Advances in Immunotherapy for Food Allergy

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Abstract

Food allergy is a life-threatening allergic disease that is increasing in prevalence with no approved curative therapy. Standard treatment of food allergy is limited to avoidance of the allergen and supportive management of allergic symptoms and anaphylaxis. Current research, however, has been focused on developing therapy that can modify the allergic immune response in both allergen-specific and non-specific methods. This review will provide an overview of these methods including oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy, modified food protein vaccines, anti-IgE monoclonal antibody adjuvant therapy, Chinese herbs, and helminth therapy.

Introduction

Food allergy is a life-threatening allergic disease that is increasing in prevalence with no curative treatments currently. Estimates of the prevalence of food allergies vary among studies, but one meta-analysis of 6 studies on food allergies in children reported that the prevalence based on oral food challenge (OFC) ranged from 1–10.8% (Rona *et al.*, 2007). A meta-analysis of 51 studies on the prevalence of food allergy estimates that the prevalence is more than 1–2% but less than 10%, because of methodological differences and the inherent uncertainty in diagnostic tests for food allergy (Chafen *et al.*, 2010). According to a survey of data from the National Center for Health Statistics on children with food allergy, the prevalence has increased by 18% from 1997 to 2007, while hospitalizations for food allergy have also tripled in the last decade (Branum and Lukacs, 2009). Standard treatment of food allergy is limited to avoidance of the allergen and supportive management of anaphylaxis (Burks *et al.*, 2011). Current research, however, has been focused on developing therapy that can modify the allergic immune response using both allergen-specific and non-specific approaches (Sicherer and Sampson, 2009). Allergen-specific immunotherapy includes oral

immunotherapy (OIT), extensively heated egg and milk diets (e.g., heat-denatured protein immunotherapy), sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), and modified recombinant food protein vaccines. Non-specific allergen immunotherapy includes the Chinese herbal formulation (FAHF-2), anti-IgE monoclonal antibody, and the use of helminthes (Nowak-Wegrzyn and Sampson, 2011). These therapies are in various stages of development ranging from animal models to phase 1 and 2 clinical trials.

Mechanisms of Allergy and Tolerance to Foods

Food allergy is thought to stem from a failure of the immune system to develop tolerance after exposure to a food protein. The immune system within the gastrointestinal tract is the largest in the body and is responsible for distinguishing food protein antigens from pathogens and commensal flora, and mounting the appropriate immune response to each. Ingested food antigens are physically and chemically broken down during digestion, and then traverse the gut epithelium, where they are taken up and processed by an antigen presenting cell (APC), often a dendritic cell. Peptides from the antigen are processed and presented in the context of major histocompatibility (MHC) class II molecules on the surface of the APC for recognition by a T cell specific for that antigenic peptide. This interaction may result in T cell activation and differentiation or alternatively anergy. In animals, tolerance has been shown to develop when the APC-T cell interaction results in the production of antigen-specific regulatory T cells (Tregs), and these Tregs actively suppress other immune cells from reacting to food antigens; this occurs when naïve mice are fed low doses of antigen. A separate form of high-dose tolerance has also been described, in which the APC-T cell interaction results in anergy or deletion of the responder T cell (Vickery *et al.*, 2011). Although the specific mechanisms of tolerance to food antigens in humans remain elusive, tolerance can be operationally defined as an active immune-mediated form of non-responsiveness (as opposed to simple ignorance). Food allergy is thought to occur when these processes fail, and the result is allergic priming initiated and propagated by a pathologic T cell response. This allergic T cell response is known as the type 2 helper cell (Th2) response, in contrast to other T helper cell responses such as Th1, Th17, Th9, etc. Th2 differentiation results from stable expression of the GATA-3 transcription factor and leads to the production of cytokines, such as interleukin-4 (IL-4), IL-5, and IL-13, that in turn stimulate production of immunoglobulin E (IgE) and activation of other effector pathways. Once this has occurred, the host will develop allergic reactions upon re-exposure to the same allergen. The deviation towards the allergic pathway can be influenced by a number of factors, including genetics, environmental factors, the intrinsic properties of the allergens themselves, as well as the nature and route of the allergenic exposure (Sicherer and Sampson, 2009; Otsu and Dreskin, 2011).

Allergen-specific Therapies

Similar to the subcutaneous injections of aeroallergens that have long been proven efficacious in allergic rhinitis, allergen-specific food immunotherapies aim to interrupt and/or reverse the immunologic events described above by introducing very small amounts of the allergen itself orally or sublingually in a controlled fashion. These therapies have been shown in randomized clinical trials to achieve immunomodulation (generally, reduction in

mast cell reactivity and allergen-specific IgE levels, accompanied by increases in allergen-specific IgG4 levels) as well as desensitization, a state where consistent daily exposure to the allergen raises the dose at which a patient will react (Jones *et al.*, 2009; Kim *et al.*, 2011a; Skripak *et al.*, 2008; Varshney *et al.*, 2011). This is a major advance in the treatment of food allergy and it is possible that the oral allergen-specific approach will result in the first clinically-approved disease-modifying interventional treatment for food allergy in the coming few years. While desensitization decreases the likelihood of life-threatening reactions to accidental ingestions, it is a transient effect that depends entirely on daily exposure to the allergen. Furthermore, the individual's exposure to the allergen is limited to only the daily dose (i.e., the diet cannot be liberalized). In contrast, true clinical tolerance would consist of a more permanent state allowing the subject to discontinue active therapy, with no reaction upon reintroduction of the allergen into the diet *ad lib*. It is important to note that clinical tolerance in humans has not been definitively linked to the immunologic tolerance described in the previous section; these terms are not interchangeable.

Oral immunotherapy

OIT consists of gradually escalating doses of allergen, administered orally in a food vehicle every day over months, with the goal of desensitization. Once a maintenance dose is achieved, the dose is not further escalated, and the individual continues to take the daily oral dose for a period of years. The proof of concept was first demonstrated in 1908, with a case report of a boy suffering from egg-induced anaphylaxis. However, scientific progress in the field remained stagnant until 1984, when Patriarca *et al.* (1984) attempted OIT to milk, fish, egg, and orange in 14 patients. Since this report, there have been a number of trials incorporating mechanistic studies that have investigated OIT with egg, milk, fish, and peanut, with some evidence of tolerating higher doses of allergen after immunotherapy, but most of these studies were limited by the lack of placebo-controlled groups for comparison (Blumchen *et al.*, 2010; Jones *et al.*, 2009; Longo *et al.*, 2008; Meglio *et al.*, 2004; Morisset *et al.*, 2007; Patriarca *et al.*, 2003; Staden *et al.*, 2007). In 2008, the first blinded, randomized, placebo-controlled trial of OIT (Narisety *et al.*, 2009; Skripak *et al.*, 2008) demonstrated that active therapy suppressed mast cell activation and raised the median threshold for milk reactivity from 40 grams at baseline to 5,140 grams after therapy, compared to no change in controls. Placebo-controlled studies demonstrating robust desensitization and immune modulation to peanut and egg were subsequently published (Burks *et al.*, 2012; Varshney *et al.*, 2011). In summary, these studies have been characterized by certain trends, with 10–20% of patients failing desensitization due to allergic side effects, 10–20% achieving partial desensitization, and 50–75% achieving desensitization (Nowak-Wegrzyn and Sampson, 2011). Though there is some evidence that a majority of patients can achieve desensitization, this success is tempered by the high rate of adverse reactions. In one study of peanut OIT, 93% of participants experienced allergic symptoms during the initiation of OIT (Hofmann *et al.*, 2009), although these were generally mild. OIT-induced anaphylaxis requiring epinephrine is uncommon.

Though allergen-specific therapies ultimately aim for clinical tolerance, none have been able to definitively prove the induction of tolerance. The study that comes closest to demonstrating tolerance is a recently published (Burks *et al.*, 2012) multi-center, double-

blind, randomized, placebo-controlled study of egg oral immunotherapy. At a planned interim analysis after 10 months of OIT, 22 of 40 (55%) of active subjects ingested 5 grams of egg during an OFC and were considered desensitized, compared to 0 of 15 in the placebo group. By 22 months of OIT, 75% of the active group had achieved desensitization, and underwent OFC again four to six weeks after stopping OIT. Ultimately, 28% of the active group developed a form of clinical tolerance the authors termed "sustained unresponsiveness," defined as the ability to eat egg *ad lib* in the diet by months 30 and 36 without symptoms. This is the first demonstration of a more permanent effect after OIT in a well-powered multi-center trial. However, spontaneous resolution is the expected natural history of egg allergy, and so it is conceivable that the participants might have outgrown their allergies even without OIT. The study was designed to minimize this possibility, and it was not frequently seen in the placebo group, although for safety reasons placebo subjects were not systematically challenged at all time-points. Overall, this study is one of the first to strongly suggest sustained unresponsiveness after OIT, an initial step in the pursuit of clinical tolerance. Much more investigation is necessary prior to concluding that reestablishing clinical tolerance to foods is a therapeutic possibility.

Extensively heated milk or egg

There is evidence that extensive heating of milk and egg, especially when mixed in a wheat-based batter and baked, can alter the conformational allergen epitopes that bind IgE and mediate the allergic reaction (Cooke and Sampson, 1997). Although it has been known clinically that some egg and milk allergic patients can eat such baked foods but not less well-cooked forms, this phenomenon has been more rigorously investigated in recent years. These patients are distinguished as heated milk-tolerant or heated egg-tolerant. In contrast, patients who cannot tolerate any forms of the allergen (heated or unheated) are referred to as heated milk-reactive or heated egg-reactive. One study of 100 milk-allergic patients found that 75% of the children with reported milk allergy tolerated heated milk when tested by heated milk OFC (Nowak-Wegrzyn *et al.*, 2008). A similar study in egg showed that of 117 subjects with documented IgE-mediated egg allergy, 74% tolerated heated egg (Lemon-Mule *et al.*, 2008). Among fifty heated milk-tolerant patients, none required epinephrine when challenged to unheated milk. In comparison, 35% of the 23 heated milk-reactive patients did require epinephrine during their unheated milk OFCs, suggesting that the heated milk-tolerant patients develop less severe reactions when exposed to unheated milk. This may represent a milder food allergy phenotype, and interestingly the same group in other studies was shown to have less basophil reactivity and a higher number of milk-specific Tregs, compared to the heated-milk-reactive group (Shreffler *et al.*, 2009; Wanich *et al.*, 2009). When this cohort of 100 patients was followed over time, another analysis was conducted that suggests but does not prove that incorporation of baked milk products into the diet of heated milk-tolerant patients may accelerate the development of unheated milk tolerance (Kim *et al.*, 2011b). This article showed that participants who incorporated baked milk into their diet were sixteen times more likely to become fully milk tolerant than the comparison group that practiced strict avoidance. This suggests that incorporation of heat-denatured proteins into the diet may have an immunotherapeutic effect.

Prior to these studies, strict avoidance was the general recommendation for food-allergic patients, based on the idea that the complete absence of exposure would help hasten the onset of spontaneous natural tolerance. Without a true randomized prospective control group, it is difficult to conclude whether baked milk exposure truly acted therapeutically to increase the likelihood of developing tolerance, or if the more rapid improvement was simply due to a milder milk allergy phenotype than the comparison group. However, the introduction of extensively heated allergens was well-tolerated by the majority of subjects, challenging the paradigm of strict avoidance. Additional study of these modified proteins as immunotherapy is necessary.

Sublingual immunotherapy

There have been few trials of SLIT for food allergy, but they generally resemble the escalation and maintenance type of OIT trials described above, with the important exception that much smaller doses are administered under the tongue; for example, whereas maintenance doses in OIT may reach 2–4 grams of protein per day, SLIT maintenance doses may be only 2–4 milligrams per day. In 2003, the first case report of SLIT for a food allergen was published, describing a patient with anaphylactic reactions to kiwi (Mempel *et al.*, 2003). Since then, studies have shown the use of SLIT in hazelnut and peach allergy, and these studies are notable for the use of placebo controlled comparison groups (Enrique *et al.*, 2005; Fernandez-Rivas *et al.*, 2009). However, their inclusion criteria did not exclude subjects with oral allergy syndrome, and as these patients are at low risk for anaphylaxis, it is difficult to extrapolate their findings to patients with true systemic/gastrointestinal food allergy. One study evaluated the use of SLIT in milk allergic patients, indicating an increase in the dose tolerated, but this was limited by the lack of a control group (de Boissieu and Dupont, 2006). Kim *et al.* (2011a) reported the first double blind, placebo-controlled trial with 18 peanut-allergic children randomized to peanut or placebo SLIT demonstrating a favorable safety profile and an immune-modifying effect. Subjects receiving active treatment were able to ingest approximately twenty times more peanut protein than the control group prior to the onset of symptoms. A large multi-center randomized placebo-controlled trial is underway for peanut allergy, but has yet to report results. Because of its ease and safety, SLIT could be an attractive immunotherapeutic option, but much more study is needed to determine if it is effective.

A recent study compared SLIT and OIT in the treatment of 30 participants with milk allergy (Keet *et al.*, 2012). The children were randomized to either SLIT only or SLIT followed by OIT at two different doses. After 60 weeks of maintenance therapy, 1 of 10 participants in the SLIT group achieved desensitization, compared to 6 of 10 patients in the lower-dose SLIT/OIT group and 8 of 10 patients in the higher-dose SLIT/OIT group. While the overall rate of allergic reactions was similar between SLIT alone and SLIT/OIT, the OIT group had more systemic reactions. Based on these findings, the group concluded that OIT was potentially more effective but also more prone to serious allergic reactions.

Epicutaneous therapy

EPIT involves the application of a patch containing a specific allergen onto the skin. In a small double blind, placebo-controlled pilot study, 18 children with milk allergy were

randomized to receive either a patch containing milk proteins or a placebo patch for three months (Dupont *et al.*, 2010). By the end of the study period, patients in the active treatment group were able to ingest on average 23.6 ml of milk, compared to 1.8 ml at baseline. The amount of cow's milk ingested in the placebo group did not change. Common side effects included local pruritus and eczema, with no severe systemic reactions. Peanut EPIT has also been studied in mouse models and currently phase 2 trials of peanut EPIT are ongoing (ClinicalTrials.gov, NCT01197053 and NCT01170286) (Mondoulet *et al.*, 2011).

Modified food protein vaccines

Modified food protein vaccines involve the delivery of allergenic proteins that have undergone point mutations of key amino acids, in order to alter the epitopes that are responsible for binding IgE. Modification of these IgE binding epitopes decreases the affinity of this interaction and should in theory enhance the safety of this approach, compared to allergen-specific approaches with native proteins. Modified food proteins have been engineered for peanut, fish, and apple (Bannon *et al.*, 2001; Ma *et al.*, 2006; Rabjohn *et al.*, 1999; Swoboda *et al.*, 2007). Li *et al.* (2003b) coadministered subcutaneous injections of modified major peanut allergens Ara h 1, 2, and 3 with a bacterial adjuvant such as *Listeria monocytogenes* in mice previously sensitized to peanut. After four weeks of these injections, mice that had received the recombinant peanut protein had decreased anaphylactic symptoms in response to a peanut challenge compared to control mice. This treatment is believed to shift the immune response from the allergic Th2 pathway to a Th1 response, based on decreased IL-5 and IL-13 cytokine levels and increased interferon-gamma (IFN-gamma) levels in splenocytes cultured from the modified peanut protein treated mice.

Other investigations have used nonpathogenic *E. coli* as an adjuvant and vector for the modified major peanut allergens Ara h 1, 2, and 3 (Li *et al.*, 2003a). As *E. coli* normally colonizes the gut, the modified heat killed *E. coli* containing the mutated proteins was administered rectally in mice for 3 weeks. Mice challenged with peanut had decreased severity of anaphylaxis. Splenocytes isolated from these mice also produced decreased Th2 cytokines and increased Th1 cytokines. Based on these findings, a phase 1 clinical trial assessing the safety of administering *E. coli* encapsulated modified peanut proteins is underway (ClinicalTrials.gov, NCT00850668).

Non-specific Immunotherapy

Chinese herbal medicine

Li and colleagues have developed a combination of Chinese herbs, known to have anti-inflammatory properties in traditional Chinese medicine, which they are testing as a treatment for food allergy. In murine models of peanut allergy, seven weeks of treatment with food allergy herbal formula (FAHF-2) successfully prevented the development of anaphylaxis up to 5 weeks post therapy (Srivastava *et al.*, 2005). Recent work in mice sensitized to multiple allergens, specifically fish, egg, and peanut, has shown that FAHF-2 can block anaphylaxis in a non-allergen-specific way (Srivastava *et al.*, 2012). An FAHF-2 product was produced for use in humans in keeping with established FDA guidelines of safety and quality control, and standardization of the batches was verified using high-

performance liquid chromatography. A phase 1 randomized double blind placebo-controlled trial of FAHF-2 was completed with 19 patients and the herbal formula was shown to be safe and well tolerated (Wang *et al.*, 2010). In this trial, the subjects were administered doses of up to 6.6 grams three times a day, with no apparent adverse effects. Phase 2 trials of FAHF-2 are ongoing (Clinicaltrials.gov, NCT00602160). While the large number of pills (10 tablets 3 times a day) is a potential limitation, this approach has the advantage of potentially treating multiple allergies at once.

Anti IgE monoclonal antibodies

Omalizumab is a humanized monoclonal antibody designed to bind IgE and block its interaction with high affinity IgE receptors that mediate the allergic reaction. The presence of drug-IgE complexes decreases the amount of free IgE, which leads to downregulation of these IgE receptors on mast cells and basophils. Omalizumab has been studied both as a non-specific immunotherapy and as an adjunct to allergen-specific immunotherapy; however, the first trial proving the efficacy of this therapy in food allergy was with a different anti-IgE antibody that has now been discontinued, TNX-901 (Leung*et al.*, 2003). This double blind study involved 84 peanut-allergic participants, who underwent baseline peanut OFCs, were randomized to either four weeks of one of three different doses of TNX-901 or placebo, and then underwent repeat OFC. Only the highest dose had a statistically significant improvement, with a mean threshold for peanut ingestion of 2,805 milligrams (approximately 9 peanuts), compared to 178 milligrams (about half of a peanut) in the control group. Of note, 24% of the patients receiving the highest dose of TNX-901 had no significant change in the threshold for peanut, suggesting that not all peanut-allergic patients would respond to this therapy.

A randomized, double blind, placebo-controlled phase II trial was initiated to study the efficacy of omalizumab in treating peanut allergy (Sampson *et al.*, 2011). The study intended to enroll 150 participants, but due to two severe anaphylactic reactions during preliminary screening OFCs, the study was terminated early. At that time, 26 subjects were randomized, with 17 receiving omalizumab. Preliminary results showed a trend towards greater doses of peanut tolerated in the active treatment group, but these were not statistically significant (p=0.054). Further investigation will be necessary to prove that omalizumab will be effective in increasing the threshold of reactivity to allergens.

Omalizumab has also been used as an adjunct to OIT in a recent study (Nadeau *et al.*, 2011). This pilot study enrolled 11 children and pretreated them with omalizumab for 9 weeks, followed by desensitization to milk over 7 to 11 weeks. Ten subjects remained in the study and 9 of these passed the final OFC. The percentage of adverse reactions was similar to that of prior milk OIT trials. A number of additional small trials testing OIT and omalizumab are also currently underway (ClinicalTrials.gov).

Parasites

Helminth parasites elicit strong immunoregulatory responses upon infecting their host and thus are being increasingly studied as an immunotherapeutic treatment in a variety of diseases, including allergic disease. In 2002, Bashir *et al.* (2002) used a mouse model for

peanut-induced anaphylaxis and infected the mice with the helminth, *Heligmosomoides polygyrus*. The helminth-infected mice had significantly decreased symptoms in response to exposure to peanut, when compared to controls. The mechanism for this reduction in anaphylactic response appeared to be due to a decrease in IL-13 and increase in IL-10 production. Another helminth that is being investigated for therapeutic efficacy is *Trichuris suis*, a helminth of the nematode family that naturally infects pigs (Jouvin and Kinet, 2012). *T. suis* ova therapy has been successfully used to improve disease severity in inflammatory bowel disease (Summers *et al.*, 2005). Phase 1 trials assessing the safety of administering *T. suis* ova orally in 6 adults with peanut or tree nut allergy were recently completed (Jouvin and Kinet, 2012). Participants ingested 8 total doses of 2,500 ova each. Side effects were mostly mild self-limited gastrointestinal symptoms. Phase 2 trials for efficacy have not yet been started.

Conclusion

Food allergy is a life-threatening allergic disease that is rising in prevalence with no approved treatments at this time. However, current research is exploring a wide variety of therapeutic options, ranging from both allergen specific to non-specific techniques. This research not only focuses on the quest for food allergy therapy, but it also better elucidates our understanding of the mechanism of tolerance to food allergies. One or more of these techniques will likely prove successful in at least diminishing the severity of food allergies through desensitization and be approved for clinical use as a disease-modifying therapy. This development will change the standard of care for these individuals in a desperately needed way, and future studies will continue to refine therapy, with the ultimate goal of establishing durable clinical tolerance.

Acknowledgments

References

Bannon GA, Cockrell G, Connaughton C, West CM, Helm R, Stanley JS, King N, Rabjohn P, Sampson HA, Burks AW. Engineering, characterization and in vitro efficacy of the major peanut allergens for use in immunotherapy. Int Arch Allergy Immunol. 2001; 124(1–3):70–72. [PubMed: 11306930]

Bashir ME, Andersen P, Fuss IJ, Shi HN, Nagler-Anderson C. An enteric helminth infection protects against an allergic response to dietary antigen. J Immunol. 2002; 169(6):3284–3292. [PubMed: 12218148]

Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, De Oliveira LC, Shreffler WG, Sampson HA, Niggemann B, Wahn U, Beyer K. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010; 126(1):83–91. e81. [PubMed: 20542324]

Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009; 124(6): 1549–1555. [PubMed: 19917585]

Burks AW, Jones SM, Boyce JA, Sicherer SH, Wood RA, Assa'ad A, Sampson HA. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. Pediatrics. 2011; 128(5):955–965. [PubMed: 21987705]

Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, Stablein D, Henning AK, Vickery BP, Liu AH, Scurlock AM, Shreffler WG, Plaut M, Sampson HA. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012; 367(3):233–243. [PubMed: 22808958]

Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, Sundaram V, Paige NM, Towfigh A, Hulley BJ, Shekelle PG. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010; 303(18):1848–1856. [PubMed: 20460624]

Cooke SK, Sampson HA. Allergenic properties of ovomucoid in man. J Immunol. 1997; 159(4):2026–2032. [PubMed: 9257870]

De Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy. 2006; 61(10):1238–1239. [PubMed: 16942579]

Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010; 125(5):1165–1167. [PubMed: 20451043]

Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, Castello JV, Alonso R, De Mateo JA, Cerda-Trias T, del San Miguel-Moncin MM, Monzon S, Garcia M, Palacios R, Cistero-Bahima A. 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]

Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz De Durana MD, Garcia BE, Gonzalez-Mancebo E, Martin S, Barber D, Rico P, Tabar AI. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009; 64(6):876–883. [PubMed: 19183164]

Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, Kamilaris J, Burks AW. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009; 124(2):286–291. [PubMed: 19477496]

Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, Shreffler WG, Steele P, Henry KA, Adair M, Francis JM, Durham S, Vickery BP, Zhong X, Burks AW. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009; 124(2):292–300. [PubMed: 19577283]

Jouvin MH, Kinet JP. Trichuris suis ova: Testing a helminth-based therapy as an extension of the hygiene hypothesis. J Allergy Clin Immunol. 2012; 130(1):3–10. [PubMed: 22742834]

Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, Steele P, Driggers S, Burks AW, Wood RA. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012; 129(2):448–455. [PubMed: 22130425]

Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, Steele P, Kamilaris J, Vickery B, Burks AW. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011a; 127(3):640–646. [PubMed: 21281959]

Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. J Allergy Clin Immunol. 2011b; 128(1):125–131. [PubMed: 21601913]

Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol. 2008; 122(5):977–983. [PubMed: 18851876]

Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003; 348(11):986–993. [PubMed: 12637608]

Li XM, Srivastava K, Grishin A, Huang CK, Schofield B, Burks W, Sampson HA. Persistent protective effect of heat-killed Escherichia coli producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. J Allergy Clin Immunol. 2003a; 112(1):159–167. [PubMed: 12847493]

Li XM, Srivastava K, Huleatt JW, Bottomly K, Burks AW, Sampson HA. Engineered recombinant peanut protein and heat-killed Listeria monocytogenes coadministration protects against peanut-induced anaphylaxis in a murine model. J Immunol. 2003b; 170(6):3289–3295. [PubMed: 12626588]

Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A. 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]

Ma Y, Gadermaier G, Bohle B, Bolhaar S, Knulst A, Markovic-Housley Z, Breiteneder H, Briza P, Hoffmann-Sommergruber K, Ferreira F. Mutational analysis of amino acid positions crucial for IgE-binding epitopes of the major apple (Malus domestica) allergen, Mal d 1. Int Arch Allergy Immunol. 2006; 139(1):53–62. [PubMed: 16293967]

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]

Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. J Allergy Clin Immunol. 2003; 111(6): 1406–1409. [PubMed: 12789247]

Mondoulet L, Dioszeghy V, Vanoirbeek JA, Nemery B, Dupont C, Benhamou PH. Epicutaneous immunotherapy using a new epicutaneous delivery system in mice sensitized to peanuts. Int Arch Allergy Immunol. 2011; 154(4):299–309. [PubMed: 20962535]

Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, Hanss C, Beaudouin E, Petit N, Kanny G. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol. 2007; 39(1):12–19.

Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011; 127(6):1622–1624. [PubMed: 21546071]

Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, Wood RA. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. J Allergy Clin Immunol. 2009; 124(3):610–612. [PubMed: 19665770]

Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, Sampson HA. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008; 122(2):342–347. [PubMed: 18620743]

Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. J Allergy Clin Immunol. 2011; 127(3):558–573. [PubMed: 21277625]

Otsu K, Dreskin SC. Peanut allergy: an evolving clinical challenge. Discov Med. 2011; 12(65):319–328. [PubMed: 22031669]

Patriarca C, Romano A, Venuti A, Schiavino D, Di Rienzo V, Nucera E, Pellegrino S. Oral specific hyposensitization in the management of patients allergic to food. Allergol Immunopathol (Madr). 1984; 12(4):275–281. [PubMed: 6507224]

Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, Buonomo A, Gasbarrini G, Di Campli C, Schiavino D. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther. 2003; 17(3):459–465. [PubMed: 12562461]

Rabjohn P, Helm EM, Stanley JS, West CM, Sampson HA, Burks AW, Bannon GA. Molecular cloning and epitope analysis of the peanut allergen Ara h 3. J Clin Invest. 1999; 103(4):535–542. [PubMed: 10021462]

Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, Sigurdardottir ST, Lindner T, Goldhahn K, Dahlstrom J, Mcbride D, Madsen C. The prevalence of food allergy: a meta-analysis. J Allergy Clin Immunol. 2007; 120(3):638–646. [PubMed: 17628647]

Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA. A phase II, randomized, doubleblind, parallelgroup, placebocontrolled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011; 127(5):1309–1310. [PubMed: 21397314]

Shreffler WG, Wanich N, Moloney M, Nowak-Wegrzyn A, Sampson HA. Association of allergen-specific regulatory T cells with the onset of clinical tolerance to milk protein. J Allergy Clin Immunol. 2009; 123(1):43–52. [PubMed: 19130927]

Sicherer SH, Sampson HA. Food allergy: recent advances in pathophysiology and treatment. Annu Rev Med. 2009; 60:261–277. [PubMed: 18729729]

Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008; 122(6):1154–1160. [PubMed: 18951617]

Srivastava KD, Bardina L, Sampson HA, Li XM. Efficacy and immunological actions of FAHF-2 in a murine model of multiple food allergies. Ann Allergy Asthma Immunol. 2012; 108(5):351–358. [PubMed: 22541407]

Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, Goldfarb J, Sampson HA, Li XM. 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]

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]

Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterology. 2005; 128(4):825–832. [PubMed: 15825065]

Swoboda I, Bugajska-Schretter A, Linhart B, Verdino P, Keller W, Schulmeister U, Sperr WR, Valent P, Peltre G, Quirce S, Douladiris N, Papadopoulos NG, Valenta R, Spitzauer S. A recombinant hypoallergenic parvalbumin mutant for immunotherapy of IgE-mediated fish allergy. J Immunol. 2007; 178(10):6290–6296. [PubMed: 17475857]

Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, Hiegel A, Kamilaris J, Carlisle S, Yue X, Kulis M, Pons L, Vickery B, Burks AW. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011; 127(3):654–660. [PubMed: 21377034]

Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. J Allergy Clin Immunol. 2011; 127(3):576–584. quiz 585–576. [PubMed: 21277624]

Wang J, Patil SP, Yang N, Ko J, Lee J, Noone S, Sampson HA, Li XM. Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. Ann Allergy Asthma Immunol. 2010; 105(1):75–84. [PubMed: 20642207]

Wanich N, Nowak-Wegrzyn A, Sampson HA, Shreffler WG. Allergen-specific basophil suppression associated with clinical tolerance in patients with milk allergy. J Allergy Clin Immunol. 2009; 123(4):789–794. [PubMed: 19348919]