

Emerging Approaches to Food Desensitization in Children

Ahmad Hamad¹ · Wesley A. Burks²

Published online: 20 April 2017
© Springer Science+Business Media New York 2017

Abstract

Purpose of Review The purpose of this review is to highlight the recent advances in food desensitization in children with food allergy.

Recent Findings Recent advancements in epicutaneous, sublingual, and oral immunotherapy for food allergy in the future may offer children with food allergy and their families a viable option to reduce risk or severity of anaphylaxis with phase III trials ongoing for two of these treatment modalities.

Summary Food allergy prevalence in children is estimated to be up to 8%. These children are at risk of significant allergic reactions and anaphylaxis. Food avoidance and use of antihistamines or epinephrine has been the standard of care for these patients. This approach also has a significant socioeconomic effects on patients and their families. Recent advancements in understanding food allergy have allowed for exploring new methods of treatment. There is an increasing interest in oral immunotherapy, epicutaneous immunotherapy, or sublingual immunotherapy for food allergy. There have been also innovative approaches to immunotherapy by modification of food allergens (to make them less allergenic while maintain their

immunogenicity) or adding adjunctive treatments (probiotics, anti-IgE, etc.) to increase efficacy or safety.

Keywords Food allergy · Desensitization · Pediatric allergy · Immunotherapy

Introduction

The prevalence of food allergy among children in the USA is rightfully a topic of much interest in epidemiology that precedes any discussion of food allergy treatments. A recent study that surveyed over 38,000 children [1] has estimated the prevalence of food allergy in children to be about 8%, which is higher than previously reported [2]. It is not just an issue of increasing number of children with food allergy but also that children are taking a longer time to outgrow their allergies than was previously thought [3]. The natural history of food allergy in children varies between different allergens with high percentage of children outgrowing milk and egg allergy but much fewer percentage outgrowing peanut and tree nut allergy [3]. This finding was the driving force behind efforts to try to find novel treatments for food allergy other than avoidance that have always been, and still are, the standard of care. Some approaches were extrapolated from success that clinicians have had in desensitizing patients with environmental or venom allergy while others are novel in their approach. Although most researchers have been focusing on developing allergen specific immunotherapy, others attempted a nonspecific approach with the aim to downregulate the allergic response in general.

Food desensitization can be defined as temporary unresponsiveness to food allergen or the ability to consume more of the allergen prior to having an allergic reaction. This status of “desensitization” is dependent on continuous taking of the

Grants from National Institutes of Health, grants from Wallace Research Foundation.

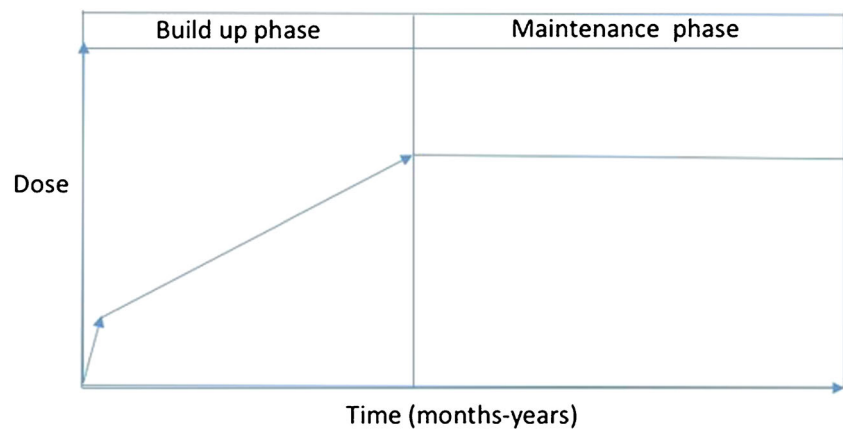
This article is part of the Topical Collection on *Pediatric Allergy and Immunology*

✉ Ahmad Hamad
ahama@med.unc.edu

¹ Division of Allergy and Immunology, Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC 27517, USA

² Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, USA

Fig. 1 Desensitization in immunotherapy



treatment. Once the patient stops the treatment, he or she is more likely to lose this “unresponsive” state over time. That period of time during which the patient is still “desensitized” to a certain amount of an allergen while not taking the treatment is known as “sustained unresponsiveness” and is very different from natural tolerance to a food allergen. The timeline and frequency of exposure between sustained unresponsiveness and tolerance continue to be a matter of debate. In this review, we will focus on methods used to achieve desensitization with or without sustained unresponsiveness.

Allergen Specific Immunotherapy

The aim of allergen specific immunotherapy is to desensitize an allergic patient to a specific allergen by using exposure to the same allergen as a treatment by administering these allergens in increasing amounts until a maintenance dose is reached then the dosing is given periodically. This is usually described in two main phases: dose escalation phase followed by a maintenance phase. During the maintenance phase, the patient continues to take a specific allergen dose periodically (mostly on a daily basis) to maintain a desensitized state. Many studies have assessed sustained unresponsiveness by holding the allergen (avoidance) for a certain period of time before testing for tolerance with a food challenge (Fig. 1). Allergen specific immunotherapy has been done using different pathways: oral (OIT), epicutaneous (EPIT), sublingual (SLIT), and subcutaneous (SCIT).

It is important to recognize the heterogeneity of all the trials that were done for food desensitization. This was described in an excellent article by Yee and Rachid [4•] with regards to OIT. The duration of up-dosing, build up, maintenance, and avoidance phases are variable. Also the dosing for each phase and specifically for the maintenance dose is variable. The primary end point for most studies depended on the dose of the challenge at the end of treatment or after avoidance which was different between different trials. Despite these limitations, there is a promising evidence that the methods used to

induce desensitization to food allergens in OIT, SLIT, or EPIT may be effective at least for protection against accidental exposure. Several trials are needed to be done before finding out the appropriate dosing range that may provide protection against accidental exposures or lower the severity of allergic reactions while having an acceptable safety profile.

Oral Immunotherapy

Despite the aforementioned limitations of studies that were done for food OIT, there is growing evidence that OIT may be effective in desensitizing allergic children to several common food allergens. Also these studies showed that it did improve quality of life for families who have children with food allergy [5].

During OIT, most of the time, the dose must be taken daily but several researchers are assessing whether less frequent dosing may be just as effective [6]. This innovative approach in dosing OIT less frequently than daily may help to increase compliance but further studies are needed to ensure safety and retained efficacy. After achieving maintenance dose of OIT, many patients are asked to continue an equivalent amount of the food allergen in their diet. Follow-up studies on children who underwent OIT in a previous trial showed that these children continued to tolerate a food equivalent in their diet safely [7, 8].

Novel methods in presenting food antigens to the immune system have been proposed in clinical trials to induce desensitization. In a multisite study [9] of AR101, a pharmaceutical formulation of defatted peanut flour was shown to be effective comparing to placebo (79 vs. 19%: passed 443 mg cumulative peanut protein). Current phase III international multicenter trials are being conducted to further evaluate this product and possibly prepare it to be available to physicians treating patients with peanut allergy (clinicaltrials.gov).

Multiple Food OIT

Although food immunotherapy studies have been focusing on treating patients with peanut or milk allergy, other studies have

been done in wheat allergy [10], egg allergy, [11] or other less common allergens. Most food immunotherapy trials have been dealing with one food allergen only. However, we know that about 30% of children with food allergy are allergic to more than one food. Nadeau et al. treated 25 peanut allergic children with other food allergy (tree nuts, sesame, dairy, or egg) with multiple OIT. They showed that OIT using multiple food allergens simultaneously is feasible and relatively safe [12]. Additional larger trials are needed to further assess the safety and efficacy of multi-OIT.

Different adjuvant therapies have been tried in OIT with goals to achieve desensitization faster, desensitize to a higher dose, or lower adverse events during treatment.

Adjuvant Therapy with OIT

Omalizumab

Many allergists have used anti-IgE therapy (omalizumab) to help starting environmental immunotherapy treatment in patients with asthma and allergic rhinitis. Omalizumab inhibits binding of IgE to its high affinity receptor on mast cells and basophils. In food allergy, Nadeau et al. [13] did the first trial on using omalizumab in rapid OIT in 11 patients with cow's milk allergy. Omalizumab was started 9 weeks prior to rapid up-dosing and continued for 16 weeks into OIT treatment. Nine subjects were able to tolerate 2 g of milk protein within 7–11 weeks of OIT. In another study, Hensen et al. [14] enrolled six peanut allergic patients in a trial where omalizumab was given 4 months prior to OIT followed by a modified rush build up while continuing omalizumab for 1 month after reaching maintenance. The patients tolerated a higher start dose after rush desensitization (100–400 mg). In a multiple food allergy desensitization study by Begin et al. [15], 25 patients took omalizumab for 8 weeks before OIT and 8 weeks after initiation of rush OIT achieving fast desensitization (4000 mg per allergen at median of 18 weeks). Schneider et al. pretreated 13 peanut allergic children with omalizumab before rapid oral desensitization to peanut allowing all of them to reach a cumulative dose of 992 mg requiring minimal or no rescue therapy on day 1 [16].

The aforementioned trials were phase I or pilot studies. Then in the first randomized control trial of using omalizumab during dose escalation in OIT (cow's milk) by Wood et al. [17], there was significant decrease in adverse events and in number of doses required to reach maintenance in those who received omalizumab vs. those who received placebo. However, there was no statistically significant difference in efficacy. These trials suggest strongly that there could be a role for omalizumab in achieving rapid desensitization when treating patients with OIT. What is unknown though is whether omalizumab pretreatment will decrease the significant GI allergic side effects of OIT. This may be particularly important for those who could not tolerate the regular up-dosing well.

Phase II trials are ongoing to continue to evaluate use of omalizumab in achieving desensitization in food allergy (<https://clinicaltrials.gov/ct2/show/NCT01781637?term=01781637>).

Probiotics and Bacterial Products

There has been increasing interest in the role of probiotics in preventing food allergy or in induction of desensitization due partially to their ability to induce Th1 response away from the Th2 response that is associated with food allergy. Tang et al. [18] did the first clinical trial for probiotics with peanut OIT vs. placebo showing higher chance of sustained unresponsiveness at 2–5 weeks after avoidance (82.1% receiving probiotics with peanut OIT vs. 3.6% receiving placebo). One limitation was the lack of OIT alone arm in the study, but authors believe that the percentage of subjects who achieved SU at 2 weeks (82%) was higher than reported in other studies. Researchers are interested in looking into using nonpathogenic *E. coli* administration rectally as another method of introducing nonpathogenic bacteria to modify response to allergens but human studies are still lacking. Still others are also looking into using synthetic oligodeoxynucleotides-containing unmethylated CpG (cytosine and guanine nucleotides) due to their ability to induce a Th1 response instead of using whole bacteria [19].

Other Adjunctive Therapies

Investigators are continuing to look at other adjunctive therapies that can be used along with OIT. One retrospective study found that patient who started with leukotriene receptor antagonists (LTRAs) while on OIT, had lower side effects and adverse reactions from OIT [20]. More research is needed before recommending LTRAs during OIT.

Sublingual Immunotherapy

SLIT has been used for several environmental allergens with products available in Europe and most recently in the USA. But this approach is a novel method to approach food allergy with fewer trials done in the USA. Typically, liquid extract is given under the tongue on a regular basis to induce desensitization. In a multicenter RCT using SLIT peanut immunotherapy, Burks et al. [21] showed that peanut SLIT is very safe with 98% of doses tolerated without severe adverse events, and patient achieved most level of desensitization with 10% achieving sustained unresponsiveness. However, many patients discontinued therapy before the end of the study. In another RCT [22] that enrolled 56 patients for 6 months found that patient who were treated for 6 months with SLIT for peach extract were able to tolerate higher amount of peach

(3–9 times) comparing to placebo group. There are currently active studies to evaluate peanut SLIT (clinicaltrials.gov).

OIT vs. SLIT

Retrospective comparison [23] of OIT and SLIT peanut immunotherapy suggested that OIT had a greater change in peanut specific IgE, IgG4, and IgE/IgG4 ratio and basophil activation. In a randomized controlled trial of peanut OIT vs. SLIT, peanut OIT was found to be more effective in desensitizing children to higher doses of peanut protein but it caused more adverse reactions compared to SLIT [24]. In the study, all 16 subjects who completed the study reached the primary outcome of at least tenfold increase in challenge threshold. However, the chance was significantly greater with OIT compared with that seen in SLIT (141-fold vs. 22-fold). These conclusions were similar when both methods of treatment were studied in milk allergy [25].

Epicutaneous Immunotherapy

EPIT is utilized by permeating the allergen into a patch with adhesives on it and then after placing the patch on the skin, because of the humidity created by the application, the allergen diffuses in the epidermis. In the epidermis, the allergen is captured by Langerhans cells that process antigens and presents them to lymphocytes in nearby lymph nodes. The epicutaneous method of delivering immunotherapy is clearly less invasive and thus may lower the risk of systemic reactions seen with other methods of immunotherapy.

In a pilot study for cow's milk in children, EPIT was found to be safe and effective in desensitizing children with CM allergy [26]. Children who were on treatment for 3 months had a tolerance of cumulative dose of 23.61 ml comparing to their baseline at 1.77 ml, while placebo group did not change from that baseline.

Two RCT were completed to study peanut EPIT using the patch delivery system described above. Both concluded that EPIT was safe, effective, and well tolerated with high adherence rate. Sampson et al. [27] randomized 221 6–55-year-old patients to placebo or 50, 100, 250 micrograms peanut protein patches for 52 weeks. All three treatment groups met their primary endpoints with largest effect noted in 250 µg group (cumulative dose +1121 mg). Jones et al. [28] randomized patients to placebo or 100 or 250 µg peanut protein patches for 52 weeks. The study met its primary endpoints with median change in tolerated cumulative dose at 43 mg for 100 µg patch and 130 mg for 250 µg patch.

Phase III trials are ongoing to study EPIT for peanut immunotherapy (clinicaltrials.gov). There are no studies to compare EPIT to SLIT or OIT directly, but the average cumulative tolerated dose after SLIT or OIT is higher than that achieved by EPIT. That is not to say that one method of

immunotherapy is superior to another as it is unknown how much a food allergic patient needs to be desensitized to. It is important to note that in next era of personalized medicine, a personalized approach to immunotherapy that takes patient's preference, goals of therapy, compliance, and potential side effects, or adverse reactions to accidental exposure may be the best approach by clinicians who may find several methods of immunotherapy available in near future in the USA.

Subcutaneous Immunotherapy

SCIT is the oldest known method of immunotherapy in environmental allergens and venom allergy. This method was tested in food allergy as well, and showed subcutaneous delivery of peanut protein to be effective in inducing desensitization in patients with peanut allergy [29] [30]. However, injections resulted in systemic adverse reactions during build up and maintenance phases. Since then, there have been significant efforts in to create food allergens molecules that are hypoallergenic yet retain their immunogenicity. This will potentially decrease the likelihood of systemic reactions while retain effectiveness of the vaccine in subcutaneous administration. Zuidmeer-Jongejan et al. in the Netherlands were successful in developing a hypoallergenic recombinant parvalbumin to be used in SCIT for fish allergy [31]. A similar approach that uses modified peanut protein is ongoing to reevaluate SCIT in inducing desensitization (clinicaltrials.gov) in patients with peanut allergy. HAL-MPE1 is a chemically modified aluminum hydroxide adsorbed peanut extract that is being studied in phase I trials for subcutaneous administration in patients with peanut allergy [http://www.jacionline.org/article/S0091-6749\(16\)32141-8/abstract](http://www.jacionline.org/article/S0091-6749(16)32141-8/abstract). It is premature to draw any conclusions about the safety or the efficacy of this method in food desensitization in children until further studies are done.

Peptide Immunotherapy

Innovative approach in processing food allergens is looking into delivering linear peptides of 10–20 amino acids that contain the allergic epitopes of a protein so they have the potential of inducing desensitization by inducing T cell unresponsiveness while not causing mast cell degranulation because they cannot cross link IgE. This method showed to be successful in preclinical trials on mice [32]. Preclinical and clinical studies in humans are clearly needed before making any conclusions about the promising effects of peptide immunotherapy.

Recombinant Protein Immunotherapy

Recombinant protein immunotherapy is a technique that relies on modifying food allergens to make them less allergenic but retain their immunogenicity. Introducing point mutations to

allergenic epitopes in a protein is one method that showed to be successful in preclinical studies in mice with peanut and fish allergens. Clinical trials using SCIT as method of treating fish allergy are ongoing in Europe <https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000276-10/IS>. This technique was tested for peanut allergy in a phase I trial of rectally administered recombinant Ara h1, 2, and 3 encapsulated in heat killed *E. coli*. Five out of ten patients had adverse reactions severe enough that they did not complete dosing, and two patients had anaphylaxis [33].

Modified Food Proteins in OIT

Although several attempts have been ongoing to intentionally modify food allergens, frequently common physical alterations to food allergens also may have an impact on the allergenicity and immunogenicity of food allergens. For example, egg OIT trials have used a variety of treatments [34] including raw egg [35], pasteurized egg, dehydrated whole egg, dehydrated egg white or cooked egg, scrambled egg or omelet, or egg powder. Although direct comparison between these treatments may be challenging due to different treatment protocols, using boiled eggs seems to be the least effective in inducing desensitization to raw eggs. Further studies are needed to identify the ideal product for egg OIT.

Nonallergen Specific Therapies

Several approaches at treatment have utilized methods that are not allergen specific and could be used regardless of the food or number of foods one is allergic to.

Anti-IgE Therapy

Humanized monoclonal anti-IgE antibodies have been shown to downregulate expression of Fc-epsilon-R1 receptors on mast cells and bind free IgE. In a trial of TNX-901 an anti-IgE IgG1, 84 patients were randomized to 150, 300, 450 mg or placebo. Those on the 450 mg dose showed significant increase in the threshold of sensitivity to peanut on oral food challenge 2–4 weeks after four doses of therapy [36]. Later, a controlled trial that assessed role of omalizumab in children with peanut allergy was aborted due to safety issues because of severe anaphylactic reactions [37] but there was a trend toward higher threshold of sensitivity in patients who reached their primary end points. Clearly, further studies are likely needed to assess the safety of anti-IgE as a monotherapy of treatment of food allergy in children. Anti-IgE therapy probably provides temporary nonspecific desensitization and the effect will wane after stopping treatment. As discussed earlier, investigators have been interested in

using anti-IgE therapy as an adjunctive therapy with food specific immunotherapy.

Chinese Herbal Medicine

Investigators have tested the efficacy of a Chinese herbal medicine FAHF-2 for food allergy but found no significance for the dose and duration of treatment despite favorable in vitro effects [38]. This was tested based on animal studies and clinical observations as the proposed mechanisms of actions were varied.

Personalized Approach to Food Desensitization

There is a great deal of information that needs to be learned about the characteristics of patients who can tolerate certain immunotherapy especially in the coming era of personalized medicine. For example, in a recent study [39] for baked milk OIT in 14 patients with baked milk allergy only three were able to reach and tolerate the maintenance daily. What makes these three patients responsive to therapy while others are not in this trial and many other trials for immunotherapy emphasizes the fact that certain patients may require different protocols or methods of immunotherapy to achieve a desired level of desensitization. In a Cochrane meta analysis that combined 106 patients on cow's milk OIT, 92% of subjects had adverse reactions; most of them are mild [40]. There is a significant number of drop out of studies due to adverse reactions or nonadherence. Developing measures to better predict those who are more likely to experience severe adverse reactions or being aware of the potential life threatening risks of nonadherence is also crucial for any future therapy for food desensitization. There are currently efforts to identify such predictive measures [41]. For example, baseline serum specific IgE levels may help predict the safety of OIT and assess patient's candidacy for such treatments [42]. In another study, lower levels of serum specific and component IgE were associated with successful desensitization in peanut SLIT as well [43].

Conclusion

There has been a tremendous improvement in our understanding of food allergy and our approach to management of food allergy in children in the past decade. Several investigators have evaluated different types of specific and nonspecific immunotherapy for treatment. Combining specific immunotherapy with nonspecific therapies such as anti-IgE antibodies have shown an improved safety of desensitization, a very important factor in all trials. Although these advancements have not necessarily been translated into clinical practice

yet, it is likely that we will see some of these advancements in desensitization to food allergens transferred into clinical practice within the next decade. There are currently phase III clinical trials to evaluate OIT and EPIT products with at least two international companies applying for FDA approval in the USA (clinicaltrials.gov).

Clinicians who choose to start their patients on any form of food oral immunotherapy (EPIT is not available for clinicians outside of clinical studies before FDA approval) should keep in mind that there is not an FDA approved product yet, there is variability in the protocols used for OIT among investigators, and there is a potential risk of anaphylaxis and significant gastrointestinal side effects. Clinicians must have a detailed conversation with families clarifying both the risks and benefits of such treatments, both short and long term with the general understanding that once the treatment is discontinued the benefits begin to wane.

A personalized approach is likely to be the future of food allergy treatments where different methods of immunotherapy may be best for different patients depending on their age, reaction history, severity of their reactions, compliance, tolerability, or other factors. Despite all current advancements, there is a significant amount of work to be done in the next few decades to understand if ongoing treatment is the best option or a cure can be identified that will induce true immunologic tolerance.

Compliance with Ethical Standards

Conflict of Interest Dr. Burks reports grants from Food Allergy & Anaphylaxis Network, grants from National Institutes of Health, grants from Wallace Research Foundation, during the conduct of the study. Dr. Hamad declares no conflicts of interest relevant to this manuscript.

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

References

Papers of particular interest, published recently, have been highlighted as:

•Of Importance

1. The Prevalence, Severity, and Distribution of Childhood Food Allergy in the United States. *PEDIATRICS*. 2011;128(1): peds.2011-0204d-peds.2011-0204d.
2. Liu A, Jaramillo R, Sicherer S, Wood R, Bock S, Burks A, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. 2010;126(4):798–806. **e14**
3. Kattan J. The prevalence and natural history of food allergy. *Current Allergy and Asthma Reports*. 2016;16(7):47.
4. Yee CRachid R. The heterogeneity of oral immunotherapy clinical trials: implications and future directions. *Current Allergy and Asthma Reports*. 2016;16:25. **The article is an excellent review of oral immunotherapy clinical trials in food allergy. There is an emphasis on the heterogeneity of these trials and what conclusions can be made based on them.**
5. Arasi S, Otani I, Klingbeil E, Bégin P, Kearney C, Dominguez T, et al. Two year effects of food allergen immunotherapy on quality of life in caregivers of children with food allergies. *Allergy, Asthma Clin Immunol*. 2014;10:57.
6. Pajno G, Caminiti L, Salzano G, Crisafulli G, Aversa T, Messina M, et al. Comparison between two maintenance feeding regimens after successful cow's milk oral desensitization. *Pediatr Allergy Immunol*. 2013;24:376–81.
7. Jones S, Burks A, Keet C, Vickery B, Scurlock A, Wood R, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol*. 2016;137:1117–27. **e10**
8. Paassilta M, Salmivesi S, Mäki T, Helminen M, Korppi M. Children who were treated with oral immunotherapy for cows' milk allergy showed long-term desensitisation seven years later. *Acta Paediatr*. 2015;105:215–9.
9. [Internet]. 2017 [cited 21 February 2017]. Available from: <http://www.aimmune.com/wp-content/uploads/2015/05/EAACI-ARC-presentation-6-7-15.pdf>
10. Rodríguez del Río P, Díaz-Perales A, Sanchez-García S, Escudero C, Patricia do Santos, Catarino M et al. Oral immunotherapy in children with IgE-mediated wheat allergy: outcome and molecular changes. *J Investig Allergol Clin Immunol*. [Internet]. 2014 [cited 21 February 2017];. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25219106>
11. Jones S, Fleischer D, Sicherer S, Wood R, Lindblad R, Stablein D, et al. Egg oral immunotherapy (OIT) induces clinical desensitization in a double-blind, placebo-controlled (DBPC) trial in egg allergic children from the consortium of food allergy research (CoFAR). *J Allergy Clin Immunol*. 2010;125:AB357.
12. Bégin P, Winterroth L, Dominguez T, Wilson S, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy, Asthma Clin Immunol*. 2014;10:1.
13. Nadeau K, Schneider L, Hoyte L, Borrás I, Umetsu D. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol*. 2011;127:1622–4.
14. Henson M, Edie A, Steele P, Kamilaris J, Kulis M, Thyagarajan A, et al. Peanut oral immunotherapy and omalizumab treatment for peanut allergy. *J Allergy Clin Immunol*. 2012;129:AB28.
15. Bégin P, Dominguez T, Wilson S, Bacal L, Mehrotra A, Kausch B, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. *Allergy, Asthma Clin Immunol*. 2014;10:7.
16. Schneider L, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu D. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol*. 2013;132:1368–74.
17. Wood R, Kim J, Lindblad R, Nadeau K, Henning A, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol*. 2016;137:1103–10. **e11. First randomized double blind placebo-controlled trial assessing role of omalizumab combined with immunotherapy.**
18. Tang M, Ponsonby A, Orsini F, Tey D, Robinson M, Su E, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol*. 2015;135:737–44. **e8. First randomized trial assessing role of probiotics**

- administration combined with peanut OIT. However, there was no OIT only group.**
19. Srivastava K, Li XM, Bannon GA, et al. Investigation of the use of ISS-linked Ara h2 for the treatment of peanut-induced allergy. *J Allergy Clin Immunol*. 2011;107:S233. **(Abstract)**
 20. Takahashi M, Taniuchi S, Soejima K, Sudo K, Hatano Y, Kaneko K. New efficacy of LTRAs (montelukast sodium): it possibly prevents food-induced abdominal symptoms during oral immunotherapy. *Allergy, Asthma Clin Immunol*. 2014;10:3.
 21. Burks A, Wood R, Jones S, Sicherer S, Fleischer D, Scurlock A, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. *J Allergy Clin Immunol*. 2015;135:1240–8. **e3**
 22. Fernández-Rivas M, Garrido Fernández S, Nadal J, Alonso Díaz de Durana M, García B, González-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy*. 2009;64:876–83.
 23. Chin S, Vickery B, Kulis M, Kim E, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. *J Allergy Clin Immunol*. 2013;132:476–8. **e2**
 24. Narisety S, Frischmeyer-Guerrero P, Keet C, Gorelik M, Schroeder J, Hamilton R, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol*. 2015;135:1275–82. **e6**
 25. Keet C, Frischmeyer-Guerrero P, Thyagarajan A, Schroeder J, Hamilton R, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol*. 2012;129:448–55. **e5**
 26. Dupont C, Kalach N, Soulaines P, Legoué-Morillon S, Piloquet H, Benhamou P. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol*. 2010;125:1165–7.
 27. Sampson H, Agbotounou W, Thébault C, Charles R, Martin L, Yang W, et al. Epicutaneous immunotherapy (EPIT) is effective and safe to treat peanut allergy: a multi-National Double-Blind Placebo-Controlled Randomized Phase IIb trial. *J Allergy Clin Immunol*. 2015;135:AB390.
 28. Jones S, Agbotounou W, Fleischer D, Burks A, Pesek R, Harris M, et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: a phase I study using the Viaskin patch. *J Allergy Clin Immunol*. 2016;137:1258–61. **e10**
 29. Oppenheimer J, Nelson H, Bock S, Christensen F, Leung D. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol*. 1992;90:256–62.
 30. Nelson H, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract I. *J Allergy Clin Immunol*. 1997;99:744–51.
 31. Zuidmeer-Jongejan L, Huber H, Swoboda I, Rigby N, Versteeg S, Jensen B, et al. Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. *Int Arch Allergy Immunol*. 2015;166:41–51.
 32. Rupa PMine Y. Oral immunotherapy with immunodominant T-cell epitope peptides alleviates allergic reactions in a Balb/c mouse model of egg allergy. *Allergy*. 2011;67:74–82.
 33. Wood R, Sicherer S, Burks A, Grishin A, Henning A, Lindblad R, et al. A phase I study of heat/phenol-killed, *E. coli* -encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy*. 2013;68:803–8.
 34. Ibanez M, Escudero C, Sánchez-García S, Rodríguez del Río P. Comprehensive review of current knowledge on egg oral immunotherapy. *J Investig Allergol Clin Immunol*. 2017;25(5):316–28. **Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26727760>**
 35. Meglio P, Giampietro P, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. *Pediatr Allergy Immunol*. 2012;24:75–83.
 36. Leung D, Sampson H, Yunginger J, Burks W, Schneider L, Shanahan W. Effect of anti-IgE therapy (TNX-901) in patients with severe peanut allergy. *J Allergy Clin Immunol*. 2003;111:S274.
 37. Sampson H, Leung D, Burks A, Lack G, Bahna S, Jones S, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol*. 2011;127:1309–10. **e1**
 38. Wang J, Jones S, Pongracic J, Song Y, Yang N, Sicherer S, et al. Safety, clinical, and immunologic efficacy of a Chinese herbal medicine (food allergy herbal formula-2) for food allergy. *J Allergy Clin Immunol*. 2015;136:962–70. **e1**
 39. Goldberg M, Nachshon L, Appel M, Elizur A, Levy M, Eisenberg E, et al. Efficacy of baked milk oral immunotherapy in baked milk-reactive allergic patients. *J Allergy Clin Immunol*. 2015;136:1601–6.
 40. Yeung J, Kloda L, McDevitt J, Ben-Shoshan M, Alizadehfard R. Oral immunotherapy for milk allergy: a systematic review. *Allergy, Asthma Clin Immunol*. 2012;8:A14.
 41. Levy M, Elizur A, Goldberg M, Nachshon L, Katz Y. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. *Annals of Allergy, Asthma & Immunology*. 2014;112:58–63. **e1**
 42. Vazquez-Ortiz M, Alvaro M, Piquer M, Dominguez O, Machinena A, Martín-Mateos M, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. *Clinical & Experimental Allergy*. 2013;44:130–41.
 43. García-Ara C, Pedrosa M, Belver M, Martín-Muñoz M, Quirce S, Boyano-Martínez T. Efficacy and safety of oral desensitization in children with cow's milk allergy according to their serum specific IgE level. *Annals of Allergy, Asthma & Immunology*. 2013;110:290–29.