an overview of the various immunotherapeutic options and current supporting evidence, as well as look towards the future of potential novel therapeutic modalities.

Keywords

food allergy; food hypersensitivity; immunotherapy; oral immunotherapy; sublingual immunotherapy

Food allergy: epidemiology

Food hypersensitivity reactions have become an increasingly burdensome issue over the last few decades; not only does the prevalence appear to have risen, but the impact on healthcare systems has also become more substantial [1,2]. Data taken from the National Electronic Injury Surveillance System (NEISS) using data from US emergency rooms indicate that there are an estimated 121,000 emergency department visits per year for food allergy-related symptoms, with approximately 3100 hospitalizations. It has been suggested that only slightly over half of the patients with probable anaphylaxis may be correctly coded when entering the hospital, implying that food allergy may be even more common than currently thought [3].

Food allergy affects 3.9% of children in the USA, with an approximate 18% increase in the past 10 years [1]. A population-based study using a US FDA questionnaire estimated the prevalence of self-reported food allergy in adults as 9.1%, with 5.3% having a doctor-diagnosed allergy [4]. While in some emergency room studies shellfish has been described as the most common allergen involved in food hypersensitivity in patients over 6 years of age, another meta-analysis noted that milk, egg, peanuts and nuts were more common in the general population [3]. Reactions to food allergens cover a wide clinical spectrum, from mild pruritis to life-threatening anaphylaxis. Although it is true that some types of hypersensitivity fade when children move to adulthood (commonly seen in cases of hen's egg and cow's milk allergies) peanut allergies tend to be persistent and are more commonly life-threatening.

To date, the major therapeutic modality of food allergy has been strict avoidance of the allergen and constant access to self-injectable adrenaline. This has been demonstrated to cause a significant strain on patient quality of life since the fear of anaphylaxis is eminent owing to the potential for accidental ingestions [5]. Studies have reported that the accidental ingestion of allergens can occur in 40–75% of patients, even in those who participate in strict avoidance, highlighting the reason for patient concern and the need for other therapeutic modalities [5–7].

Mechanisms of reactivity

A major concept underlying our views of food allergy is that it occurs owing to a defect in oral tolerance. This is the natural immunoregulatory process that generates active suppression immunity to antigens experienced via the intestinal tract [8]. The mechanisms underlying oral tolerance are being revealed to be increasingly complex, with evidence for anergy (a state of unresponsiveness induced by overstimulation) or death in reactive T cells, both natural regulatory CD4⁺ T cells (thymus-derived FoxP3⁺ cells), inducible regulatory CD4⁺ T cells (peripherally derived) and TGF- β -secreting Th3 cells, as well as more novel regulatory cell subsets, such as IL-10-producing B cells and regulatory CD8⁺ T cells. TGF- β has been defined as a critical regulator of this entire process [9], and other cells that are capable of TGF- β production, such as macrophages, may also contribute. We have demonstrated that food allergy is associated with a loss of TGF- β and FoxP3 expression within the intestine using a murine model that utilizes oral antigen exposure [10]. Children with food allergies have also been found to exhibit reduced numbers of circulating IL-10-producing cells and TGF- β -producing T cells within their intestinal mucosa [11,12]. In a murine model, oral administration of TGF- β enhanced oral tolerance and reduced antigen-specific IgE levels [13]. CD103, an integrin that is highly expressed at intestinal mucosal sites, is expressed on a subset of dendritic cells that have a potent capacity to induce FoxP3⁺ regulatory CD4⁺ T cells [14,15], suggesting that the intestinal mucosal is a specialized environment for promoting regulatory control over the immune system. Despite this wealth of knowledge, there is still debate regarding whether food allergy is the consequence of oral/intestinal antigen exposure and subsequent failure in oral tolerance, or if other routes of sensitization are important. In particular, the skin has been proposed as a potential site of food allergen sensitization [16]. In a murine model, epicutaneous exposure to peanut proteins was able to promote specific IgE and IL-4 responses [17], as well as preventing the ability to mount subsequent oral tolerance responses. However, while skin exposure to food allergens (e.g., protein contamination of peanut oils used in skin creams) may explain the increase in some allergies seen across many countries, studies on the diversity of food allergies would appear to reflect an influence of regional diets. For example, in a study of 107 cases of severe anaphylaxis in 2002, there were five cases of anaphylaxis to snail: the study was performed in Paris, France [18]. Consequently, it is likely that, while topical exposure to food allergens may explain certain food allergies, others may reflect a true failure in oral tolerance mechanisms.

Focus on prevention

Given the limitations in current food allergy treatment, prevention has become a major focal point, especially with regard to pregnant women and neonates. The prevailing theory had been that food avoidance in infants was a cornerstone in preventing the development of food allergy and this was then extrapolated to pregnant women. Recently, however, this stance has been reversed. In January 2008, the American Academy of Pediatrics (AAP) reversed its stance on delaying the introduction of dairy, eggs and nuts (after 4–6 months of age, when other solid foods are introduced), stating that there was “no current convincing evidence that delaying their introduction has significant protective effect on the development of atopic disease” [19]. Studies in other countries where certain allergenic foods are introduced early have had disparate

results. In Germany, infants that were randomized to extensively hydrolyzed milk formulas versus cow's milk had a lower incidence of atopic disease at 6 years compared with those given cow's milk [20]. However, in Israel, the incidence of peanut allergy is markedly lower (0.04%) than in other Western countries (1%) [21]. One theory behind this is that children are introduced to peanut products much earlier in Israel than in other Western countries, and this may cause a form of high-dose tolerance [22–24]. However, alternate explanations for this low rate of peanut allergy include different formulations of peanut products and low ingestion rates of peanuts in Israel [21,25]. In the USA and the UK since the 1980s, the practice of food avoidance at an early age has been widely adopted as a protective measure against atopy and food allergy development. The observations in Israel have prompted further investigation into whether early and regular exposure, particularly in high-risk individuals such as those with a positive family history, may decrease the risk for food allergy. This is currently being explored in the Learning Early About Peanuts (LEAP) study, a randomized control trial to explore whether early peanut protein exposure in high-risk children may be more efficacious than avoidance [101]. Similarly, a large multidisciplinary project, EuroPrevall, funded by the EU and involving 24 countries, has also been investigating the patterns of food allergy in various countries and how different practices affect prevalence [26]. The results of such studies will be interesting with regard to avoidance practices and preventative strategies towards food allergies.

Mechanisms of immunotherapy

Despite the relative successes of immunotherapy approaches for allergic rhinitis and asthma, the precise mechanisms of action remain poorly defined. However, the majority of studies focus on three main outcomes: the generation of 'protective' antibody responses, reduction in the responsiveness of effector cells and changes in the T-cell cytokine balance.

The concept of 'blocking' antibodies that could reduce IgE-mediated allergic responses had been proposed previously [27,28], but it was not until 1968 that they were identified as IgG type [29]. In this study, Lichtenstein *et al.* demonstrated that the success of immunotherapy appeared to depend on the induction of an IgG response. As research focused more onto the specific IgG isotypes, it has emerged that IgG₄ may play an important role in immunotherapy. While IgG₁ appears within the early phases of immunotherapy, IgG₄ is produced in significant amounts after long-term treatment [30,31]. However, it is important to consider the results of studies on immunotherapy for bee venom. Here, it has been demonstrated that immunotherapy can actually increase the specific IgE response, as well as the IgG₄ response [32]. As a result, the ratio of IgE to IgG₄ may be more important than absolute numbers.

Desensitization of the effector cells in allergy is another mechanism through which immunotherapy might function. After IgE-mediated stimulation, mast cells and basophils can undergo desensitization that leaves them refractory to subsequent stimulation [33]. The initial, low-dose exposures administered in immunotherapy may promote a local desensitization that facilitates control during the increased doses. Notably, recent mechanistic studies have demonstrated that pharmacological inhibition of spleen tyrosine kinase (Syk), critical in IgE-mediated degranulation, did not alter the desensitization of either mast cells or basophils [34]. As such, desensitization may be achieved while degranulation is prevented. The clinical significance of this approach remains to be established.

A major component of immunotherapy appears to be the alteration of the T-cell responses to the allergen, via either skewing of the proallergic Th2 response towards a Th1 or via the induction of regulatory T cells (Tregs). Tregs can be thymically derived (natural) or antigen specific (inducible). Both can exert potent suppression of immune responses via a diverse range of mechanisms that have become increasingly diverse [35]. The secretion of cytokines with suppressive functions is one major mechanism, and they include IL-10 and TGF- β , which have

been found to be important in food allergy [11,12]. TGF- β also provides a link between induced Tregs and Th17 cells as both require TGF- β for differentiation. Th17 cells are found mostly at barrier surfaces and function as protection against microorganisms, as well as performing a regulatory function against effector cells [36]. IL-35 is a newer Treg-derived cytokine with a suppressive function that has not yet been investigated, although early reports have suggested that human Tregs may not express IL-35 [37]. Other mechanisms include sequestering of IL-2, which is important for effector T-cell proliferation, and more direct mechanisms, such as granzyme-mediated cytotoxicity, or alteration of dendritic cell functions via CTLA-4-CD80/CD86 engagement, LAG-3/MHC class II engagement or CD39-mediated inactivation of extracellular ATP [35].

Early history of allergen-specific immunotherapy for food allergy

Native Americans explored this modality in the 1800s for suppressing immune reactions, as certain populations ate poison ivy leaves to prevent contact hypersensitivity reactions [38]. In the 1900s, this was further explored in a laboratory setting with guinea pigs and subcutaneous injection of egg protein [39]. Immunotherapy was primarily studied with regard to respiratory allergy treatment and food allergy immunotherapy was relatively ignored until the middle of last century. In 1930, a young child with fish allergy was successfully desensitized [40]. In 1977, one of the first multipatient studies for subcutaneous immunotherapy was conducted, with some benefit but a high rate of adverse reactions [41].

The first well-documented study of immunotherapy was carried out a few decades later, and remains a cornerstone of further investigation. Nelson *et al.* conducted a double-blind, placebo-controlled trial with the injection of aqueous peanut extract in peanut-allergic patients, using a rush protocol with maintenance doses for approximately 1 year [42]. Patients in the treatment group were able to tolerate higher amounts of peanuts at the 1-year food challenge, but only three out of six remained tolerant of the maintenance dose. In addition, systemic reactions were common and the safety profile was intolerable. Owing to the severe adverse reactions seen in food allergen immunotherapy via the subcutaneous route, this therapeutic modality has been dropped and within the last few decades there has been a more dedicated approach to studying immunotherapy delivered by other means [42,43].

Sublingual immunotherapy

Given the systemic reactions associated with injection immunotherapy, sublingual immunotherapy (SLIT) was developed. The majority of literature focuses on SLIT for environmental allergens, with markedly positive results. One of the first SLIT studies using food was performed by Enrique *et al.* in a double-blind placebo-controlled trial of hazelnut allergy [44]. A total of 23 adults were evaluated and divided into active treatments ($n = 12$) and placebo ($n = 11$). The active treatment group received a 4-day build-up in clinic, followed by 3 months of home administration of hazelnut extract via a sublingual technique. Systemic reactions occurred in 0.2% only during the rapid build-up phase and solely required oral antihistamine for treatment. After 3 months of therapy, there was repeat double-blind food challenge in which the mean quantity causing any type of reaction increased from 2.3 g (pretreatment) to 11.56 g (post-treatment) in the hazelnut extract group ($p = 0.02$). IgG₄ and IL-10 levels also increased in the active group after treatment. In the placebo group, there was no significant increase in quantity of peanut tolerated (3.5 g pretreatment to 4.1 g post-treatment). Approximately 50% of patients that underwent hazelnut SLIT were able to tolerate the highest dose of 20 g (15–20 hazelnuts), which may be sufficient to confer protection against accidental ingestions.

Another study expanded the scope by applying sublingual immunotherapy to various food hypersensitivities – cow's milk, whole egg, albumin, apple, beans, wheat and cod [45]. A total

of 42 children were in the experimental group and ten children were in the control group. A double-blind, placebo-controlled food challenge was first administered, after which the treatment group underwent a sublingual–swallow desensitization protocol. In this method, the allergen was initially placed under the tongue and held there for a few minutes, then swallowed. After completion, all patients were asked to eat the allergenic food at least twice a week to maintain tolerance. The protocol was somewhat standardized, as it was based on the investigators' prior studies [45–47], but involved very small numbers of patients for certain foods (one patient each for apple and beans). In addition, by its design, this study included both sublingual and oral exposures. However, the treatment was performed for a variable time of 5–10 months, and results demonstrated an improvement in skin prick tests, decreases in specific IgE and increases in specific IgG₄ compared with controls. More importantly, double-blind, placebo-controlled food challenge was negative in all patients who successively completed the desensitization protocol and was positive in all controls. However, patients with severe allergic reactions were excluded from the study, thereby minimizing those patients who may have exhibited significant adverse reactions, and there was no long-term follow-up, thus tolerance could not be assessed. Other case reports have investigated sublingual rush desensitization to cow's milk and sheep's milk with successful results [48].

Oral immunotherapy

Oral immunotherapy (OIT) has a similar mechanism to that of SLIT, except the allergen is immediately swallowed. The majority of early studies focused on hen's egg and cow's milk OIT.

Meglio *et al.* examined children with cow's milk allergy; 18 out of 21 children were at least partially desensitized to cow's milk after a 6-month OIT protocol [49]. The theory behind these 'partial responders' is that desensitization could help with reducing the risk of severe anaphylactic reactions with accidental ingestion. A decrease in food-specific IgE and an increase in specific IgG₄ was also noted. The concern with some of these studies, especially in cow's milk hypersensitivity, is that natural tolerance may have played a role in these results, since it is relatively common for children to outgrow this allergy.

A larger study of 60 children with severe milk allergy randomized them to either treatment (OIT) or controls (milk-free diet for 1 year) [50]. Both groups initially reacted to a food challenge in order to qualify and had an elevated milk-specific IgE. The treatment group underwent an in-patient rush phase and then continued a dose-escalating maintenance phase over 1 year, which was personalized to each patient. A total of 36% were able to tolerate the goal dose (150 ml) at 1 year, while 54% could tolerate at least 5 ml and 10% could not tolerate any amount owing to their symptoms. Every member of the control group had a positive food challenge at the end of 1 year. The treatment group did achieve statistical significance. However, the concern was the large number of adverse reactions, including four children who needed epinephrine. In addition, there was no long-term follow-up to assess tolerance induction.

Oral immunotherapy for hen's egg allergy was assessed in a study of seven children who underwent a rush protocol with the goal of desensitization in order to prevent severe reactions with accidental ingestions [51]. All patients underwent a doubling dose of hen's egg protein approximately every 30 min until the highest tolerated dose was determined. A maintenance phase was then continued for 24 months. Three out of seven subjects tolerated accidental ingestions while all patients were able to ingest more egg protein at the study's conclusion compared with at its beginning. Another more recent study of hen's egg OIT involved a rush protocol of six children; at the study conclusion all subjects could ingest one whole egg without adverse reaction [52]. There was a decrease in egg-specific IgE with an increase in TGF- β_1 ,

but rather surprisingly – given its role in tolerance and immunosuppression – a decrease in IL-10.

Peanut allergy OIT has become a more recent focus, especially since very severe reactions can occur with peanut hypersensitivity, making accidental ingestions more worrisome. One case report discusses a 38-year-old woman with peanut allergy who underwent oral desensitization [53]. At the end of a 7-day rush phase, she underwent a maintenance phase for 6 months. She has continued to eat 40 g of peanuts three-times a week daily for an indefinite period of time; moreover, she was able to tolerate peanut-containing products without issues. Another case study of a young girl with severe peanut allergy who had several severe reactions with accidental ingestions underwent OIT with similar results [54].

The safety of peanut OIT has been of particular interest, given the intolerable reactions seen with subcutaneous peanut immunotherapy initially and the higher potential of anaphylaxis [55]. Adverse reactions and safety profiles were particularly addressed in a recent study of 28 children with peanut allergy [55]. Reactions were most common during the initial escalation day; four out of 28 required epinephrine during that period and, in total, 78% had some type of reaction. However, home-dosing was fairly well tolerated, with only 3.5% experiencing symptoms, generally classified as mild. Asthma was found to correlate with having a higher risk of respiratory symptom-associated adverse reactions. A total of 93% tolerated the 3900 mg peanut food challenge at the end of the study, while all experienced symptoms in response to 50 mg at the beginning of the study. While there were a high incidence of reactions overall, it appears that this number is lower and the reactions less severe than prior peanut immunotherapy trials and may be tolerable if participants are monitored closely [42,43,55]. Particular triggers, or predisposing factors, were further identified by another group, with the suggestion that addressing these issues may improve the safety profile of peanut OIT [56]. These potential triggers, identified during home-dosing, were noted to be: concurrent illness, suboptimally controlled asthma, timing of dose administration after food ingestion, physical exertion after dosing and dosing during menses. Incorporating these factors within a peanut OIT protocol may help to diminish adverse reactions; this particular group suggested a set of recommendations to help attain this goal. Jones *et al.*, in a recent peanut study, evaluated 29 children after an OIT protocol for clinical response and immunologic changes [57]. After 18 months, peanut-specific IgE decreased, IgG₄ increased and secretion of IL-10, IL-5, IFN- γ and TNF- α increased. There were no severe reactions during the protocol and any symptoms were controlled with diphenhydramine and albuterol alone. However, an oral food challenge was not conducted immediately following the end of the study; this is planned for after 3 years of maintenance therapy so that the authors can assess true tolerance.

The rates of success vary between 70 and 80% throughout all the OIT studies, although it is somewhat difficult to generalize given the inconsistencies in protocol, patient selection and definition of ‘success’ [49–57]. This is one of the major drawbacks of the various OIT studies, in that ‘success’ is variably defined, sometimes being referenced to tolerance and other times to desensitization. ‘Desensitization’ refers to the ability to ingest an allergen without symptoms, but an amount of the allergen must be ingested daily, while ‘tolerance’ refers to the ability to ingest an allergen without symptoms after the cessation of daily maintenance ingestion [58]. In general, the rates of success refer to desensitization but do not address the ability to attain tolerance. There are currently no defined markers of tolerance, which is one difficulty. Another difficulty is that, in order to truly assess clinical tolerance, studies must be conducted over a long-term period of time to differentiate between natural tolerance and induced tolerance. Cow's milk OIT is one specific area in which this is a particular difficulty, as it has been reported that as few as 20% of children will have cow's milk allergy that persists into adulthood, making the line between natural tolerance and induced tolerance particularly small [59].

Meglio *et al.*, after their initial study of cow's milk OIT, did a longer-term follow-up 4 years after the conclusion [49,60]. A total of 15 out of 21 children (71%) after the initial study tolerated the end goal dose of 200 ml, while three children had to be taken out of the study owing to intolerable side effects. At the 4-year follow-up, all of the children in the initial 'success group' were still tolerant of cow's milk. However, the lack of a control group makes it difficult to interpret whether this was accomplished through OIT or whether this was a manifestation of natural tolerance. Staden *et al.* randomized 45 children to either hen's egg or cow's milk OIT or to an elimination group [61]. After approximately 21 months of daily maintenance dosing, children in the treatment group underwent a secondary elimination diet for 2 months. After the final challenge, nine out of 25 (36%) demonstrated permanent tolerance while three out of 25 (12%) were tolerant with regular intake but had reoccurrence of symptoms after 2 months of allergen avoidance. This is compared with the control group that had a 35% tolerance rate, suggesting that there was no difference after cessation of daily allergen and thus no achievement of true tolerance. However, there was a total of 64% who were partial or full responders, and who may benefit from daily ingestion to prevent severe reactions after accidental ingestions. Whether the strenuous nature of daily treatment is worth that level of outcome is still unclear, and further studies are needed in order to fully assess this, but may end up being best made by the parents of an affected child.

Other issues are still noteworthy for critical appraisal of the current OIT studies. There is no standardized protocol, which makes it difficult to compare outcomes, as the doses and protocol time periods have very wide variability. Some authors have focused on outlining specific protocols, but the majority of studies have their own self-generated protocols [51,56]. In addition, aside from a few well-conducted trials, most studies do not contain adequate control groups, leading to difficulties in interpretation. The majority of the studies are in children, who are known to have a different natural history of their allergenicity; therefore, studies conducted on adults would be useful to circumvent this issue. The subjective nature of this type of research must also be addressed; the severity of reactions may be interpreted differently by investigators as well as within different populations, while some studies chose to eliminate severe responders while others do not. To date, no objective criteria have been defined for these purposes.

New potential therapeutic directions

■ Heat-denatured proteins

While still involving OIT, this notion involved using extensively heated foods. IgE binding can include specificity to both sequential and conformational epitopes, which have been well described. Heat can cause denaturation of the tertiary structure that may disrupt the conformational epitopes. One group further evaluated this notion in cow's milk, finding that, of 93 children reactive to milk, 73% tolerated extensively heated milk products [62]. Another group saw similar results in children with hen's egg allergy being challenged with baked egg products [63]. This may represent another avenue to explore with regard to OIT. However, while IgE against conformational epitopes have been demonstrated for egg and milk [64], other food allergies have been more commonly associated with recognition towards linear epitopes, such as with peanuts [65]

■ Peptide immunotherapy

One of the major drawbacks of OIT is the potential for severe systemic reactions, since whole allergens are associated with this risk owing to the presence of B-cell epitopes that can crosslink IgE. Peptide-based strategies can avoid this by eliminating B-cell epitope sequences and thus prevent the crosslinking of IgE, while relying heavily on T-cell epitopes. This was initially studied in cat hyper-sensitivity, with significant clinical improvement in symptoms [66,67]. Studies have yet to reach the clinical trial stage in food allergy, but this may be a future direction.

However, caution may be needed since, in studies investigating immunotherapy for autoimmune disease, peptide immuno therapy has the potential to elicit anaphylaxis and death in mice [68].

■ Mutated allergens

This concept involves engineering antigenic epitope-free proteins through PCR mutagenesis and, similarly to peptide immunotherapy, allow for an antigen that influences specific T cells without crosslinking IgE. This has been investigated in peanut allergy, where mutated Ara h 1, 2 and 3 (HKE-MP123) have been engineered to be expressed by *Escherichia coli* and then administered rectally in a murine peanut allergy model [69]. The outcome demonstrated a potential difference between the treated group and sham-treated mice, specifically in histamine levels and IgE, while also suggesting a shift from a Th2 to Th1 response. Another trial investigated an apple allergen, Mal d 1, and demonstrated that the mutant allergen caused a decrease in food challenge reactivity compared with the native allergen [70].

■ Anti-IgE therapy

Anti-IgE is a humanized mouse monoclonal IgG antibody directed against the human IgE molecule which binds to freely circulating IgE, thereby rendering it unable to bind to its specific high-affinity receptor (FcεRI) on mast cells and basophils. This works through an ‘allergen nonspecific’ approach, whereby it can be effective against multiple different allergens. Anti-IgE has already been studied in asthma and allergic rhinitis, with reductions in multiple areas of interest, including medication use and allergic symptoms [71]. Given the success of these studies, humanized monoclonal anti-IgE (TNX-901) has recently been applied to peanut hypersensitivity in a well-conducted, double-blind, placebo-controlled, dose-ranging clinical trial, with the conclusion that the subjects receiving the highest dose (450 mg) had increased tolerance compared with before the trial [72]. However, approximately a quarter had no change in tolerance after receiving anti-IgE. Other drawbacks include the high price of anti-IgE and issues with anaphylaxis. Another trial utilizing a different anti-IgE antibody preparation (omalizumab) was discontinued owing to safety concerns with the protocol [73]. Despite these concerns, it is intriguing to propose that anti-IgE may be useful as a ‘facilitator’ to inducing tolerance. For example, by preventing the IgE-mediated anaphylactic reactions, the severity or frequency of adverse events may be sufficiently controlled to allow SLIT or OIT to be safely utilized.

■ Chinese remedies

Using traditional Chinese medicine, there has been the development of two food allergy herbal formulas – FAHF-1 (which contains extracts of 11 traditional Chinese herbs) and FAHF-2 (which contains extracts of nine herbs). These studies have used a murine model that mimics peanut allergy and demonstrate that FAHF-2 blocked anaphylaxis both early (during the development of peanut hypersensitivity) and late (after peanut hypersensitivity was fully established), primarily through the suppression of histamine release and Th2 responses [74]. In these mice, anaphylactic reactions were actually prevented by FAHF-2 after multiple peanut challenges for multiple months, although the doses of FAHF-2 needed are relatively large (30–60 mg/kg). Despite this, FAHF-2 is now being explored in human food allergy – a Phase I open-label study is currently under review [75].

Executive summary

Epidemiology of food allergy

- Food allergy affects approximately 4% of children and 5% of adults in the USA.

- Food allergy is responsible for approximately 121,000 emergency department visits per year in the USA.

- Accidental ingestions can occur in 40–75% of patients.

- Current therapeutic strategies include food elimination and strict avoidance.

Mechanisms of reactivity

- Oral tolerance typically controls immune responses to foods.

- Route of allergen exposure may vary.

Focus on prevention

- There is no role for delaying the introduction of potentially allergenic foods according to the American Academy of Pediatrics.

- Some recent interest in the concept of early food introduction to prevent food hypersensitivity.

Mechanisms of immunotherapy

- Antibody balance between IgE and IgG₄ may be important.

- Desensitization of effector cells may prevent reactivity.

- Promoting regulatory T cells may restore unresponsiveness to foods.

Concept of immunotherapy

- The mechanism of immunotherapy is probably via a shift from primarily Th2 to Th1 dominant response.

- The goal is to induce a clinical tolerance, which may be similar to natural tolerance in nonallergic individuals.

- Immunotherapy protocols, including rush protocol, are varied in their conditions.

History of early immunotherapy

- Immunotherapy was first explored in the 19th and early 20th Centuries.

- Subcutaneous immunotherapy was evaluated with peanuts; however, the side-effect profile was intolerable.

Sublingual immunotherapy

- There have been favorable studies in environmental allergens in the past.

- A hazelnut sublingual immunotherapy study demonstrated that this method may confer a benefit against accidental ingestion.

- Another trial with various food allergens had negative food challenges in all treatment groups at the end of the study.

Oral immunotherapy

- The oral immunotherapy protocol involves immediately swallowing allergen.

- Meglio *et al.* found a decrease in allergen-specific IgE and an increase in specific IgG₄ with this protocol.

- Another large RCT did achieve statistical significance, but with a large number of adverse reactions.

- Peanut allergy oral immunotherapy (OIT) is a more recent development, with the safety profile being the primary focus.
- Recent safety studies have concluded that peanut OIT is probably better tolerated than peanut subcutaneous immunotherapy.
- A set of recommendations and predisposing risk factors has been constructed to help improve the safety of peanut OIT.
- A major issue with OIT is whether true clinical tolerance or merely desensitization is the outcome. The results of a few longitudinal studies are discussed.
- Other areas that have still not been fully addressed within OIT are standardized protocols, age of patients and lack of control groups.

New potential therapeutic directions

- Various alternatives to OIT include heat-denatured proteins, peptide immunotherapy and mutated allergens.
- Allergen-nonspecific therapies include anti-IgE, FAHF-2 and worm-egg therapy. In particular, use of Chinese medicine may be an interesting future treatment for food allergy.

■ Worm eggs

Studies investigating *Schistosoma japonicum* egg antigens can induce the productions of CD4⁺/CD25⁺ Tregs in asthma, causing a decrease in airway inflammation and probably inhibiting asthma development in murine models [76]. This has not been formally studied in food hypersensitivity, but is another potential future direction and is being considered for effectiveness in food allergy models.

Conclusion & future perspective

There have been a growing number of studies in food allergy and immunotherapy within the last few decades, but only a few well-controlled, randomized trials demonstrate some benefit of this type of intervention. Further studies are needed in order to address some of the issues raised in this review, but OIT has overall promise to help prevent severe allergic reactions. Other therapeutic modalities on the horizon include peptide immunotherapy, anti-IgE and Chinese complementary medicines. Combining ‘facilitator’ compounds to inhibit severe reactions with ‘inducer’ approaches to promote desensitization or tolerance may prove beneficial, particularly for patient safety. The exploration of these techniques will be exciting developments in the future of food allergy.

Acknowledgments

Paul J Bryce received NIH/NIAID funding for the production of this work (Grant number: R21AI078525). 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.

Bibliography

Papers of special note have been highlighted as:

- of interest
- ■ of considerable interest

1. Branum AM, Lukacs SL. Food allergy among US children: trends in prevalence and hospitalizations. NCHS data brief 2008;(10):1–8. [PubMed: 19389315]
2. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J. Allergy Clin. Immunol* 2001;108(1):133–140. [PubMed: 11447395]
3. Ross MP, Ferguson M, Street D, Klontz K, Schroeder T, Luccioli S. Analysis of food-allergic and anaphylactic events in the national electronic injury surveillance system. *J. Allergy Clin. Immunol* 2008;121(1):166–171. [PubMed: 18206508]
4. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J. Allergy Clin. Immunol* 2007;120(3):638–646. [PubMed: 17628647]
5. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann. Allergy Asthma Immunol* 2001;87(6):461–464. [PubMed: 11770692]
6. Boyano-Martinez T, Garcia-Ara C, Pedrosa M, Diaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. *J. Allergy Clin. Immunol* 2009;123(4):883–888. [PubMed: 19232704]
7. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J. Pediatr* 2000;137(6):749–755. [PubMed: 11113829]
8. Weiner HL. Oral tolerance. *Proc. Natl Acad. Sci. USA* 1994;91(23):10762–10765. [PubMed: 7971958]
9. Faria AM, Weiner HL. Oral tolerance and TGF- β -producing cells. *Inflamm. Allergy Drug Targets* 2006;5(3):179–190. [PubMed: 16918481]
10. Ganeshan K, Neilsen CV, Hadsaitong A, Schleimer RP, Luo X, Bryce PJ. Impairing oral tolerance promotes allergy and anaphylaxis: a new murine food allergy model. *J. Allergy Clin. Immunol* 2009;123(1):231–238. E234. [PubMed: 19022495]
11. Perez-Machado MA, Ashwood P, Thomson MA, et al. Reduced transforming growth factor- β 1-producing T cells in the duodenal mucosa of children with food allergy. *Eur. J. Immunol* 2003;33(8):2307–2315. [PubMed: 12884306]
12. Scott-Taylor TH, Hourihane JB, Harper J, Strobel S. Patterns of food allergen-specific cytokine production by T lymphocytes of children with multiple allergies. *Clin. Exp. Allergy* 2005;35(11):1473–1480. [PubMed: 16297145]
13. Ando T, Hatsushika K, Wako M, et al. Orally administered TGF- β is biologically active in the intestinal mucosa and enhances oral tolerance. *J. Allergy Clin. Immunol* 2007;120(4):916–923. [PubMed: 17606291]
14. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, et al. A functionally specialized population of mucosal CD103⁺ DCS induces Foxp3⁺ regulatory T cells via a TGF- β and retinoic acid-dependent mechanism. *J. Exp. Med* 2007;204(8):1757–1764. [PubMed: 17620361]
- 15■. Yamazaki S, Bonito AJ, Spisek R, Dhodapkar M, Inaba K, Steinman RM. Dendritic cells are specialized accessory cells along with TGF- β for the differentiation of Foxp3⁺ CD4⁺ regulatory T cells from peripheral Foxp3 precursors. *Blood* 2007;110(13):4293–4302. [PubMed: 17699744] [Demonstrates a subset of gut-resident dendritic cells with the potential to promote regulatory T cells]
16. Fox AT, Sasieni P, Du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J. Allergy Clin. Immunol* 2009;123(2):417–423. [PubMed: 19203660]
- 17■. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. *Clin. Exp. Allergy* 2005;35(6):757–766. [PubMed: 15969667] [Establishes that sensitization via the skin can promote allergic responses to food]
18. Moneret-Vautrin DA, Kanny G, Morisset M, Rance F, Fardeau MF, Beaudouin E. Severe food anaphylaxis: 107 cases registered in 2002 by the allergy vigilance network. *Allerg. Immunol. (Paris)* 2004;36(2):46–51.
19. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121(1):183–191. [PubMed: 18166574]

20. Von Berg A, Filipiak-Pittroff B, Kramer U, et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the german infant nutritional intervention study (GINI). *J. Allergy Clin. Immunol* 2008;121(6):1442–1447. [PubMed: 18539195]
21. Levy Y, Broides A, Segal N, Danon YL. Peanut and tree nut allergy in children: role of peanut snacks in Israel? *Allergy* 2003;58(11):1206–1207. [PubMed: 14616145]
22. Bock SA, Atkins FM. The natural history of peanut allergy. *J. Allergy Clin. Immunol* 1989;83(5):900–904. [PubMed: 2715549]
23. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J. Allergy Clin. Immunol* 2008;122(5):984–991. [PubMed: 19000582] [Suggests that early exposure to food allergens may promote tolerance and reduce allergy in later life]
24. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102(1):E6. [PubMed: 9651458]
25. Burks AW. Early peanut consumption: postpone or promote? *J. Allergy Clin. Immunol* 2010;123(2):424–425. [PubMed: 19203661]
26. Keil T, McBride D, Grimshaw K, et al. The multinational birth cohort of EuroPrevall: background, aims and methods. *Allergy* 2009;65(4):482–490. [PubMed: 19793062]
27. Cooke RA, Barnard JH, Hebal S, Stull A. Serological evidence of immunity with coexisting sensitization in a type of human allergy (hay fever). *J. Exp. Med* 1935;62(6):733–750. [PubMed: 19870445]
28. Loveless MH. Immunological studies of pollinosis: IV. The relationship between thermostable antibody in the circulation and clinical immunity. *J. Immunol* 1943;47:165–180.
29. Lichtenstein LM, Holtzman NA, Burnett LS. A quantitative *in vitro* study of the chromatographic distribution and immunoglobulin characteristics of human blocking antibody. *J. Immunol* 1968;101(2):317–324. [PubMed: 4174497] [Definitively demonstrates that IgG can mediate immunotherapy effects]
30. Peng Z, Lee HB, Proud D, Naclerio R, Adkinson NF Jr. Ragweed IgE and IgG4 antibody in nasal secretions during immunotherapy. *Clin. Exp. Allergy* 1990;20(5):571–579. [PubMed: 2253090]
31. Peng ZK, Naclerio RM, Norman PS, Adkinson NF Jr. Quantitative IgE- and IgG-subclass responses during and after long-term ragweed immunotherapy. *J. Allergy Clin. Immunol* 1992;89(2):519–529. [PubMed: 1740582]
32. Akdis CA, Akdis M, Blesken T, et al. Epitope-specific T cell tolerance to phospholipase A2 in bee venom immunotherapy and recovery by IL-2 and IL-15 *in vitro*. *J. Clin. Invest* 1996;98(7):1676–1683. [PubMed: 8833918]
33. Macglashan D Jr, Lavens-Phillips S, Katsushi M. IgE-mediated desensitization in human basophils and mast cells. *Front. Biosci* 1998;3:D746–D756. [PubMed: 9680509]
34. Macglashan D Jr, Udem BJ. Inducing an anergic state in mast cells and basophils without secretion. *J. Allergy Clin. Immunol* 2008;121(6):1500–1506. E1501–E1504. [PubMed: 18539198] [Evidence that desensitization can be discriminated from degranulation]
35. Shevach EM. Mechanisms of Foxp3⁺ T regulatory cell-mediated suppression. *Immunity* 2009;30(5):636–645. [PubMed: 19464986]
36. Weaver CT, Hatton RD. Interplay between the Th17 and treg cell lineages: A (co-) evolutionary perspective. *Nature Rev. Immunol* 2009;9(12):883–889. [PubMed: 19935807]
37. Bardel E, Larousserie F, Charlot-Rabiega P, Coulomb-L'hermine A, Devergne O. Human CD4⁺ CD25⁺ Foxp3⁺ regulatory T cells do not constitutively express IL-35. *J. Immunol* 2008;181(10):6898–6905. [PubMed: 18981109]
38. Dakin R. Remarks on a cutaneous affection, produced by certain poisonous vegetables. *Am. J. Med. Sci* 1829;7:98–99.
39. Wells H. Studies on the chemistry of anaphylaxis: III. Experiments with isolated proteins, especially those of the hen's egg. *J. Infect. Dis* 1911;9:147–151.
40. Freeman J. 'Rush' inoculation, with special reference to hay-fever treatment. *Lancet* 1930;215(5562):744–747.
41. Miller JB. A double-blind study of food extract injection therapy: a preliminary report. *Ann. Allergy* 1977;38(3):185–191. [PubMed: 320918]

42. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol* 1997;99(6 Pt 1):744–751. [PubMed: 9215240]
43. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *J. Allergy Clin. Immunol* 1992;90(2):256–262. [PubMed: 1500630]
44. 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* 2005;116(5):1073–1079. [PubMed: 16275379]
45. Patriarca G, Nucera E, Pollastrini E, et al. Oral specific desensitization in food-allergic children. *Dig. Dis. Sci* 2007;52(7):1662–1672. [PubMed: 17245630]
46. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment. Pharmacol. Ther* 2003;17(3):459–465. [PubMed: 12562461]
47. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepato-gastroenterology* 1998;45(19):52–58. [PubMed: 9496487]
48. Nucera E, Schiavino D, Buonomo A, et al. Sublingual-oral rush desensitization to mixed cow and sheep milk: a case report. *J. Investig. Allergol. Clin. Immunol* 2008;18(3):219–222.
49. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004;59(9):980–987. [PubMed: 15291907]
50. 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* 2008;121(2):343–347. [PubMed: 18158176]
51. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J. Allergy Clin. Immunol* 2007;119(1):199–205. [PubMed: 17208602]
52. Itoh N, Itagaki Y, Kurihara K. Rush specific oral tolerance induction in school-age children with severe egg allergy: one year follow up. *Allergol. Int* 2010;59(1):43–51. [PubMed: 19946197]
53. Patriarca G, Nucera E, Pollastrini E, et al. Oral rush desensitization in peanut allergy: a case report. *Dig. Dis. Sci* 2006;51(3):471–473. [PubMed: 16614954]
54. Mansfield L. Successful oral desensitization for systemic peanut allergy. *Ann. Allergy Asthma Immunol* 2006;97(2):266–267. [PubMed: 16937764]
55. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J. Allergy Clin. Immunol* 2009;124(2):286–291. 291.E1–E6. [PubMed: 19477496] [Outlines the risks and incidence of adverse reactions during immunotherapy for peanut allergy]
56. Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. *J. Allergy Clin. Immunol* 2009;124(6):1351–1352. [PubMed: 19913285]
57. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J. Allergy Clin. Immunol* 2009;124(2):292–300. 300.E1–E97. [PubMed: 19577283]
58. Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. *Ann. Rev. Med* 2009;60:261–277. [PubMed: 18729729]
59. Benhamou AH, Schappi Tempia MG, Belli DC, Eigenmann PA. An overview of cow's milk allergy in children. *Swiss Med. Wkly* 2009;139(21–22):300–307. [PubMed: 19492195]
60. Meglio P, Giampietro PG, Gianni S, Galli E. Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy – follow-up at 4 yr and 8 months. *Pediatr. Allergy Immunol* 2008;19(5):412–419. [PubMed: 18221476]
61. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007;62(11):1261–1269. [PubMed: 17919140]
62. Nowak-Węgrzyn A, Bloom KA, Sicherer SH, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J. Allergy Clin. Immunol* 2008;122(2):342–347. 347.E1–E2. [PubMed: 18620743]
63. Konstantinou GN, Giavi S, Kalobatsou A, et al. Consumption of heat-treated egg by children allergic or sensitized to egg can affect the natural course of egg allergy: hypothesis-generating observations. *J. Allergy Clin. Immunol* 2008;122(2):414–415. [PubMed: 18585768]

64. Vila L, Beyer K, Jarvinen KM, Chatchatee P, Bardina L, Sampson HA. Role of conformational and linear epitopes in the achievement of tolerance in cow's milk allergy. *Clin. Exp. Allergy* 2001;31(10):1599–1606. [PubMed: 11678861]
65. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, *in vitro* IgE function, and heterogeneity of allergenic peanut epitopes. *J. Allergy Clin. Immunol* 2004;113(4):776–782. [PubMed: 15100687]
66. Norman PS, Ohman JL Jr, Long AA, et al. Treatment of cat allergy with T-cell reactive peptides. *Am. J. Respir. Crit. Care Med* 1996;154(6 Pt 1):1623–1628. [PubMed: 8970345]
67. Yang M, Mine Y. Novel T-cell epitopes of ovalbumin in Balb/C mouse: potential for peptide-immunotherapy. *Biochem. Biophys. Res. Commun* 2009;378(2):203–208. [PubMed: 19022223]
68. Smith CE, Eagar TN, Strominger JL, Miller SD. Differential induction of IgE-mediated anaphylaxis after soluble vs. cell-bound tolerogenic peptide therapy of autoimmune encephalomyelitis. *Proc. Natl Acad. Sci. USA* 2005;102(27):9595–9600. [PubMed: 15983366]
69. 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* 2003;112(1):159–167. [PubMed: 12847493]
70. Bolhaar ST, Zuidmeer L, Ma Y, et al. A mutant of the major apple allergen, mal d 1, demonstrating hypo-allergenicity in the target organ by double-blind placebo-controlled food challenge. *Clin. Exp. Allergy* 2005;35(12):1638–1644. [PubMed: 16393331]
71. Milgrom H, Fick RB Jr, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 study group. *N. Engl. J. Med* 1999;341(26):1966–1973. [PubMed: 10607813]
72. Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N. Engl. J. Med* 2003;348(11):986–993. [PubMed: 12637608]
73. Sampson HA. A Phase II, randomized, double-blind, parallel-group, placebo-controlled, oral food challenge trial of xolair (omalizumab) in peanut allergy (TOPS). *J. Allergy Clin. Immunol* 2007;119:S1117.
74. Srivastava KD, Kattan JD, Zou ZM, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J. Allergy Clin. Immunol* 2005;115(1):171–178. [PubMed: 15637565]
75. Li XM. Traditional Chinese herbal remedies for asthma and food allergy. *J. Allergy Clin. Immunol* 2007;120(1):25–31. [PubMed: 17560638]
76. Yang J, Zhao J, Yang Y, et al. *Schistosoma japonicum* egg antigens stimulate CD4 CD25 T cells and modulate airway inflammation in a murine model of asthma. *Immunology* 2007;120(1):8–18. [PubMed: 17042799]

■ Website

101. Main website for the Learning Early About Peanuts study. www.leapstudy.co.ukw