Oral Immunotherapy for Food Allergy

Robert A. Wood, MD
Director, Pediatric Allergy and Immunology
Department of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, MD USA
rwood@jhmi.edu

Conflicts of interest:

Research support from:

- National Institutes of Health
- Astellas
- Aimmune
- DBV
- HAL-Allergy

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0143

Abstract:

Food allergy is a potentially life-threatening condition with no approved therapies apart from avoidance and injectable epinephrine for treatment of acute allergic reactions. Oral immunotherapy (OIT) is an experimental treatment in which patients consume gradually increasing quantities of the food to which they are allergic in attempt to induce some level of desensitization. While desensitization is possible in most patients, OIT carries significant risks for allergic reactions and the ability to induce longer term tolerance has not yet been established. This review focuses on select studies of OIT for the treatment of common food allergies such as cow's milk, hen's egg, and peanut.

Key Words: food allergy, oral immunotherapy, cow's milk, hen's egg, peanut, desensitization, tolerance, sustained unresponsiveness, skin prick test (SPT), immunoglobulin E (IgE), omalizumab

Resumen:

La alergia alimentaria es una condición potencialmente mortal para la que no existen tratamientos aprobados, excepto la evitación y la epinefrina para tratar reacciones alérgicas graves. La inmunoterapia oral (OIT) es un tratamiento experimental en el cual los pacientes ingieren cantidades gradualmente crecientes del alimento al que son alérgicos, con el fin de inducir algún nivel de desensibilización. Si bien la desensibilización es posible en la mayoría de los pacientes, OIT conlleva riesgos importantes de reacciones alérgicas y la capacidad de inducir tolerancia a más largo plazo todavía no ha sido establecida. Este artículo de revisión se centra en una selección de estudios de OIT para el tratamiento de alergias a alimentos comunes, como son la leche de vaca, huevos de gallina y cacahuete.

Palabras clave: Alergia alimentaria. Inmunoterapia oral. Leche de vaca. Huevo de gallina. Cacahuete. Desensibilización. Tolerancia. Falta de respuesta sostenida. Prick test. Inmunoglobulina. Omalizumab

doi: 10.18176/jiaci.0143

Introduction:

Food allergy is now estimated to affect up to 8% of children and up to 2-3% of adults in the U.S. [1,2]. Cow's milk, hen's egg, peanut, tree nut, wheat, soy, fish, and shellfish are the foods most often associated with food allergy in the U.S. [2]. Food allergy is potentially life threatening and has a major impact of quality of life [3,4]. Avoidance is currently the only approved therapy for food allergy and while effective, avoidance diets can be difficult and may also put children at risk of nutritional deficiencies and impaired growth [5,6]. While at least 80% of milk- and egg-allergic children are expected to achieve natural tolerance to these foods by adulthood, only 15-20% of peanut or tree nut allergic individuals "outgrow" their allergies [7]. Peanut allergy is common in Westernized countries, affecting 1-2% of children in the U.S. [4,8], and peanut is implicated in over half of all fatal food allergy-related deaths in the U.S. [9,10]. Effective therapies for peanut and other common food allergies are therefore highly desirable.

What is Oral Immunotherapy (OIT)?

OIT involves mixing an allergenic food into a vehicle and consuming it in gradually increasing doses. [11] OIT protocols vary in the type of food and vehicle used, with some using commercially available foods in their natural forms (e.g. liquid milk or peanut flour) while others use specifically prepared products such as dehydrated egg white. Currently, although OIT essentially uses food materials, research studies in the U.S. require Investigational New Drug (IND) approval and these FDA regulated forms of therapy require additional standards and safeguards. For example, allergenic proteins must be identified and quantified and the product must be shown to be free of microbial contaminants.

Most OIT protocols include an initial escalation phase, followed by dose build-up phase and maintenance phases with considerable variability depending on the study (see Figure 1) [11]. The initial escalation phase is typically conducted over one to two days, using rapid up-dosing starting from a very small dose - that is extremely unlikely to cause any adverse reaction - and progressing to a dose that is still likely safe for home administration. Generally, the initial doses are in microgram quantities of allergenic protein which progress to several milligrams by the end of this phase. If well tolerated, the dose is escalated incrementally (usually biweekly or weekly) until a target maintenance dose is reached or the subject reaches dose-limiting symptoms. There is considerable variation between studies regarding the target maintenance dose, ranging from 300 to 4000 mg. Maintenance therapy continues with daily administration in the home, and the length of maintenance therapy varies considerably, lasting from a few

doi: 10.18176/jiaci.0143

months to several years [12]. Tables 1-3 illustrate some of the variability in study design in terms of maintenance dosing, length of therapy, and outcomes.

Efficacy of OIT

The potential efficacy of food OIT depends on the defined endpoints, including the ability to tolerate the treatment, the induction of a transient state of desensitization alone, and/or the development of a more durable state of clinical tolerance, which is often referred to as "sustained unresponsiveness" (SU) [13,14]. Desensitization is defined as a temporary increase in the threshold for reactivity, with maintenance of the desensitized state requiring continued consumption of the allergenic protein to prevent the reappearance of reactivity. In some trials, subjects who are successfully desensitized are then required per protocol to restrict the allergenic food from their diet for a period of weeks to months, after which another oral food challenge is conducted to determine whether or not they have achieved SU. While all studies have demonstrated that the majority of patients treated with OIT can be successfully desensitized to a particular food, SU is less commonly achieved. This lack of sustained protection against allergic symptoms has important implications for the future of oral immunotherapy and reinforces the experimental nature of this treatment.

Summary of Clinical Trials:

Peanut OIT

The use of subcutaneous peanut immunotherapy was first reported in 1992, but this approach was abandoned due to an unacceptable systemic reaction rate [15]. Following 2 case reports of successful peanut OIT in 2006 [16,17], the first open label trial of peanut OIT was published in 2009 in a prospective cohort study [18,19]. This study showed successful desensitization and an overall reassuring safety profile, as well as immunologic changes consistent with those seen in other forms of immunotherapy. Using a maintenance dose of 1800 mg of peanut protein, at 36 months 93% of the 29 patients who completed the protocol were able to tolerate an oral challenge with a cumulative dose of 3.9 grams of peanut protein [18]. In 2010, Blumchen et al reported a study of 23 children maintained on 500 mg peanut protein daily over a 9 week period, with a 60% success rate for passing an oral food challenge at the completion of treatment [20].

In 2011 Varshney et al reported the first multicenter, randomized, double-blind, placebo-controlled study of peanut OIT [21]. The study included 28 subjects, ages 1 through 16, who underwent treatment with peanut or placebo to a daily maintenance dose of 4 grams for about one year. Three patients withdrew early due to adverse reactions but in a post-treatment

doi: 10.18176/jiaci.0143

double-blind, placebo-controlled food challenge (DBPCFC), the 16 subjects who completed active OIT were able to ingest a maximum cumulative dose of 5 grams of peanut protein (~16 peanuts) compared to the placebo group of 9 subjects who tolerated a median of 280 mg of peanut. The study also showed a significant decrease in skin test responses as well as changes in serum IL-5 and IL-13 levels and CD4+CD25+FoxP3+ T-regulatory cells in the active group compared to the placebo.

In 2011, Anagnostou et al. published a prospective cohort study of peanut OIT, in which 22 children received daily maintenance dosing of 800 mg of peanut protein for 32 weeks [22]. They demonstrated a significant increase in peanut challenge threshold, with 86% of subjects tolerating up-dosing and 14/22 (64%) tolerating 6.6g of peanut protein at the completion of treatment. In 2014, the same group completed a peanut OIT RCT using a maintenance dosing of 800mg [23]. In the first phase, each arm underwent 26 weeks of peanut OIT versus peanut avoidance, after which subjects underwent a food challenge to 1400 mg of peanut protein. In the active OIT group 24 of 39 participants (62%) had no reaction compared to no participants in the control group. The second phase allowed participants in the control group to receive active peanut OIT, with 84% of the active group at the end of the first phase and 91% of the control group at the end of the second phase able to tolerate daily ingestion of 800 mg protein for 26 weeks.

The first study of SU following peanut OIT was published in 2014 [14]. Twenty-four subjects ages 1 to 16 completed OIT with maintenance dosing of 4000 mg of peanut protein for up to 5 years. One month after stopping OIT, 50% of the subjects demonstrated SU to a 5000 mg oral challenge. Those subjects demonstrating SU were also found to have greater evidence of immunomodulation with smaller skin test results, lower peanut IgE levels, including Ara h 1 and Ara h 2, and lower ratios of peanut-specific IgE/total IgE. In another study that was designed primarily to compare peanut SLIT to OIT, while OIT was far superior to SLIT, only 4 of 20 subjects on OIT were shown to have SU [24].

A more recent study of peanut OIT focused on a younger population of patients between the ages of 9 and 36 months [25]. In this open label RCT, subjects were randomized to goal maintenance doses of 300 or 3000 mg/d. Overall, in the intent-to-treat analysis, 29 of 37 (78%) subjects achieved SU 4 weeks after completing treatment, with similar rates in the 300 mg (85%) and the 3000 mg groups (71%) after a median treatment period of 29 months. Per-protocol, the overall proportion achieving SU was 29 of 32 (91%). It was also reassuring that the therapy appeared well tolerated even in these younger children.

doi: 10.18176/jiaci.0143

Egg OIT

Two early studies from Patriarca et al reported on small numbers of patients treated with egg OIT, demonstrating successful desensitization in a majority of patients [26,27]. In another early trial, Buchanan et al reported on 7 children aged 14 months to 7 years treated with 24 months of egg OIT with a maintenance dose of 300 mg of daily, with 57% passing an oral food challenge at treatment completion [28]. In a follow up study at the same center, patients treated with a higher, individualized dose (median 2400mg) for a median of 33 months reported a SU rate of 75% (6 of 8 subjects) one month after stopping treatment [29].

In one of the first randomized OIT trials, Staden et al reported on 45 children who were treated with either egg or milk OIT, with maintenance dosing of 1.6 g/day or 3.5 g/day, respectively, or an avoidance diet as a control [30]. Eleven of the patients were egg allergic. Although the milk and egg results were not reported separately, after a median of 21 months of therapy, 16/25 (64%) were able to introduce the allergenic food into their diet, 9 with complete tolerance and 7 with partial tolerance, compared to 7 of 20 (35%) children in the control group. Morisset et al also published a randomized study of 60 children with milk allergy and 90 children with egg allergy [31]. Patients were randomized to OIT or allergen avoidance, and after 6 months of treatment 69% of those receiving egg OIT were successfully desensitized.

In 2012 Burks et al published results of the first multicenter, double-blind, randomized, placebo-controlled trial of egg OIT. Fifty-five subjects 5–11 years of age were treated with a maintenance dose of 2 grams of egg protein, with egg DBPCFCs performed at 10 and 22 months [13]. For those without reaction at the 22 month challenge, OIT was discontinued for 6-8 weeks with a repeat food challenge to test for SU. At the 10 month DBPCFC, none of the placebo patients (n=15) were desensitized compared to 55% of those treated with active OIT. After 22 months of OIT, 30 of 40 subjects (75%) were effectively desensitized, but only 11 (28%) demonstrated SU on re-challenge 6 to 8 weeks later.

Other studies of egg OIT have included small RCTs by Dello Iacono et al and Meglio et al with desensitization rates of 80 – 90%, including children with severe egg allergy, and two studies using rush protocols with desensitization induced in as little 5 days [32-35].

Milk OIT

As with egg, Patriarca et al reported the first studies of milk OIT, with desensitization rates of 65.5% and 100% in two small trials [26,27]. Meglio et al reported a pilot study in 2004 of 21 children treated with 6 months of OIT that resulted in a 72% success rate of tolerating a target dose of 200 mL of cow's milk (CM) daily, with an additional 14% of subjects achieving partial desensitization [36]. Of note, at a 4 year follow up, 70% had at least partial milk

doi: 10.18176/jiaci.0143

tolerance, with significant reductions in serum-specific CM IgE and skin prick test results [37]. A number of other non-randomized milk OIT studies also demonstrated overall success in achieving desensitization [38-40].

As noted above for egg OIT, the first RCT trial of milk OIT was reported by Staden et al [30]. In 2008, Longo et al reported an RCT of 60 children with a history of severe CM allergy and high CM-specific IgE levels, randomized to milk OIT or avoidance [41]. While all those in the control group failed the DBPCFC at the 1 year mark, 36% of treated subjects passed the OFC and an additional 54% were partially tolerant. 2008 also marked the first placebo-controlled OIT trial in a study of milk OIT by Skripak et al [42], demonstrating a rise in the median milk challenge threshold from 40 mg at baseline to 5140 mg after just 3-4 months of treatment, with no change in the placebo group. A follow up open-label study using individualized, ongoing milk intake demonstrated the ability to tolerate from 1000 to 16,000mg (median 7000 with 33% tolerating 16,000mg) of CM protein over 3 to 17 months of follow-up [43].

Other studies of milk OIT included those of Pajno et al in 2010 [44], as well as a study from the same group in 2013 suggesting that maintenance dosing after desensitization can be done with equal success daily or twice weekly [45]. Martorell et al completed a RCT in 2011 of 60 children ages 24 to 36 months demonstrating desensitization in 90% at 1 year [46] and in 2012 Salmivesi et al published an RCT in school aged children showing similar effectiveness of milk OIT [47].

In 2012 Keet et al also published an open-label RCT comparing milk OIT to sublingual immunotherapy (SLIT) [48]. All subjects were initially treated with SLIT, after which they were randomized to continue SLIT or convert to OIT. The study demonstrated greater efficacy with OIT as well as a higher incidence of significant adverse effects. The study also examined SU after stopping therapy for one and 6 weeks, showing that only 40% of subjects passed an OFC when treatment was discontinued for 6 weeks, and two lost protection in the first week off therapy. An additional follow up report of 32 patients from the Skripak and Keet milk OIT studies showed only 31% of subjects appeared to be fully milk tolerant 3 to 5 years after completing treatment, with many patients appearing to lose tolerance after successfully completing treatment, even some with demonstrated SU [49].

It has been clearly shown over the past decade that many patients with milk allergy are able to tolerate milk that has been extensively heated, and that this exposure helps to promote eventual tolerance to unheated milk. [50] A recent study by Goldberg et al sought to use this concept in a study in which patients who had been unable to tolerate milk OIT were treated with OIT using baked milk [51]. Unfortunately, in this highly select group of patients with severe milk

doi: 10.18176/jiaci.0143

allergy, only 3 of 14 achieved the primary outcome of tolerating 1.3 grams of baked milk. Of the 11 treatment failures, 8 failed because of IgE-mediated reactions and 3 did not complete the program because of non-IgE-mediated factors.

OIT to Other Foods and Multi-Allergen OIT

While most research to date has focused on milk, egg, and peanut, there is great interest in the potential to treat other common food allergies. Studies are currently ongoing using OIT to treat wheat, tree nut, fish, and possibly other food allergies. A recent study by Sato et al investigated the efficacy of OIT in patients with wheat-induced anaphylaxis. [52] The treatment was open label with a historical control group of untreated patients, using a dose was 200 grams of Japanese wheat noodles that contained 5.2 grams of wheat protein. Sixteen of the 18 subjects achieved the target dose, 11 of whom (61.1%) passed a SU OFC 2 weeks later. The authors concluded that even in patients with very severe wheat allergy, OIT using boiled noodles was safe and effective. [53]

There is also interest in the potential to treat multiple foods simultaneously, especially given the fact that so many children are allergic to more than one food. Numerous multi-allergen food OIT studies are currently underway, some with and some without co-administration of omalizumab. To date, preliminary data from one study demonstrated similar reaction rates and efficacy comparing mono-therapy with peanut to OIT using up to five foods, [54] while a second Phase 1 study demonstrated successful desensitization to multiple foods using rush OIT after pre-treatment with omalizumab. Reaction rates were relative low with a median of 3.2 reactions per 100 doses.[55]

Immunologic changes with OIT

The mechanisms by which OIT induces desensitization, and possibly longer term effects, remain under active investigation. Studies have consistently demonstrated certain specific immunologic changes, including increases in food-specific IgG4 and decreased basophil and mast cell responsiveness [13,14,18,56]. Some studies have shown alterations in the binding pattern of antigen to antigen-specific IgE, either by reduction in the diversity of epitope recognition or altered IgE affinity [57]. After 6-12 months of OIT, there appears to be a shift away from Th2 cytokine production towards a pro-inflammatory profile characterized by increased production of IL-1β and TNFα [18]. Syed et al demonstrated increased function of antigen-specific CD4+CD25+FoxP3+ T regulatory cells following OIT supporting the theory of active suppression of immune responses [56,58].

doi: 10.18176/jiaci.0143

Gorelik et al studied the mechanisms and duration of suppression of immune responses during peanut immunotherapy in the study by Narisety noted above.[59,60] They found that spontaneous and allergen-induced basophil reactivity, including IL-4 production, were suppressed during dose escalation and after 6 months of maintenance dosing. Many markers of immunologic suppression reversed after withdrawal from immunotherapy and, more surprisingly, in some cases during ongoing maintenance therapy. The authors concluded that while both peanut OIT and SLIT induce rapid suppression of basophil effector functions, dendritic cell activation, and T_H2 cytokine responses during the initial phases of immunotherapy, in many patients suppression appeared to be transient.

Begin et al addressed changes in allergen-specific T-cell phenotypes during immunotherapy. [61] While prior studies have shown an overall skewing of the pathological TH2 response toward a normal TH1 or regulatory T-cell response, questions have been raised about the specificity of this approach and whether these changes result from a reprogramming of existing allergen-specific clones (re-education hypothesis) or from their replacement by different clones to determine the dominant response (replacement hypothesis). They undertook next-generation sequencing of peanut-proliferative TCR β in subjects undergoing peanut OIT, and found an extremely diversified polyclonal response with a very small fraction of consistent clones over time.

Safety of OIT

Adverse reactions are very common with OIT, with overall rates similar for each of the foods studied to date. Reactions are generally mild and local symptoms such as oral itching are most common. Abdominal pain is the most common symptom leading to withdrawal from treatment, and moderate reactions, such as wheezing, vomiting, and urticaria occur in a small percent of all doses. However, given that doses are given daily over an extended period of treatment, the risk for each patient is substantial. For example, in a study of milk OIT in young children, 47% of subjects developed moderate reactions over the course of treatment [46]. More severe reactions requiring treatment with epinephrine and beta-agonists are most common during dose escalation but can also occur during maintenance therapy [24,41,42,44,46]. Wasserman *et al* reported that 95 reactions requiring epinephrine occurred during peanut OIT for 352 patients [62]. It is especially concerning that most severe reactions occur unpredictably, with a dose that has been previously tolerated, often associated with co-factors such as infection, exercise, anxiety, or allergen co-exposure [19,23,42,43].

A major impediment to moving these treatments to clinical practice is the high percent of patients who cannot tolerate OIT. Overall, 10-20% of subjects have dropped out of OIT trials,

with rates as high as 36%. While some participants have withdrawn due to anaphylaxis or other acute reactions, the vast majority of withdrawals are due to chronic abdominal pain. Eosinophilic esophagitis has been documented in some of these cases and it is not clear how frequently undiagnosed disease may complicate OIT [63,64]. Further studies directed at minimizing adverse reactions are therefore critically important to move these treatments forward toward clinical use.

Adjunctive Therapies

Several potential adjunctive therapies to OIT have been studied, with the goal of improving both safety and/or efficacy. Two initial pilot studies have examined the use omalizumab in combination with OIT, one with milk and the other with peanut [65,66], with both studies suggesting that OIT can be escalated more rapidly when combined with omalizumab, although adverse reactions were still relatively common.

Two more recent randomized trials also studied the adjunctive effects of omalizumab. In the first, Wood et al studied the addition of omalizumab or placebo to open label milk OIT [67]. At the completion of treatment, 88.9% of the omalizumab-treated subjects and 71.4% of the placebo-treated subjects passed the 10-g "desensitization" OFC (P =.18). Two months later, SU was demonstrated in 48.1% in the omalizumab group and 35.7% in the placebo group (P =.42). Adverse reactions were significantly reduced during OIT escalation in omalizumab-treated subjects with regard to the percent of doses symptoms (2.1% vs 16.1%, P =.0005), dose-related reactions requiring treatment (0.0% vs 3.8%, P =.0008), and doses required to achieve maintenance (198 vs 225, P =.008). The authors concluded that omalizumab led to improvements in measurements of safety but not efficacy.

In the second study, open label omalizumab was used in a placebo-controlled study of peanut OIT [68]. After 12 weeks of treatment with omalizumab, subjects underwent a rapid 1-day desensitization of up to 250 mg of peanut protein, followed by weekly increases up to 2000 mg. The median peanut dose tolerated on the initial desensitization day was 250 mg for omalizumab-treated subjects versus 22.5 mg for placebo-treated subjects. Subsequently, 79% of subjects receiving omalizumab tolerated 2000 mg of peanut protein 6 weeks after stopping omalizumab versus 12% of those receiving placebo (P < .01). Overall reaction rates were not significantly lower in omalizumab-treated versus placebo-treated subjects (odds ratio, 0.57; P = .15), although omalizumab-treated subjects were exposed to much higher peanut doses. The authors concluded that omalizumab allows subjects with peanut allergy to be rapidly desensitized and that in a majority of subjects, this desensitization is sustained after omalizumab is discontinued.

doi: 10.18176/jiaci.0143

It has also been suggested that probiotics may have adjuvant effects for inhalant allergen immunotherapy. [69] Tang et al expanded this concept to food immunotherapy with a trial adding the probiotic Lactobacillus rhamnosus to peanut OIT or placebo. [70] The primary outcome was induction of possible SU 2 to 5 weeks after discontinuing OIT, which was achieved in 82.1% receiving OIT and 3.6% receiving placebo. While these results are limited by the fact that the probiotic treatment was not placebo-controlled, and that the period off treatment was as short as 2 weeks, this is a higher proportion of subjects achieving SU than has been seen in other studies, raising the possibility that probiotics may truly enhance this effect.

Case reports and small open trials have been conducted with a number of other adjunctive therapies, including interferon gamma, ketotifen, and leukotriene receptor antagonists (LRTAs) [71-75]. In 2013, a randomized single-blind placebo-controlled study of 6 subjects undergoing peanut OIT showed that ketotifen premedication at 2 mg twice daily might reduce the incidence of gastrointestinal symptoms during active OIT [73]. Further, Takahashi et al. studied the use of montelukast with OIT in a retrospective study of 5 children, where LTRA intervention appeared to help patients reach their target dose [74]. Each of these possible adjunctive therapies requires further study.

VI. Future considerations/Summary

Food allergy is common and potentially life-threatening. Despite the significant impact of food allergy on patients and health care systems, there are currently no approved therapies for food allergy apart from strict avoidance. Milk, egg, and peanut OIT studies have consistently shown successful desensitization, although longer lasting tolerance does not appear likely at this stage of investigation. Further mechanistic studies are needed to improve understanding of the immunologic changes induced by OIT, and to identify biomarkers of response. Safety is a significant concern as adverse events are common during OIT, limiting its use in some patients. Incorporation of novel therapies such as modified food allergens, probiotics, and other immunomodulator therapies in conjunction with OIT are underway with the goals of improving both safety and efficacy. Larger, well designed randomized, placebo-controlled trials are needed to determine the efficacy and acute and long-term safety of OIT before it can be implemented in general clinical practice.

doi: 10.18176/jiaci.0143

References:

1. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e9-17. doi: 10.1542/peds.2011-0204. PubMed PMID: 21690110.

2. 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):1848-56. doi: 10.1001/jama.2010.582. PubMed PMID: 20460624.

3. Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol. 2011;11(3):236-42. doi: 10.1097/ACI.0b013e3283464cf0. PubMed PMID: 21464708.

4. Sicherer SH, Sampson HA. Food allergy. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S116-25. doi: 10.1016/j.jaci.2009.08.028. PubMed PMID: 20042231.

5. Kim J, Kwon J, Noh G, Lee SS. The effects of elimination diet on nutritional status in subjects with atopic dermatitis. Nutr Res Pract. 2013;7(6):488-94. doi: 10.4162/nrp.2013.7.6.488. PubMed PMID: 24353835; PMCID: 3865272.

6. Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food allergies affect growth in children. J Allergy Clin Immunol Pract. 2015;3(1):133-4 e1. doi: 10.1016/j.jaip.2014.11.004. PubMed PMID: 25577638; PMCID: 4291552.

7. Nowak-Wegrzyn A, Sampson HA. Future therapies for food allergies. J Allergy Clin Immunol. 2011;127(3):558-73; quiz 74-5. doi: 10.1016/j.jaci.2010.12.1098. PubMed PMID: 21277625; PMCID: 3066474.

8. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. Cochrane Database Syst Rev. 2012;9:CD009014. doi: 10.1002/14651858.CD009014.pub2. PubMed PMID: 22972130.

9. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol. 2007;119(4):1016-8. doi: 10.1016/j.jaci.2006.12.622. PubMed PMID: 17306354.

10. Wensing M, Penninks AH, Hefle SL, Akkerdaas JH, van Ree R, Koppelman SJ, Bruijnzeel-Koomen CA, Knulst AC. The range of minimum provoking doses in hazelnut-allergic patients as determined by double-blind, placebo-controlled food challenges. Clin Exp Allergy. 2002;32(12):1757-62. PubMed PMID: 12653168.

11. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. Journal of Allergy and Clinical Immunology. 2016;137(4):973-82. doi: 10.1016/j.jaci.2016.01.001.

12. Kulis M, Wright BL, Jones SM, Burks AW. Diagnosis, Management, and Investigational Therapies for Food Allergies. Gastroenterology. 2015. doi: 10.1053/j.gastro.2015.01.034. PubMed PMID: 25633563.

13. 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, Consortium of Food Allergy R. Oral immunotherapy for treatment of egg allergy in children. The New England journal of medicine. 2012;367(3):233-43. doi: 10.1056/NEJMoa1200435. PubMed PMID: 22808958; PMCID: 3424505.

14. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, Burk C, Hiegel A, Carlisle S, Christie L, Perry TT, Pesek RD, Sheikh S, Virkud Y, Smith PB, Shamji MH, Durham SR, Jones SM, Burks AW. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. The Journal of allergy and clinical immunology. 2014;133(2):468-75. doi: 10.1016/j.jaci.2013.11.007. PubMed PMID: 24361082; PMCID: 3960331.

15. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. The Journal of allergy and clinical immunology. 1992;90(2):256-62. PubMed PMID: 1500630.

16. Patriarca G, Nucera E, Pollastrini E, De Pasquale T, Lombardo C, Buonomo A, Roncallo C, Pecora V, Musumeci S, Altomonte G, Alonzi C, Schiavino D, Gasbarrini G. Oral rush desensitization in peanut allergy: a case report. Dig Dis Sci. 2006;51(3):471-3. doi: 10.1007/s10620-006-3157-4. PubMed PMID: 16614954.

17. Mansfield L. Successful oral desensitization for systemic peanut allergy. Ann Allergy Asthma Immunol. 2006;97(2):266-7. doi: 10.1016/S1081-1206(10)60026-9. PubMed PMID: 16937764.

18. 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. The Journal of allergy and clinical immunology. 2009;124(2):292-300, e1-97. doi: 10.1016/j.jaci.2009.05.022. PubMed PMID: 19577283; PMCID: 2725434.

19. 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. The Journal of allergy and clinical immunology. 2009;124(2):286-91, 91 e1-6. doi: 10.1016/j.jaci.2009.03.045. PubMed PMID: 19477496; PMCID: 2731305.

20. 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 e1. doi: 10.1016/j.jaci.2010.04.030. PubMed PMID: 20542324.

21. 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. The Journal of allergy and clinical immunology. 2011;127(3):654-60. doi: 10.1016/j.jaci.2010.12.1111. PubMed PMID: 21377034; PMCID: 3060783.

22. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy. 2011;41(9):1273-81. doi: 10.1111/j.1365-2222.2011.03699.x. PubMed PMID: 21414048.

23. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, Palmer C, Deighton J, Ewan P, Clark A. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-304. doi: 10.1016/S0140-6736(13)62301-6. PubMed PMID: 24485709; PMCID: 4255069.

24. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, Wood RA. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. The Journal of allergy and clinical immunology. 2014. doi: 10.1016/j.jaci.2014.11.005. PubMed PMID: 25528358.

25. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, Keet CA, Kulis M, Orgel KG, Guo R, Steele PH, Virkud YV, Ye P, Wright BL, Wood RA, Burks AW. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. Journal of Allergy and Clinical Immunology. 2016. doi: 10.1016/j.jaci.2016.05.027.

26. 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):459-65. PubMed PMID: 12562461.

27. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. Hepatogastroenterology. 1998;45(19):52-8. PubMed PMID: 9496487.

28. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, Steele PH, Pons L, Helm RM, Lee LA, Burks AW. Egg oral immunotherapy in nonanaphylactic children with egg allergy. The Journal of allergy and clinical immunology. 2007;119(1):199-205. doi: 10.1016/j.jaci.2006.09.016. PubMed PMID: 17208602.

29. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol. 2010;105(6):444-50. doi: 10.1016/j.anai.2010.09.030. PubMed PMID: 21130382; PMCID: PMC3026291.

30. 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):1261-9. doi: 10.1111/j.1398-9995.2007.01501.x. PubMed PMID: 17919140.

31. 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):12-9. PubMed PMID: 17375736.

32. Meglio P, Giampietro PG, 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. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(1):75-83. doi: 10.1111/j.1399-3038.2012.01341.x. PubMed PMID: 22882430.

33. 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. doi: 10.2332/allergolint.09-OA-0107. PubMed PMID: 19946197.

34. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a

randomized controlled trial. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(1):66-74. doi: 10.1111/j.1399-3038.2012.01349.x. PubMed PMID: 22957889.

35. Garcia Rodriguez R, Urra JM, Feo-Brito F, Galindo PA, Borja J, Gomez E, Lara P, Guerra F. Oral rush desensitization to egg: efficacy and safety. Clin Exp Allergy. 2011;41(9):1289-96. doi: 10.1111/j.1365-2222.2011.03722.x. PubMed PMID: 21457166.

36. 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):980-7. doi: 10.1111/j.1398-9995.2004.00542.x. PubMed PMID: 15291907.

37. 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):412-9. doi: 10.1111/j.1399-3038.2007.00670.x. PubMed PMID: 18221476.

38. Zapatero L, Alonso E, Fuentes V, Martinez MI. Oral desensitization in children with cow's milk allergy. J Investig Allergol Clin Immunol. 2008;18(5):389-96. PubMed PMID: 18973104.

39. Alvaro M, Giner MT, Vazquez M, Lozano J, Dominguez O, Piquer M, Dias M, Jimenez R, Martin MA, Alsina L, Plaza AM. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. Eur J Pediatr. 2012;171(9):1389-95. doi: 10.1007/s00431-012-1739-z. PubMed PMID: 22576806.

40. Sanchez-Garcia S, Rodriguez del Rio P, Escudero C, Garcia-Fernandez C, Ramirez A, Ibanez MD. Efficacy of oral immunotherapy protocol for specific oral tolerance induction in children with cow's milk allergy. Isr Med Assoc J. 2012;14(1):43-7. PubMed PMID: 22624442.

41. 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. The Journal of allergy and clinical immunology. 2008;121(2):343-7. doi: 10.1016/j.jaci.2007.10.029. PubMed PMID: 18158176.

42. 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. The Journal of allergy and clinical immunology.

2008;122(6):1154-60. doi: 10.1016/j.jaci.2008.09.030. PubMed PMID: 18951617; PMCID: 3764488.

43. 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. The Journal of allergy and clinical immunology. 2009;124(3):610-2. doi: 10.1016/j.jaci.2009.06.025. PubMed PMID: 19665770; PMCID: 2739248.

44. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, Passalacqua G. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105(5):376-81. doi: 10.1016/j.anai.2010.03.015. PubMed PMID: 21055664.

45. Pajno GB, Caminiti L, Salzano G, Crisafulli G, Aversa T, Messina MF, Wasniewska M, Passalacqua G. Comparison between two maintenance feeding regimens after successful cow's milk oral desensitization. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(4):376-81. doi: 10.1111/pai.12077. PubMed PMID: 23692328.

46. Martorell A, De la Hoz B, Ibanez MD, Bone J, Terrados MS, Michavila A, Plaza AM, Alonso E, Garde J, Nevot S, Echeverria L, Santana C, Cerda JC, Escudero C, Guallar I, Piquer M, Zapatero L, Ferre L, Bracamonte T, Muriel A, Martinez MI, Felix R. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297-304. doi: 10.1111/j.1365-2222.2011.03749.x. PubMed PMID: 21481024.

47. Salmivesi S, Korppi M, Makela MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr. 2013;102(2):172-6. doi: 10.1111/j.1651-2227.2012.02815.x. PubMed PMID: 22897785.

48. 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. The Journal of allergy and clinical immunology. 2012;129(2):448-55, 55 e1-5. doi: 10.1016/j.jaci.2011.10.023. PubMed PMID: 22130425; PMCID: 3437605.

49. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. The Journal of allergy and clinical immunology. 2013;132(3):737-9 e6. doi: 10.1016/j.jaci.2013.05.006. PubMed PMID: 23806635; PMCID: 3759832.

50. Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk- and egg-containing diet in the management of milk and egg allergy. J Allergy Clin Immunol Pract. 2015;3(1):13-23; quiz 4. doi: 10.1016/j.jaip.2014.10.001. PubMed PMID: 25577613.

51. Goldberg MR, Nachshon L, Appel MY, Elizur A, Levy MB, Eisenberg E, Sampson HA, Katz Y. Efficacy of baked milk oral immunotherapy in baked milk-reactive allergic patients. Journal of Allergy and Clinical Immunology. 2015;136(6):1601-6. doi: 10.1016/j.jaci.2015.05.040.

52. Sato S, Utsunomiya T, Imai T, Yanagida N, Asaumi T, Ogura K, Koike Y, Hayashi N, Okada Y, Shukuya A, Ebisawa M. Wheat oral immunotherapy for wheat-induced anaphylaxis. Journal of Allergy and Clinical Immunology. 2015;136(4):1131-3e7. doi: 10.1016/j.jaci.2015.07.019.

53. Sato S, Yanagida N, Ogura K, Imai T, Utsunomiya T, Iikura K, Goto M, Asaumi T, Okada Y, Koike Y, Syukuya A, Ebisawa M. Clinical studies in oral allergen-specific immunotherapy: differences among allergens. Int Arch Allergy Immunol. 2014;164(1):1-9. doi: 10.1159/000361025. PubMed PMID: 24943470.

54. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, Trela A, Hoyte E, O'Riordan G, Seki S, Blakemore A, Woch M, Hamilton RG, Nadeau KC. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1. doi: 10.1186/1710-1492-10-1. PubMed PMID: 24428859; PMCID: 3913318.

55. Begin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, Trela A, Tavassoli M, Hoyte E, O'Riordan G, Blakemore A, Seki S, Hamilton RG, Nadeau KC. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy Asthma Clin Immunol. 2014;10(1):7. doi: 10.1186/1710-1492-10-7. PubMed PMID: 24576338; PMCID: 3936817.

56. Gorelik M, Narisety SD, Guerrerio AL, Chichester KL, Keet CA, Bieneman AP, Hamilton RG, Wood RA, Schroeder JT, Frischmeyer-Guerrerio PA. Suppression of the immunologic response to peanut during immunotherapy is often transient. The Journal of allergy and clinical immunology. 2014. doi: 10.1016/j.jaci.2014.11.010. PubMed PMID: 25542883.

57. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, Scurlock AM, Gimenez G, Bardina L, Sampson HA, Burks AW. Peanut oral immunotherapy modifies IgE and IgG4

responses to major peanut allergens. J Allergy Clin Immunol. 2013;131(1):128-34 e1-3. doi: 10.1016/j.jaci.2012.10.048. PubMed PMID: 23199605; PMCID: 3529994.

58. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, Berglund JP, Tsai M, Maecker H, O'Riordan G, Galli SJ, Nadeau KC. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). The Journal of allergy and clinical immunology. 2014;133(2):500-10. doi: 10.1016/j.jaci.2013.12.1037. PubMed PMID: 24636474; PMCID: 4121175.

59. Gorelik M, Narisety SD, Guerrerio AL, Chichester KL, Keet CA, Bieneman AP, Hamilton RG, Wood RA, Schroeder JT, Frischmeyer-Guerrerio PA. Suppression of the immunologic response to peanut during immunotherapy is often transient. The Journal of allergy and clinical immunology. 2015;135(5):1283-92. doi: 10.1016/j.jaci.2014.11.010. PubMed PMID: 25542883; PMCID: 4426213.

60. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, Wood RA. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. The Journal of allergy and clinical immunology. 2015;135(5):1275-82 e1-6. doi: 10.1016/j.jaci.2014.11.005. PubMed PMID: 25528358; PMCID: 4430665.

61. Bégin P, Nadeau KC. Changes in peanut-specific T-cell clonotype with oral immunotherapy. Journal of Allergy and Clinical Immunology. 2015;135(6):1636-8e3. doi: 10.1016/j.jaci.2015.03.010.

62. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR, Paul MM, Sugerman RW, Lee JO, Lester MR, Mendelson LM, Nacshon L, Levy MB, Goldberg MR, Elizur A. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014;2(1):91-6. doi: 10.1016/j.jaip.2013.10.001. PubMed PMID: 24565775.

63. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. The Journal of allergy and clinical immunology. 2012;129(4):1155-7. doi: 10.1016/j.jaci.2011.11.042. PubMed PMID: 22236725.

64. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. Ann Allergy Asthma Immunol. 2011;106(1):73-4. doi: 10.1016/j.anai.2010.10.010. PubMed PMID: 21195949.

65. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. The Journal of allergy and clinical immunology. 2013;132(6):1368-74. doi: 10.1016/j.jaci.2013.09.046. PubMed PMID: 24176117; PMCID: 4405160.

66. 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):1622-4. doi: 10.1016/j.jaci.2011.04.009. PubMed PMID: 21546071; PMCID: 3396422.

67. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, Plaut M, Sampson HA. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. The Journal of allergy and clinical immunology. 2015. doi: 10.1016/j.jaci.2015.10.005. PubMed PMID: 26581915.

68. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, Heimall J, Makhija M, Robison R, Chinthrajah RS, Lee J, Lebovidge J, Dominguez T, Rooney C, Lewis MO, Koss J, Burke-Roberts E, Chin K, Logvinenko T, Pongracic JA, Umetsu DT, Spergel J, Nadeau KC, Schneider LC. Omalizumab facilitates rapid oral desensitization for peanut allergy. Journal of Allergy and Clinical Immunology. 2016. doi: 10.1016/j.jaci.2016.08.010.

69. Van Overtvelt L, Moussu H, Horiot S, Samson S, Lombardi V, Mascarell L, van de Moer A, Bourdet-Sicard R, Moingeon P. Lactic acid bacteria as adjuvants for sublingual allergy vaccines. Vaccine. 2010;28(17):2986-92. doi: 10.1016/j.vaccine.2010.02.009. PubMed PMID: 20175969.

70. Tang MLK, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. Journal of Allergy and Clinical Immunology. 2015;135(3):737-44.e8. doi: 10.1016/j.jaci.2014.11.034.

71. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. The Journal of allergy and clinical immunology. 2015;135(3):737-44 e8. doi: 10.1016/j.jaci.2014.11.034. PubMed PMID: 25592987.

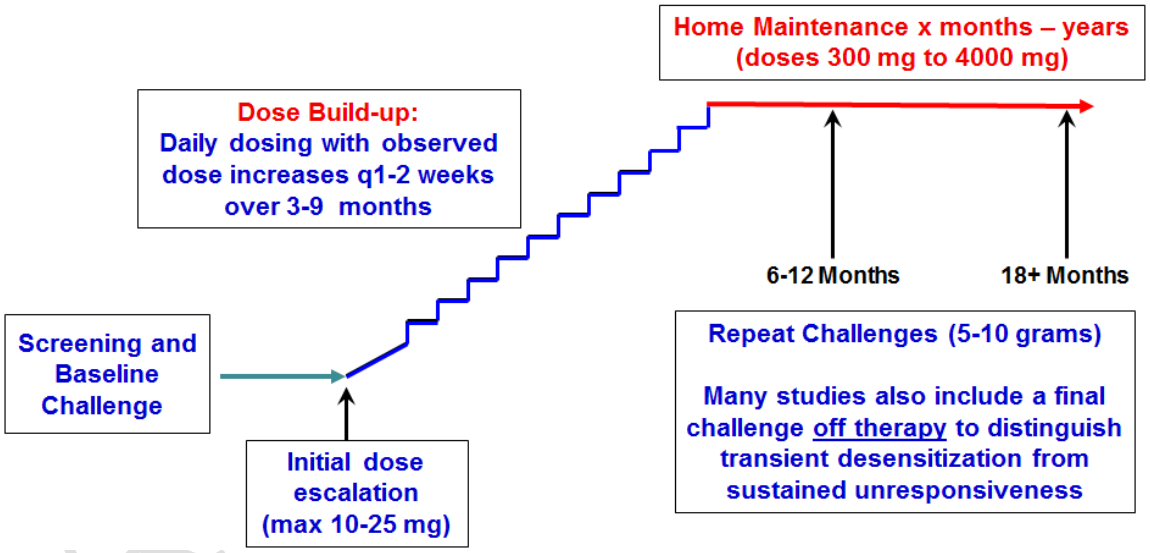
72. Noh G, Lee SS. A pilot study of interferon-gamma-induced specific oral tolerance induction (ISOTI) for immunoglobulin E-mediated anaphylactic food allergy. J Interferon Cytokine Res. 2009;29(10):667-75. doi: 10.1089/jir.2009.0001. PubMed PMID: 19642905.

73. Jagdis A, Berlin N, Barron C, Giruparajah M, Leader N, Maclachlan S, Sussman GL. Effect of ketotifen premedication on adverse reactions during peanut oral immunotherapy. Allergy Asthma Clin Immunol. 2014;10(1):36. doi: 10.1186/1710-1492-10-36. PubMed PMID: 25031584; PMCID: 4099498.

74. 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(1):3. doi: 10.1186/1710-1492-10-3. PubMed PMID: 24438769; PMCID: 3904422.

75. Lee SJ, Noh G, Lee JH. In Vitro Induction of Allergen-Specific Interleukin-10-Producing Regulatory B Cell Responses by Interferon-gamma in Non-Immunoglobulin E-Mediated Milk Allergy. Allergy Asthma Immunol Res. 2013;5(1):48-54. doi: 10.4168/aair.2013.5.1.48. PubMed PMID: 23277878; PMCID: 3529229.

Figure 1: Typical Approach to Food OIT



Representative OIT Trials

Author	Year	Design	Subject Age	Maintenance dose	Duration	Conclusions
Peanut						
Jones (18)	2009	Open label	1 - 16	1800 mg	36 months	93%passed 3.9 gram peanut OFC
Blumchen (20)	2010	Randomized open label	3 - 14	500 mg	7-day rush escalation, 8 weeks maintenance	64% reached their maintenance dose of 500 mg peanut
Varshney (21)	2011	Randomized, placebo-controlled	3 - 11	2000 mg	48 weeks	84% passed 5000 mg peanut OFC
Anagnostou (22)	2011	Open label	4 - 18	800 mg	32 weeks	64% tolerated 6.6 g OFC
Anagnostou (23)	2014	Randomized, placebo-controlled	7 - 16	800 mg	26 weeks	62% tolerated 1400 mg challenge
Vickery (14)	2014	Open label	1 - 16	Up to 4000 mg	Up to 5 years	1 month after OIT stopped, 50% achieved SU to 5000 mg OFC
Narisety (60)	2014	Randomized, placebo-controlled	7 - 13	2000 mg	12 months	Significantly greater increase in OFC threshold in OIT versus SLIT, low rate of SU
Vickery (25)	2016	Randomized clinical trial	9 – 36 months	300 vs 3000 mg	29 months (median)	Overall 91% SU, no difference between doses
Egg						
Buchanan (28)	2007	Open label	1 - 16	0.3 g	24 months	57% passed 8 gram OFC . 29% SU after 3-4 month period ofavoidance
Vickery (29)	2010	Open label	3-13	0.3 to 3.6 g	18-50 months	75% SU 1 month after stopping OIT

Burks (13)	2012	Randomized, placebo-controlled	5-11	1.6 g	22 months	75% passed 10 gram OFC, but only 28% with SU
Milk						
Longo (41)	2008	Randomized open label	5-17	150 mL	10-day rush escalation, 1 year maintenance	36% tolerated 150 mL or more, 54% partially tolerant (5-150 mL)
Skripak (42)	2008	Randomized, placebo-controlled	6-17	500 mg milk protein	23 weeks	Median milk challenge threshold rose from 40 mg to 5140 mg after OIT
Martorell (46)	2011	Randomized, placebo-controlled	2-3	200 mL	1 year	90% showing complete desensitization
Keet (48)	2012	Randomized, placebo-controlled	6-17	1000-2000 mg	60 weeks	70% of patients receiving OIT passed an 8g OFC, SU in only 40% after 6 weeks.