

Oral Food Desensitization

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Abstract The immunologic interactions in the gastrointestinal tract are extensive and complex. In most cases, the end result of this activity is one of tolerance, which refers to the inhibition of an immune response. However, in a minority of cases, food allergy develops, and this seems to be increasing in prevalence. We continue to learn about the mechanisms involved in these processes and the factors that may promote tolerance as opposed to allergy. At this point, management of food allergy consists of allergen avoidance and readiness to manage an accidental exposure reaction, but using current knowledge of gastrointestinal immunity, researchers are investigating immunomodulatory approaches that will provide “active” therapy for food allergy and induce tolerance. Oral immunotherapy is one important therapy being studied, and in this article, we review recent results from studies of this potential treatment for food allergy.

Keywords Oral immunotherapy · Food allergy · Oral tolerance · Sublingual immunotherapy · Anaphylaxis · Peanut allergy · Egg allergy · Milk allergy · Desensitization

Introduction

In recent years, the prevalence and public awareness of IgE-mediated food allergy appear to be increasing. Although up to 35% of individuals self-report a food allergy, studies from North America indicate that more accurate estimates are likely about 5% in children and 3% to 4% among adults [1•]. A small group of foods (milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish) accounts for most food allergic reactions. Data from the United Kingdom and the United States indicate that the prevalence of peanut allergy in particular has recently doubled and now likely exceeds 1% among school-aged children [2, 3], although some recent evidence indicates that this increase may have plateaued [4].

There is also some suggestion that food allergic reactions have become more severe, with increasing hospitalization rates related to food allergy and anaphylaxis [5, 6]. Although fatal food allergic reactions are, fortunately, very uncommon [7], food allergy has been shown to adversely impact emotional quality of life, physical functioning, and quality of school life; it also frequently interferes with family activities and social events. This may be due to the ubiquitous nature of the potential threat and the knowledge that accidental ingestions are common and may occur at any time. Many patients and families make decisions about activities such as eating at restaurants, participating in social activities such as sleepovers and play dates, and homeschooling based on concerns about accidental exposure reactions [8•].

The current standard of care for food allergy focuses on two elements: strict avoidance of the allergen, which necessitates the utmost vigilance, and constant preparedness to manage a reaction to an accidental exposure. Ironically, this approach to management, while currently the best way

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to ensure an individual's safety, also may lead to greater levels of anxiety; a recent study showed that quality of life among children and mothers who took chances and ate products with "may contain nuts" labels was higher than it was among those who did not [9]. A need clearly exists for "active" therapies that will allow food allergic individuals to tolerate their specific food allergens. Fortunately, multiple studies are under way—at various stages of research—that are investigating such therapies [10]. This article focuses on some of the more recent studies involving one of those, oral immunotherapy (OIT), which may eventually allow patients and families to manage food allergy in a way that will be significantly more satisfying than what is currently available.

The Gastrointestinal Tract and Oral Tolerance

The gastrointestinal tract has been described as the body's largest immunologic organ. A single epithelial layer lines the gastrointestinal tract and receives multiple daily exposures to a variety of proteins from foods and micro-organisms [11]. Although intestinal antigen exposures are complex and frequent, the "normal" end result of these exposures is one of tolerance, and development of allergy occurs in only a small percentage of individuals. The phenomenon of tolerance refers to the active inhibition of an immune response. This has long been observed. In the 1800 s, Dakin [12] described populations of Native Americans who were able to tolerate contact hypersensitivity reactions by ingesting poison ivy leaves, and in the early-1900s, Wells [13] demonstrated that guinea pigs could be protected from developing anaphylaxis to injected egg protein if they were fed the protein orally first.

Chase [14] further characterized oral tolerance as a T-cell-mediated process. In murine experiments, when subcutaneous immunization was followed by a subcutaneous challenge with the same antigen, robust antibody and cell-mediated immune responses ensued. These immune responses were significantly blunted if the initial exposure before the subcutaneous challenge was an oral one. And when T cells from orally sensitized mice were transferred to naïve mice, response to a subcutaneous challenge was again reduced, indicating that oral exposure can induce an active inhibition of an immune response (tolerance) and that this inhibition is T-cell mediated [14].

We now know more about the specific mechanisms and key factors involved in the development of tolerance. Gastric acidity as well as pancreatic, gastric, and small intestinal brush border proteases render proteins less immunogenic through destruction of conformational epitopes [11]. The role of gastric acidity in reducing immunogenicity has been demonstrated in a murine model: mice

fed caviar in combination with antacids produced caviar-specific IgE and had positive immediate-type skin tests to caviar, whereas mice fed extract without antacids did not display such responses [15]. Also in mice, the importance of luminal enzymes in promoting tolerance was illustrated: whereas a peptic digest of bovine serum albumin was shown to be tolerogenic when administered orally or through ileal injection, untreated bovine serum albumin was tolerogenic only when ingested orally, and immunogenic after ileal injection [16].

For proteins that do not undergo luminal digestion, there are several ways of encountering the mucosal immune system beneath the epithelium. Subepithelial dendritic cells extend processes into the lumen and sample ingested antigen. Peyer's patches, lymphoid structures located throughout the small intestine and rectum, are composed of a B-lymphocyte core committed to IgA production and smaller numbers of peripheral T lymphocytes. These structures sit below specialized epithelial cells, known as *M cells*, which can take up particulate antigens and deliver them to dendritic cells for B-cell presentation in Peyer's patches. Soluble antigens are thought to cross the epithelium through transcellular or paracellular routes directly, leading to T-cell or macrophage encounters in the lamina propria or to direct entry into the circulation [11]. Properties of specific antigens as well as the host influence whether tolerance ensues. Soluble antigens generally are more tolerogenic than particulate ones, though in seeming contradiction to this idea, most food allergens are soluble [17]. Solubility can be affected by the method of food preparation. For example, roasting peanuts decreases their solubility and enhances binding of peanut-specific IgE [18]. Absorption rates may differ depending on food properties, but whether and how this relates to food allergy has not been studied extensively.

The timing of initial exposure to a food allergen also likely influences the development of tolerance. In mice, the age of oral antigen introduction seems to be one of the key factors in determining whether tolerance or an immune response is induced [17]. This issue is being researched actively in humans. For example, in comparing Jewish children in the United Kingdom with those in Israel, there is a 10-fold greater prevalence of peanut allergy among those in the United Kingdom—a difference not accounted for by variations in atopy, class, genetic background, or peanut allergenicity. Because peanuts are introduced to children earlier and in larger quantities in Israel, delaying introduction in the United Kingdom may be hindering the achievement of tolerance [19]. The Learning Early About Peanut Allergy study is currently investigating the role of timing in the development of allergy. Children from "at-risk" groups for peanut allergy (based on prior studies) have been recruited to eat peanuts regularly beginning within the

first year of life or to delay introduction until age 3 years. The proportion in each group with peanut allergy will be compared at 5 years; completion of the study is anticipated in 2013 [20].

Oral antigen dose also seems important in determining which of two distinct effector mechanisms mediates the development of tolerance. In animal models, high doses of antigen lead to lymphocyte anergy or clonal deletion. Anergy arises when T-cell–receptor ligation occurs in the absence of costimulatory signals (such as the soluble cytokine interleukin-2, or interactions between CD28 on T cells and CD80 and CD86 counterreceptors on antigen-presenting cells). Fas-mediated apoptosis results in clonal deletion, which is blocked by the proinflammatory cytokine interleukin-12. [11, 21–23]. Regulatory T cells appear to play a central role in the low-dose model. Among children with milk allergy, those who can tolerate extensively heated milk products (who typically outgrow their milk allergy sooner) were recently shown to have a higher percentage of milk allergen–specific CD25⁺CD27⁺ regulatory T cells compared with those who did not tolerate the heated forms [24].

If tolerance is the usual end result of oral exposure to dietary proteins, food allergy can be thought of as a breakdown in this process [10, 11]. The remainder of this article summarizes some of the work that is being done to attempt to induce tolerance among food allergic individuals. When discussing these efforts, it is important to distinguish between the concepts of desensitization and tolerance. Desensitization is a process that has long been used for patients with drug allergy, for example, whereby effector cells are rendered less reactive or nonreactive through rapid escalating administration of an allergen. In this process, once regular (typically daily) administration ceases, the individual returns to his or her previous level of reactivity. The goal of any type of immunotherapy, however, is achievement of tolerance, which indicates a long-lasting effect that persists well beyond the time at which daily administration of the allergen ceases [25, 26]. Subcutaneous injection immunotherapy is widely used for inhalant allergens and has been shown to have an immunomodulating effect [27]. This was studied and found to be somewhat effective for food allergens but is no longer being investigated or practiced because of an unacceptably high rate of severe systemic reactions [28, 29]. Investigators thus continue to research alternatives to injection immunotherapy for foods; this article focuses on those involving oral allergen administration.

Oral Immunotherapy

Both sublingual immunotherapy (SLIT) and OIT have been studied for treatment of food allergy, although reports on

OIT thus far have been more extensive. In SLIT, allergen exposure occurs via a liquid extract placed under the tongue, and studies have documented success with hazelnut, cow's milk, and kiwi allergies [30–34]. Patients receiving OIT consume a protein powder that is made from a specific food allergen and then mixed with a vehicle food. With both SLIT and OIT, patients typically begin with a fairly low dose of antigen that increases at regular intervals until a daily maintenance dose is achieved. Results of OIT studies generally have been encouraging. In one of the earlier OIT studies, Patriarca et al. [35] desensitized more than 75% of their patients to a variety of food allergens. Meglio et al. [36] successfully desensitized a similar percentage of milk allergic patients.

In a more recent pilot study of egg OIT, seven individuals without a history of egg anaphylaxis completed a 24-month protocol in which they gradually increased daily doses of egg protein [26]. Similar to immunologic changes seen with traditional inhalant injection immunotherapy [37], participants experienced a mean increase in egg-specific IgG with no significant change in specific IgE. All were able to ingest significantly more egg protein during a double-blind, placebo-controlled food challenge (DBPCFC) at the end of the study compared with study onset. With respect to the question of desensitization versus tolerance, however, only two continued to tolerate the full amount of egg after 3 to 4 months off OIT, indicating that this study induced desensitization, but not tolerance, in the majority.

Whereas most published OIT protocols involve a period of months to reach maintenance doses, a rush protocol was evaluated in nine children with cow's milk allergy, four of whom had experienced anaphylaxis to milk [38]. Patients were admitted to the hospital, and rush OIT was performed in a single-blind fashion, using soy milk for blinding. Six of nine were able to advance to maximal doses within 3 to 7 days; reactions were common but generally mild. One patient was treated with salbutamol for “moderate” wheezing, and none received epinephrine or steroids.

OIT with peanut has been less well-documented, although prior case reports have described success with this [39, 40]. Clark et al. [41] recently reported a small study of peanut OIT in four children 9 to 13 years of age, with peanut allergy confirmed by DBPCFC and by skin and serum testing. Starting OIT doses were determined based on threshold associated with a reaction during initial challenge. Once-daily doses were increased every 2 weeks under observation in a clinical research facility. Once participants reached a daily dose of 800 mg of peanut protein for 6 weeks, they underwent open challenges to peanut to a maximum dose of 12 peanuts (2.39–2.76 g of protein). Three of 4 were able to eat 12 peanuts during the final challenge, and the fourth tolerated 10 peanuts but developed mild abdominal pain after the final 2. All

achieved increases in their thresholds from 48- to 478-fold in magnitude. Reactions to daily dosing were not uncommon but were mostly mild, and none required treatment with epinephrine. Although it was small, the study suggests that these individuals are desensitized and thus likely protected from accidental peanut exposure reactions while on daily OIT, but it did not assess the possible impact on tolerance.

The results of a larger, open-label peanut OIT study were recently published [42•]. This study was notable not only for achieving desensitization to peanuts but for assessing developments in humoral and cellular immunity associated with this process. After reaching 300 mg of peanut protein as daily maintenance, 27 of 29 (93%) participants ingested 3.9 g of peanut protein on open challenge with no more than mild symptoms; the other two participants stopped after 2.1 g, one because of parental anxiety and one because of mild urticaria and a single episode of vomiting. This analysis did not include a challenge following OIT completion, but this will be pursued after 3 years of maintenance therapy. Multiple immunologic changes were documented in these individuals. Titrated skin prick test results decreased significantly beginning at 6 months, as did basophil reactivity to peanut antigen within 4 months. Median initial serum peanut-specific IgE increased after 3 months of treatment, then decreased significantly versus baseline after 18 months. Peanut-specific IgG levels increased significantly by 3 months and remained high until 24 months before returning to baseline by 33 months, while peanut IgG₄ levels increased significantly by 3 months and remained elevated throughout the study. In an allergen-binding assay, participants' serum factors inhibited IgE–peanut complex formation. Cytokine profiles were observed over time on OIT, and somewhat surprisingly, the expected transition from a T-helper type 2 profile to a T-helper type 1 profile was not seen. Regulatory T cells expressing forkhead box P3 increased over the first 12 months on OIT before declining. Unique to this study, T-cell microarray analyses before and after treatment were performed, and these demonstrated downregulation of genes related to apoptosis. We hope that further understanding of the immunologic implications will lead to more success with this therapy.

Oral Immunotherapy Studies with Control Groups

As most children do not retain their milk and egg allergies indefinitely, and even with peanut allergy, about 20% of children develop tolerance over time [1•], it is important to ask whether OIT leads to a change in these studies, or if these children were destined to “outgrow” these allergies at that time without any intervention. Studies that include control groups thus are important to help us understand the

impact of OIT. Rolinck-Werninghaus et al. [43] initially published results of three individuals enrolled in a randomized, placebo-controlled study of OIT for cow's milk or egg in which desensitization, but not tolerance, was achieved. Two years later, the same group published results from 45 individuals, using the same protocol, with a treatment arm receiving OIT and a control group maintaining an elimination diet [44]. After reaching a home daily dose of 250 mL of milk or 4.5 g of egg protein, participants discontinued daily dosing and resumed an elimination diet for 2 months, following which a DBPCFC was performed. In this larger, more recent study, similar percentages (~35%) in both the treatment and placebo groups displayed tolerance by passing the DBPCFC off therapy, although there were a number of “partial responders” to OIT, which increased the rate of any response to 64%.

Longo et al. [45] also included a control group in a study of milk OIT in 60 children 5 years of age or older with histories of severe allergic reactions to milk ingestions. Allergy was confirmed by reaction to 0.8 mL or less of whole milk on DBPCFC. About 80% of participants had milk-specific IgE levels greater than 100 kU/L, and the remainder had levels between 85 and 100 kU/L, with mean skin prick test wheal sizes of 11 to 12 mm. Half received immunotherapy for 1 year, and half were observed with conventional elimination management. OIT began with 10 days of steadily increasing amounts of milk ingestion, beginning with drops of diluted milk, all administered with participants in the hospital. Escalating doses were administered several times per day, and after discharge, participants increased daily doses every other day until a daily dose of 150 mL was reached. Fifteen of 30 in the treatment group showed significant declines in serum milk-specific IgE levels, with no change seen in the observation group. Of those treated with OIT, 36% were able to tolerate a single feeding of 150 mL in an open feeding at the end of 1 year, 54% could ingest 5 to 150 mL with no reaction, and 10% (3 children) could not complete the study because of respiratory or abdominal symptoms. Conversely, most of the children in the observation group saw no change in their milk reaction threshold, and none were able to tolerate 5 mL. Almost all individuals in the OIT group experienced allergic symptoms during the protocol, primarily involving urticaria and angioedema; intramuscular epinephrine was used on four individuals during the inpatient phase and on one as an outpatient. None experienced hypotension or loss of consciousness, and none required intravenous fluids, resuscitation, or intubation. This study is notable for its inclusion of individuals with severe reaction histories. Although these results are encouraging for the prospect of desensitization, they do not address the question of tolerance.

A randomized, double-blind, placebo-controlled study of milk OIT was published in 2008 [46•]. Nineteen partic-

ipants 6 to 17 years of age with milk allergy confirmed by challenge were enrolled. Those in the treatment group (12 of the 19) advanced to home doses with a maximum of 500 mg for 3 to 4 months before a final DBPCFC was performed at study conclusion. On initial challenge, both groups reacted at a median threshold of 40 mg. This amount increased to a median tolerated dose of 5140 mg in the treatment group at the end of the study, whereas every patient in the placebo group continued to react at 40 mg. Challenges were not performed off OIT, so this was also a protocol that addressed desensitization, but not tolerance. Immunologically, no significant change was seen in milk-specific IgE levels in either group. While other studies of food OIT documented declines in food-specific IgE levels [44, 45, 47], the authors pointed out that those declines typically are not seen until after 6 to 24 months of treatment. Milk-specific IgG₄ levels did increase in the treated group, although the degree of increase did not correlate statistically with clinical changes.

Following the double-blind, placebo-controlled phase of this study, participants who successfully completed OIT and tolerated more than 2540 mg of milk in their final challenges were eligible for an open-label maintenance study to evaluate the safety of continued milk ingestion after OIT and the efficacy in allowing individuals to tolerate increasing amounts of cow's milk protein [48]. Fifteen continued maintenance OIT for 3 to 17 months, with steadily increasing daily doses individualized based on thresholds and reaction histories. Individuals were able to tolerate increasing daily dose amounts, as the median increased from 500 to 4000 mg. At the end of open-label dosing, 13 participants were challenged with a maximum cumulative dose of 16,000 mg, and 6 were able to tolerate the entire amount. The remaining seven reacted at 3000 to 16,000 mg. Challenge reactions tended to be mild, with none receiving epinephrine. Reactions to home doses were not uncommon, with local reactions the most frequent (17% of doses), and the frequency of reactions generally declining over time on maintenance OIT. Many home-dose reactions were not treated; of all home doses, 3.8% resulted in treatment with diphenhydramine, and 0.2% (six doses among four individuals) with epinephrine. The authors did highlight the unpredictable nature of reactions, with several systemic reactions occurring at previously tolerated doses, frequently in association with exercise or viral illness. With respect to immunologic parameters, the authors' previous suspicions were confirmed, as milk-specific IgE levels decreased with time on OIT, and milk IgG₄ levels continued to increase; skin test reactivity also disappeared in most. The study demonstrates that thresholds continue to increase over time on maintenance OIT; future studies will need to determine how essential regular intake is to maintaining tolerance.

Safety of Oral Immunotherapy

Because the current standard of care consists of avoidance and readiness to manage an accidental exposure reaction, concerns obviously exist regarding therapies such as OIT that regularly expose an allergic individual to an allergen. Investigators analyzed the large, open-label peanut OIT study discussed above [42••] to examine safety at all stages of the protocol: initial escalation day, buildup, and home dosing [49]. Of note, individuals with a history of severe, life-threatening anaphylaxis to peanut ingestion or poorly controlled asthma were excluded from this study. Individuals kept daily symptom diaries throughout the home-dosing stage. At the time of analysis, 20 of 28 had completed all 3 study phases. The frequency and severity of reactions were greatest on the initial (desensitization) day, and least with home dosing. During initial desensitization, 93% of participants experienced some type of reaction. These were generally mild and most frequently upper respiratory, although 15% received epinephrine for severe skin symptoms. Risk of symptoms during the buildup phase was 46%, and no individual experienced severe symptoms. Home doses seemed to be the safest, with only a 3.5% estimated risk of any reaction among the more than 10,000 home doses administered. When these reactions occurred, they also were most commonly mild, although two individuals did receive epinephrine; interestingly, both had tolerated the same dose the day before, and both were able to complete the study. The authors favorably contrast the reaction rates seen in this study with data from the earlier subcutaneous peanut immunotherapy study, in which 23% of rush and 39% of maintenance injections were associated with systemic reactions [29], although they caution that this study was performed in a select group of patients and that more studies are needed to ensure safety.

This group published a recent update on reactions to peanut OIT, identifying five patterns that seem to indicate a higher risk for reacting to a previously tolerated dose [50]: concurrent illness (particularly with fever), suboptimally controlled asthma, timing of dose administration after food ingestion (reactions more common on an empty stomach), physical exertion after dosing, and dosing during menses. It is interesting to note that without these factors present, many of the doses had been tolerated for weeks to months. Previous investigators studying egg and milk OIT also identified "augmentation factors" that seemed to predispose individuals to reactions [44]. Recognizing these factors (infection, exercise, pollen allergy, and irregular intake) allowed doses to be temporarily reduced and seemed to prevent subsequent reactions. Understanding and recognizing these factors will likely continue to be important to further improve the safety profile of OIT.

Conclusions

Although the current standard of care for food allergy requires constant alertness on the part of patients and their families, the prospect of active therapy in the not-too-distant future seems real. Researchers are investigating multiple approaches to treatment. One of these, OIT, seems to be effective at inducing desensitization and relatively safe under appropriate supervision. Reactions to home OIT doses generally have been mild, and it remains an unanswered question if individuals who undergo treatment with several foods will experience an “additive effect” that causes multiple milder reactions to lead to a more severe reaction. Most of the completed studies have also not investigated how long desensitization will last, but tolerance (which persists beyond the point at which an individual is receiving daily doses) remains the ultimate goal. Mechanisms are still being understood, and multiple questions remain about this therapy, including how to identify the best candidates as well as those at risk of reactions, optimal doses, and duration and route of therapy. Investigators hope to answer these and other questions before OIT moves beyond the research setting and into widespread clinical use, but for patients with food allergies along with their families and physicians, there seems to be reason for optimism.

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