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Desensitization for Peanut Allergies in Children

Rekha D. Jhamnani, M.D.[1]
Pamela Frischmeyer-Guerrerio, M.D. Ph.D.[2,*]

Address
[1]National Institutes of Health, 10 Clinical Center Drive, Bethesda, MD, 20892, USA
[*,2]National Institutes of Health, 4 Memorial Drive, Building 4, Room 228, Bethesda, MD, 20892, USA
Email: pamela.guerrerio@nih.gov

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Opinion Statement

Immunotherapy for peanut allergy has been an exploding topic of study within the last few years. Sublingual, epicutaneous, and oral immunotherapy are being investigated and show promise in the treatment of peanut allergy. Oral immunotherapy has shown the most clinical benefit; however, sublingual and epicutaneous immunotherapy appear to have the most favorable safety profiles. Most studies to date suggest that only a minority of subjects achieve sustained unresponsiveness to peanut after discontinuation of immunotherapy. Recent efforts have been focused on identifying adjunct therapies, such as omalizumab, that may assist patients in achieving peanut desensitization more quickly and with greater success. Several underlying immunologic mechanisms, including a switch from IgE to IgG4 production and induction of T regulatory cells, have been studied although more research is needed to identify reliable biomarkers. This article will describe the immunotherapy approaches that are being investigated to induce peanut desensitization, and highlight the benefits and risks of these therapies that need to be considered before they are ready for routine clinical practice.

Introduction

Peanut allergy is the most common cause of fatal food-induced allergic reactions in the USA [1] and is a growing public health concern. The prevalence of peanut allergy in children in 2008 was 1.4 % compared with 0.8 % in 2002, and 0.4 % in 1997 [2]. Although other food allergies are often outgrown, only 20 % of children outgrow their peanut allergy, making it a lifelong disease for most affected patients [3]. The only treatment currently available remains avoidance and injectable epinephrine [4]. However, the persistent fear and uncertainty of ingesting a food contaminated with peanut, and the potential for severe reactions, markedly diminishes quality of life for both patients and their families. Recently, the Learning Early About Peanut Allergy (LEAP) study suggested that peanut allergy may

largely be preventable in high-risk infants through early dietary introduction, but the need remains for viable effective treatments for those patients with established disease [5]. In the last few decades, several immunotherapeutic approaches aiming to alter the natural history of peanut allergy have been investigated. While the ideal treatment for peanut allergy would provide for lasting tolerance, defined by the absence of symptoms after food ingestion even after periods of prolonged avoidance, immunotherapy for peanut allergy has shown the most success in inducing a state of desensitization in which patients must regularly ingest peanut in order to remain nonreactive [6]. Currently desensitization to peanut via oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) has been investigated and shows promise (Table 1). Reactions during desensitization and overall safety of patients should be considered. In this article we will review various modalities of peanut desensitization, mechanisms of desensitization, and the limitations of these new investigational treatments.

Methods of Immunotherapy

Initial efforts to treat peanut allergy using traditional subcutaneous immunotherapy (SCIT) were attempted in two studies in the 1990s [7, 8]. In the largest of these studies, Nelson and colleagues investigated 12 adult patients with IgE-mediated peanut allergy. Six of the subjects served as untreated controls and the remaining six were treated with subcutaneous injections of peanut extract via a rush protocol until maintenance (0.5 ml of 1:100 wt/vol) was attained. These patients were then maintained on weekly injections of peanut for at least 1 year. All subjects underwent double-blind, placebo-controlled, oral peanut challenges at the start of the study, after 6 weeks, and again at 1 year. All treated subjects achieved maintenance dosing and exhibited increased tolerance to peanut during challenge in contrast to the untreated group who showed no overall change in peanut sensitivity. However, three out of the six treated subjects required dose reductions during maintenance therapy due to systemic reactions, and all but one required treatment with multiple doses of epinephrine [7]. Thus, while this study suggested that an immunotherapeutic approach may be beneficial in

Table 1. Methods, benefits, and main side effects of peanut immunotherapy methods

Immunotherapy method	Method of delivery	Benefits	Main side effects
SCIT[a]	Subcutaneous injection	Efficacious in treatment of aeroallergen allergy	High rate of systemic reactions
SLIT[b]	Peanut extract placed under the tongue and then swallowed daily	Lower side effect profile	Mostly oropharyngeal symptoms
EPIT[c]	Patch with allergen applied daily to intact skin	Allergen ingestion not required	Contact dermatitis
OIT[d]	Ingest allergen mixed into food vehicle daily	Higher efficacy rate	Potentially greater frequency and severity of reactions; EoE[e]

[a]Subcutaneous immunotherapy
[b]Sublingual immunotherapy
[c]Epicutaneous immunotherapy
[d]Oral immunotherapy
[e]Eosinophilic esophagitis

patients with anaphylactic peanut allergy, alternative methods of delivering antigen were needed given the high rate of serious adverse reactions with SCIT.

One approach that has sparked interest in recent years, in part because of its generally favorable safety profile, has been sublingual immunotherapy (SLIT; Table 1). With SLIT, the subject places a small amount of peanut extract under the tongue, holds it there for a few minutes and then either spits it out or swallows it. The oral mucosa is rich in tolerogenic antigen presenting cells so SLIT may induce tolerance using lower doses of allergen, which presumably will lead to fewer side effects. The amount of peanut extract used generally varies from micrograms (μg) to milligrams (mg). In a randomized double-blind placebo-controlled study by Kim et al., children aged 1 to 11 years received peanut SLIT or placebo in escalating doses for 6 months followed by maintenance dosing of 2000 μg of peanut protein for 6 months. By the end of the study, subjects receiving SLIT were able to consume 1710 mg of peanut protein vs. 85 mg of peanut protein in placebo controls, and therefore were expected to be protected against most accidental ingestions of peanut [9]. In another multicenter randomized control trial of 40 subjects aged 12–37 years conducted by Fleischer et al., subjects in the active treatment arm received 44 weeks of SLIT and 70 % of this group achieved desensitization vs. 15 % in the placebo group. The median consumed dose increased from 3.5 mg to 496 mg of peanut flour in the SLIT responders. However, no subjects in this study were able to complete the primary outcome of passing a 5-g (g) peanut challenge [10•]. In a follow-up study, Burks et al. sought to assess the long-term clinical outcomes for the subjects who were initially randomized to low-dose peanut SLIT (1386 μg/day) and continued daily treatment for 3 years as well as those who crossed-over from placebo to high-dose peanut SLIT (3696 μg/day) who were treated for 2 years. Only 4 of 37 (10.8 %) SLIT participants passed a 10-g oral food challenge to peanut powder and achieved sustained unresponsiveness 8 weeks after discontinuation of SLIT. No difference in clinical outcomes was observed between subjects who received high vs. low-dose peanut SLIT, although no definitive conclusions could be drawn due to a high rate of subject drop-out [11••].

Epicutaneous immunotherapy (EPIT) has shown promise in animal studies and is now being investigated as a potential therapeutic strategy for peanut allergy in humans (Table 1) [12]. EPIT consists of placing a patch containing a layer of allergen on intact skin daily. A condensation chamber develops between the skin and the patch creating an accumulation of water that solubilizes the allergen and allows for its entry into the epidermis. The allergen is then captured by Langerhans cells, which process the allergen and present it to lymphocytes within draining lymph nodes [13]. In the Viaskin Peanut's Efficacy and Safety (VIPES) study, 221 subjects 6–55 years of age were randomized to a 50 μg peanut patch, a 100 μg patch, a 250 μg patch, or placebo for 12 months. The most effective response was seen in the 250 μg patch group who exhibited a 50 % response rate (defined as the ability to tolerate 1000 mg of peanut protein or a 10-fold increase in eliciting dose of peanut protein during challenge compared to baseline) vs. 25 % in the placebo group (p = 0.0108) [14]. One hundred and seventy-one of the subjects in the original trial are now being treated in an open-label extension of the study for an additional 24 months. Among the 33 subjects who received the highest dose patch (250 μg) for 24 months, 23 (69.7 %) were found to respond after completing 2 years of EPIT. In this study, children (aged 6–11 years) tended to show a more favorable response compared to adolescents or adults [15]. The Consortium for Food Allergy Research (CoFAR) recently launched a multicenter, randomized,

double-blind, placebo-controlled trial of EPIT in 75 peanut allergic patients (adults and children). Subjects were randomized to a 100 μg Viaskin patch, 250 μg Viaskin patch, or placebo and will undergo food challenge. Results are pending.

One of the most-studied immunotherapeutic strategies to treat peanut allergy has been oral immunotherapy (OIT; Table 1). OIT consists of mixing an allergen into a food vehicle. The subject then ingests gradually increasing quantities until a maintenance dose is reached, which is then consumed daily. Generally, protocols involve an initial escalation phase, home dosing with interval office visits for buildup, and then a maintenance phase. In 2009, the first open-label peanut OIT trial was published. In this trial, subjects were maintained on 1800 mg of peanut protein after an initial buildup phase. After 3 years, 27/29 (93 %) of subjects were able to pass an oral challenge to 3.9 g of peanut protein [16]. In 2010, Blumchen and colleagues treated 23 children between the ages of 3 and 14 years with peanut OIT following a 7-day rush protocol. Subjects who were not protected to 0.5 g of peanut after the initial week-long rush phase underwent a long-term buildup protocol with biweekly dose increases until 0.5 g of peanut was attained. Maintenance dosing (at a minimum of 0.5 g and maximum of 2 g of peanut daily) was then continued for 8 weeks, after which subjects were instructed to strictly avoid all peanut exposure for 2 weeks before undergoing a final double-blind placebo-controlled oral food challenge. The majority of subjects did not reach the intended 0.5 g protective dose of peanut after rush buildup and thus went on to long-term buildup and eventually maintenance therapy. After a median period of 7 months, 14 out of 22 subjects (64 %) reached this 0.5 g threshold. At the end of the trial, patients tolerated a median of 1 g of peanut compared with 0.19 g of peanut before OIT [17].

In 2011, the first multicenter, randomized, double-blind, placebo-controlled study of peanut OIT was performed. Twenty-eight pediatric subjects (aged 1–16 years) were randomized to placebo or peanut flour up to a maintenance dose of 4 g daily. After 1 year, 16 patients in the treatment group were able to ingest 5 g of peanut compared with 9 subjects in the placebo arm who tolerated a median of 280 mg of peanut [18]. In a prospective cohort study of 22 children in 2011, subjects were treated with a maintenance dose of 800 mg of peanut protein for 32 weeks. Sixty-four percent of patients tolerated 6.6 g of protein at the end of treatment, representing a thousand-fold increase in median tolerated peanut dose from baseline. The same group of researchers completed a phase II randomized controlled trial of peanut OIT in 2014 where they enrolled 104 children aged 7–16 years. Updosing was performed gradually in 2-week increments to a target maintenance dose of 800 mg daily. After 26 weeks of therapy, 84 % of the active group was able to tolerate daily ingestion of 800 mg of peanut protein, and 62 % of these subjects passed a 1400 mg peanut protein food challenge compared with 0 % in the peanut avoidance arm. Participants in the control arm were then crossed-over to peanut OIT and 91 % of this group was able to tolerate 800 mg of peanut protein daily after 26 weeks [19••].

Recently, Bird et al. experimented with a shorter buildup phase for peanut OIT. A modified entry dose of peanut flour was used based on the subject's threshold of reactivity. Buildup dosing occurred every 2 weeks and after 4 months of maintenance therapy, participants underwent a 5 g double-blind placebo-controlled oral food challenge. Subjects then continued to consume 2 g of peanut daily. Out of 11 subjects, 9 achieved maintenance dosing, and all 9 patients passed a 5 g peanut food challenge. This pilot study suggested that subjects could achieve maintenance

dosing in a shorter time frame without necessarily compromising efficacy [20•]. In 2014, Vickery and colleagues completed the first study to demonstrate "sustained unresponsiveness" after peanut OIT. This term was defined as the ability to consume peanut without symptoms after a period (4 weeks in this study) of stopping OIT. The concept of sustained unresponsiveness was novel in that it raised the possibility that patients potentially would not have to regularly consume peanut to maintain clinical tolerance after completing OIT. In this study, 39 subjects (1–16 years of age) were enrolled and 24 completed the protocol. Participants were treated for up to 5 years with a maximum maintenance dose of 4 g of peanut protein daily. A month after stopping OIT, 50 % of the subjects (12/24) showed "sustained unresponsiveness" and passed a 5 g double-blind placebo-controlled food challenge [21••].

While peanut OIT studies have generally shown greater efficacy than those testing SLIT, only a few studies have compared these modalities head-to-head. In a retrospective study comparing oral food challenge outcomes after 12 months of peanut SLIT (maintenance dose 2 mg/day) vs. OIT (4000 mg/day), Chin et al. found that eliciting dose thresholds were lower and more variable in subjects who received SLIT compared to OIT [22]. A randomized, double-blind, placebo-controlled study directly comparing peanut SLIT and OIT was published in 2014. Twenty-one subjects aged 7–13 years were randomized to receive active SLIT/placebo OIT or placebo SLIT/active OIT. Subjects were built-up to a maintenance dose of 3.7 mg/day for SLIT and 2000 mg/day for OIT. After 12 months of treatment, participants who received active OIT tolerated a significantly higher threshold dose of peanut at challenge than those who received active SLIT (7246 mg vs. 496 mg, respectively). However, patients in the OIT group experienced more adverse reactions requiring treatment with antihistamines, beta-agonists, and injectable epinephrine. The OIT group also experienced more intolerable symptoms, most of which were oropharyngeal, leading to early withdrawal [23••]. Thus, while OIT may be more effective at inducing desensitization, this favorable clinical benefit may come at the cost of greater side effects. Sustained unresponsiveness was evident in only a small minority of the subjects regardless of treatment modality.

Immunologic Mechanisms

The mechanisms that underlie peanut desensitization are not well elucidated. Most efforts to understand the immunologic changes that accompany immunotherapy have focused on changes in antibody levels as well as effector responses by mast cells and basophils. Consistent with the patterns that have been observed during immunotherapy for other allergic conditions, allergen-specific IgE tends to decline below baseline during the course of treatment (after an initial uptick) while IgG4 rises. Vickery et al. demonstrated that peanut OIT may also alter peanut-specific antibody repertoires for the major peanut allergens, Arah1-3, with an increase in polyclonal IgG4 responses and a concurrent decrease in IgE diversity (without change in antibody affinity) following treatment [24].

IgG4 is thought to suppress peanut-induced basophil and mast cell activation by both competing with IgE for binding to peanut allergen as well as by binding to the inhibitory FcγRIIb receptor on the surface of these cells [25]. In general, skin prick test responses to peanut, a measure of mast cell reactivity, decrease

over the course of treatment. Likewise, basophil activation, indicated by surface expression of CD63 and CD203c following peanut stimulation, also tends to be suppressed during both SLIT and OIT [9, 16, 19••, 26•, 27, 28, 29•]. In some cases, the changes in mast cell and basophil reactivity were not allergen-specific [26•, 27]. Furthermore, there is some evidence that this reduction in effector cell activation may only be transient, and in some cases, may revert despite continued exposure to peanut [27]. In the aforementioned Narisety trial that compared peanut OIT and SLIT, OIT generally led to greater changes in skin test responses to peanut as well as peanut-specific IgE and IgG4 levels, but it is not clear whether this relates to the enhanced efficacy of OIT [23••]. Few of these immunologic parameters have correlated strongly with clinical responses, although a lower baseline peanut IgE level may predict a more favorable outcome [9, 22, 30].

Like other food allergies, peanut allergy is associated with a primarily T helper 2 (Th2)-dominated cytokine response. Most studies suggest that SLIT and OIT reduce the Th2 response to peanut, but the suppression may not be complete or persistent [28]. Immunotherapy may also induce populations of T regulatory cells (Tregs) that are capable of suppressing T effector responses to peanut but some studies have not seen an increase in this cell subset [21••, 29•]. Clearly more work is needed to understand the underlying immunologic mechanisms that underlie peanut desensitization, and whether any of these parameters will be useful biomarkers for predicting clinical outcomes.

Adjunct Therapies

The majority of immunotherapy studies to date have suggested that most patients with peanut allergy can be successfully desensitized. Increasing attention is now being focused on ways to improve the safety of this treatment, as well as to enhance the ability of these therapies to provide long-term protection against reactions, even after immunotherapy is discontinued. One idea to achieve this goal has been to combine immunotherapy with a probiotic bacterial adjuvant in order to promote tolerogenic mechanisms. Tang and colleagues recently completed a double-blind, placebo-controlled trial where 62 children (1–10 years of age) were randomized to either the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007) given in combination with peanut OIT (maintenance dose 2 g peanut protein/daily) or placebo for 18 months. In the subjects receiving OIT and probiotic, 89.7 % were desensitized, vs. 7.1 % of participants in the placebo group. Furthermore, possible sustained unresponsiveness was achieved in 82.1 % of the OIT/probiotic group vs. 3.6 % of children in the placebo group [31•]. While this study suggests that OIT in combination with a daily probiotic may be clinically effective, additional studies are needed to determine the relative contribution from OIT vs. probiotic in inducing the benefits from the combined therapy and whether the combination is truly more effective than OIT alone.

A recent study by Schneider and colleagues investigated the utility of omalizumab as an adjunctive therapy to improve the efficacy of peanut OIT and mitigate the risks. Omalizumab is a humanized monoclonal antibody that reduces free IgE levels. Thirteen subjects with confirmed IgE-mediated peanut allergy were pretreated with omalizumab for 12 weeks and then peanut OIT was initiated. All 13 participants tolerated the desensitization doses given over the

first day of OIT and reached the goal dose of 500 mg of peanut flour with minimal or no symptoms. Twelve of the thirteen subjects (92 %) achieved the maximum maintenance therapy dose of 4 g of peanut protein daily over a median of 8 weeks. At this point, omalizumab was discontinued and subjects continued on peanut OIT alone for an additional 6 months. All twelve of these subjects were able to pass an 8 g peanut flour challenge at the end of this time. Over the course of the study, only 2.0 % of the doses were associated with reactions, and most were mild. Six of the 13 subjects experienced only mild or no allergic reactions, five subjects had moderate reactions, and two subjects had severe symptoms, all of which responded rapidly to treatment [32••]. This study suggests that omalizumab may allow for more rapid desensitization with fewer side effects; larger double-blind placebo-controlled studies are underway to confirm these findings.

Side Effects and Adverse Events

As with any new treatment, the safety and side effects of immunotherapy for peanut allergy must be considered before this intervention could be recommended for widespread clinical use. Most reported side effects from SLIT have been mild in nature and consist of mainly oropharyngeal symptoms and gastrointestinal upset. In the aforementioned study by Kim et al., less than 1 % of home doses of SLIT required treatment with an antihistamine or epinephrine [9]. Although less studied, EPIT also appears to be generally well tolerated with side effects mainly including local eczematous skin reactions at the patch site. Other side effects include pruritus, erythema, edema, or urticaria at the patch site. These local skin reactions were mostly mild to moderate in severity and resolved over time. Less than 1 % of subjects dropped out due to severe dermatitis [14].

In patients undergoing OIT, the most common reported side effects are mouth itching and swelling and abdominal pain, but generalized itching, nausea, vomiting, diarrhea, urticaria, angioedema, rhinitis, wheezing, and laryngeal edema have all been reported. In some cases, these symptoms have required treatment with epinephrine, and at times have been severe enough to warrant discontinuation of OIT [18, 19••, 20•, 32••]. The high rate of gastrointestinal symptoms in participants receiving OIT has raised the concern that this treatment may promote the development of eosinophilic esophagitis (EoE). In a literature review exploring the association between OIT and EoE, twelve studies reported EoE after oral immunotherapy for foods. Eight of these studies were retrospective case series, three were individual case reports, and one was a randomized controlled trial that included 40 children undergoing egg oral immunotherapy. It was estimated that approximately 2.7 % of patients undergoing any type of oral immunotherapy developed EoE. EoE often resolved after discontinuation of OIT [33]. Whether the clinical benefit of OIT outweighs the side effects of this therapy remains controversial.

Conclusion

Over the last few years there has been significant progress in the development of treatment methods for food allergy and specifically peanut allergy. While peanut

OIT appears to be the most efficacious at desensitizing patients, SLIT and perhaps EPIT are associated with more favorable safety profiles. Some of the mechanisms underlying peanut immunotherapy have been elucidated, but more research is required in order to fully understand the complex immunologic changes that occur with the various forms of food immunotherapy. A greater understanding of these mechanisms could potentially lead to the discovery of useful biomarkers to track success of treatment. Only a minority of subjects have achieved sustained unresponsiveness in most peanut immunotherapy trials to date. More research is needed to investigate the ability of adjuvants and other adjunctive therapies to promote long-lasting tolerance as well as safety. While the results of recent immunotherapy trials for peanut allergy have been promising, further investigation is needed to optimize the risk/benefit ratio of these treatments before they are ready for routine clinical use.

Compliance with Ethical Standards

Conflict of Interest

Dr. Rekha D. Jhamnani declares that she has no conflict of interest.

Dr. Pamela Frischmeyer-Guerrerio declares that she has no conflict of interest.

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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.

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