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Oral Desensitization for Food Hypersensitivity

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Synopsis

Over the past 20 years, food allergy has become an increasingly prevalent international health problem primarily in developed countries[1]. An explanation for this increased prevalence is currently under investigation as it is not well understood. Allergic reactions can result in life threatening anaphylaxis over a short period of time, so the current standard of care dictates strict avoidance of suspected trigger foods and accessibility to injectable epinephrine. Intervention at the time of exposure is considered a rescue therapy rather than a disease modifying treatment. In recent years, investigators have been studying allergen immunotherapy as a way to promote induction of oral tolerance. These efforts have shown some promise towards a viable disease modifying therapy for food allergies. This review will examine the mechanisms of oral tolerance and the breakdown that leads to food allergy, as well as the history and current state of oral and sublingual immunotherapy development.

Keywords

food allergy; oral tolerance; oral immunotherapy; sublingual immunotherapy

Introduction

Food allergies are adverse reactions to foods that have an immunologic basis, as opposed to food intolerance, which does not involve the immune system. The clinical reactions that occur in food allergy may be IgE mediated or non-IgE mediated. Non-IgE mediated

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reactions to foods can involve other components of the immune system and will not be discussed in this review. Typical IgE mediated symptoms of a reaction may include hives, swelling, vomiting, abdominal pain, wheezing, dyspnea, and shock. These symptoms occur within a few minutes and up to 2 hours following ingestion of the food. Food related anaphylaxis is the leading cause of anaphylaxis that is treated in emergency departments in America and Europe and is estimated to cause as much as 30,000 anaphylactic reactions, 2000 hospital admissions, and 200 deaths per year in the United States alone[2]. In general, food allergies have been on the rise, affecting 6–8% of children less than 4 years of age, and approximately 4% of Americans over 10 years of age[3, 4]. The prevalence of food allergy is also increasing over time. The true prevalence of food allergy has been difficult to establish since most prevalence studies have focused on the most common foods and studies differ in design and definition of food allergies. It has been estimated by the Centers for Disease Control and Prevention that over a ten year period, the prevalence of childhood food allergy increased by 18% with approximately 3.9% of children currently being affected[5]. Recent guidelines by a National Institute of Allergy and Infectious Diseases (NIAID) expert panel released in December 2010 have focused on a “best practice” clinical guideline on the diagnosis and management of food allergies[6].

The most common food allergens in the United States include milk, egg, peanuts, tree nuts, wheat, soy, fish, and shellfish[6]. Among these foods, allergies to peanuts and tree nuts are considered quite significant as they may be life-long and reactions can often be quite severe. It is estimated that only 21% of children with peanut allergy spontaneously outgrow their allergy[7]. Furthermore, clinical reactions in peanut allergic patients are the most common causes of food related anaphylaxis[8]. In contrast, milk and egg allergies generally resolve in a majority of children with the allergies compared to those with peanut, tree nut, fish, or shellfish allergy. Despite this trend, recent data has shown that milk and egg allergies are becoming more persistent and children may be outgrowing these allergies by adolescence rather than in the first 5–6 years of life, as it had been previously thought[9, 10].

While fatal reactions to foods implicated in food allergy are not common[11], the burden of disease is very significant not only to the patients but to the families, schools, and communities of the patients. In a study on quality of life in children with peanut allergy compared to children with insulin dependent diabetes mellitus, the patients with peanut allergy reported a poorer quality of life[12]. Fear of a potential reaction such as severe anaphylaxis and needing to take preventative measures may affect participation in social activities, eating outside the home, and choosing to home school children[13].

Once a patient is given a diagnosis of food allergies, the current standard of care dictates strict avoidance of the food allergen and ensuring availability of rescue medications in the case of a mild or severe reaction. These medications are typically an antihistamine such as diphenhydramine for milder symptoms, and injectable epinephrine for more severe, life threatening symptoms. A food allergy action plan is recommended for patients and their families to have available as a guide during a suspected reaction.

Aside from avoidance, active disease modifying therapy for food allergy has been studied in recent years. Traditional subcutaneous immunotherapy, also known as “allergy shots,” has been studied over 10 years ago, and this type of therapy was able to induce desensitization. However, due to the high rate of systemic reactions during immunotherapy[14, 15], this type of treatment is not appropriate. Given the safety issues from subcutaneous immunotherapy, oral immunotherapy and sublingual immunotherapy has been more heavily studied and will be the focus of this review.

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Gastrointestinal Immunity and Oral Tolerance

The largest immunologic organ in the body is the GI tract, which has continual exposure to the external environment through the large surface area of its epithelial layer. Through this large surface area, a tremendous amount and variety of food proteins come in contact with our immune cells. Rather than mount an immune response against these proteins, the "normal" reaction of the immune system is not to react to them. This concept is known as tolerance, which refers to active suppression by the immune system of an immune response. A failure to develop oral tolerance or a loss of oral tolerance is hypothesized to be the primary problem in food allergy[16].

When a food is ingested in a non-allergic person, the food proteins are broken down and digested by gastric acids and digestive enzymes within the lumen of the GI tract. This process decreases the immunogenicity of the proteins. The normal process of digestion may be disrupted and lead to a breakdown in oral tolerance induction[17]. The lining of the GI tract consists of a single layer of epithelium overlying loose connective tissue containing lymphocytes. Food protein antigens are absorbed by a number of specialized cells including the dendritic cell, microfold cell (or M cell), and epithelial cells themselves. These cells may then process and present the food antigens to gut-associated lymphoid tissues (in the case of GI dendritic cells), subepithelial antigen-presenting cells (in the case of M-cells), or to primed T-cells (in the case of epithelial cells)[17].

The development of tolerance relies on a number of important factors. These include: the form and dose of the antigen, genetics of the host, normal intestinal flora of the host, and age of the host. As mentioned above, gastric acidity in addition to gastrointestinal proteases are important in normal digestion, and a breakdown in this process leads to a change in the form of the antigen. Antigens in the soluble form are more tolerogenic than antigens in particulate form. The solubility of food proteins may be affected by how the foods are prepared. In peanuts, for example, roasting decreases the solubility and enhances binding of peanut-specific IgE[18].

The dose of food antigen exposure influences how oral tolerance develops. High doses of antigen favor an anergy-driven pathway to tolerance while low doses of antigen promote a suppressive pathway to tolerance via Regulatory T cells. Regulatory T cells (Tregs) are a subset of T lymphocytes that possess the ability to decrease the proliferative activity of other lymphocytes. The pathway to high dose tolerance involves T-cell receptor ligation in the absence of costimulatory signals such as soluble Interleukin-2 (IL-2), or interactions between CD28 on T cells with either CD80 or CD86 on antigen presenting cells[17]. Low dose tolerance can be achieved by the action of Tregs and CD8+ T cells through production of cytokines such as IL-10 and TGF–β. An important clinical model of food allergy occurs in a condition where Tregs fail to develop, known as IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked). In patients with IPEX, significant food allergies develop along with eczema, endocrinopathy, enteropathy, and immune dysregulation[19].

The genetics of the host influence the development of tolerance, but the role of genetic factors has not been as clearly understood. In murine models, strain-dependent susceptibility to food allergy has been demonstrated, while in humans, limited studies examining associations between specific HLA antigens with food allergies has shown variable results. There is some evidence that in peanut allergies, specific HLA class-II genotypes may be found in a higher frequency of peanut allergic patients compared to controls[17]. This area continues to be investigated. The normal flora of the host also may affect tolerance

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induction, suggested by some evidence in studies of germ free versus conventional murine models.

The age of the host is another factor that may be important in the development of tolerance. Early introduction of allergen may be important to prevent the development of food allergies in young children. In some countries where a peanut-based snack is introduced in the diet of young children (such as Israel), the rates of peanut allergies are low compared to other countries with children that are genetically similar (such as Jewish children in the United Kingdom)[20, 21]. A study investigating the role of age and timing, in the development of allergy is currently underway in the United Kingdom. This study, the Learning Early About Peanut Allergy (LEAP) study, involves children between 4–10 months of age who are randomized to either eat peanuts regularly three times a week or to avoid peanuts through the age of 3 years. Study completion is anticipated by 2013 (http://www.leapstudy.co.uk).

These normal mechanisms and factors that influence the development of oral tolerance are lost or insufficient in patients with food allergy. Methods to regain or induce tolerance are now being studied. It is important to understand the difference between desensitization and tolerance when reviewing immunotherapy. Desensitization is a state in which effector cells involved in a specific immune response develop reduced reactivity or become nonreactive upon increased introduction of an allergen. In a desensitized state, an individual may be nonreactive while regularly receiving the allergen. However, when the regular administration ends, the previous amount of reactivity returns. This is not the goal of immunotherapy, which is to reach a state of tolerance, where the nonreactive state remains present permanently.

Oral Immunotherapy (OIT)

Oral immunotherapy involves the regular administration of small amounts of allergen by the oral route to first rapidly induce desensitization then over time induce tolerance to the allergen. Some reports have considered immunotherapy that is ingested and immunotherapy that is administered sublingually as two forms of oral immunotherapy. For the purposes of this review, oral immunotherapy (OIT) will refer specifically to ingested immunotherapy and sublingual immunotherapy (SLIT) will refer to immunotherapy that is administered under the tongue. Patients undergoing OIT generally ingest a mixture of protein powder in a vehicle food such as apple sauce. Patients undergoing SLIT generally receive a small amount of liquid extract under their tongue. Both treatments are typically initiated in a controlled setting where gradually increasing doses of allergen are given up to a targeted dose. Following this, in standard protocols, the majority of dosing is done at home.

Although there have been scattered reports in the literature on the use of OIT for food allergy over the last 100 years, the majority of research on OIT has occurred in the last 25 years beginning with work by Patriarca, who demonstrated the successful treatment of allergies to cow’s milk, egg, fish, and fruits with standardized OIT protocols [22]. Bauer, in a 1999 case report of a 12 year old girl with cow’s milk allergy, showed that OIT using a rush protocol could also be effective [23]. Further work by Patriarca showed that clinical desensitization using OIT was accompanied by changes in allergen-specific IgE and IgG4 similar to that seen in subcutaneous aeroallergen immunotherapy [24, 25]. Although skepticism in the scientific community remained, these studies suggested that the defect in oral tolerance causing food allergy could potentially be overcome through OIT. This realization, combined with the rise in public awareness of food allergies, set the stage for the significant increase in OIT research seen over the past 5 years (Table 1).

To broaden the scope of OIT, the next generation of OIT studies shifted the focus of treatment from adults to children and began to investigate the potential of OIT to induce

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long term tolerance. In a pilot study of OIT for egg allergy in children [26], Buchanan demonstrated the safety of a 24 month egg OIT protocol involving a modified rush desensitization phase, build-up phase, and maintenance phase. Successful desensitization by the protocol was demonstrated by double-blind, placebo-controlled food challenges (DBPCFC) but, no conclusions could be made regarding long-term tolerance. A randomized study of OIT versus an elimination diet for cow's milk allergy and egg allergy by Staden focused on the persistence of induced tolerance as measured by DBPCFC 2 months after the discontinuation of therapy [27]. This larger study of 45 children, 25 receiving OIT and 20 on elimination diets, demonstrated similar rates of allergy resolution in the OIT and elimination diet groups marked by significant reductions in allergen-specific IgE. However, partial responders in the OIT group also showed reduced allergen-specific IgE but to a lesser degree, whereas non-responders showed no change in allergen-specific IgE. This result suggested immunological suppression through OIT but its effectiveness in inducing tolerance remained unclear.

A common criticism of the early OIT studies was the exclusion of patients with more severe disease. To address this concern, Longo conducted a study of OIT on children with severe reactions to cow's milk that typically resulted in exclusion from other OIT studies [28]. In addition, the children were greater than age 5 and had larger levels of cow's milk-specific IgE (> 85 kU/L) making it less likely that they would naturally outgrow the allergy. Significantly more children in the OIT group became fully tolerant to cow's milk after the treatment compared to those on an elimination diet (36% versus 0%). In addition, 16 of the 19 children who did not become fully tolerant were able to ingest larger amounts of cow's milk than the control group potentially offering limited protection from accidental ingestions. Importantly, side effects in this highly allergic group were very common although only 3 of the 30 subjects on OIT were unable to complete the protocol. Nevertheless, the study demonstrated that OIT could be efficacious in almost any type of allergic patient.

Studies to this point compared OIT to the standard of care, namely a strict elimination diet. To more rigorously define the effects of OIT, Skripak, in children with cow's milk allergy, conducted the first double-blind, placebo-controlled study of OIT [29]. In agreement with prior studies, children receiving cow's milk OIT had a significant increase in reaction threshold when compared to placebo with an average cumulative dose of 5140 mg versus 40 mg respectively. More importantly, children receiving cow's milk OIT reported symptoms with 45% of daily doses compared to only 11% reported by the placebo group. Although the majority of reported symptoms with cow's milk OIT were local, about 10% of all OIT doses required treatment with an antihistamine and 0.2% (4 doses) required epinephrine compared to 1% and 0% for each treatment respectively in the placebo group. Although the question of whether the reported symptoms truly required treatment can be raised, it must be remembered that the vast majority of dosing in current OIT protocols is performed at home without medical supervision.

Before 2009, the literature on the treatment of peanut allergy, widely considered a more severe and lifelong food allergy, consisted mostly of sporadic case reports with larger OIT studies focused on cow's milk and egg allergy. Since then, the results of 3 independent prospective studies of OIT for peanut allergy have been published. Clark described 4 children with challenge documented peanut allergy who underwent peanut OIT [30]. Side effects with dosing were common but mild in nature despite the presumed increased severity of peanut allergy. All 4 children had significant increases in threshold, each ingesting between 10 to 12 peanuts (2.38 to 2.76 grams peanut protein) during the post-intervention challenge. A subsequent study by Jones not only verified these challenge results in a larger cohort but also was the first attempt to broadly define the immune changes underlying OIT's

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effects [31]. The protocol was remarkably successful as 27 of 29 children safely completed a 16 peanut (3900 mg peanut protein) food challenge. The remaining 2 children discontinued the challenge after 9 peanuts (2100 mg), considerably more than expected in a typical accidental ingestion.

More importantly, Jones demonstrated that underlying the clinical benefits of OIT were changes to multiple aspects of the immune system leading to the dampened allergic response. These changes included not only the decrease in allergen-specific IgE and increase in allergen-specific IgG4 previously demonstrated by others (Table 1), but also a suppression of mast cells and basophils, an increase in T regulatory cells (T_{Regs}), and a change in cytokine profile. Additionally, microarray analysis of patient T cells revealed changes in several apoptotic pathways although the significance of this result is still unknown. Blumchen, in 14 children with challenge documented peanut allergy, demonstrated that the increase in threshold shown by Clark and Jones persisted despite the discontinuation of OIT for 2 weeks prior to challenge [32]. Cytokine analysis demonstrated a clear decrease in T_H2 cytokines without a concomitant increase in T_H1 cytokines arguing against OIT causing a shift in the T_H1/T_H2 skewing. Rather a decrease in IL-2 was noted possibly suggesting clonal anergy or deletion as a possible mechanism of OIT.

Sublingual Immunotherapy (SLIT)

Amidst the increased attention on OIT, some small studies investigated the potential for immunotherapy by the sublingual route. Like OIT, sublingual immunotherapy (SLIT) involves the regular administration of a small amount of allergen, but in contrast to OIT where the allergen is ingested, with SLIT, it is held under the tongue for an arbitrary amount of time, typically 1 to 5 minutes. The hypothesized advantages of this modality include direct absorbance into the blood stream with avoidance of first pass metabolism in the liver, and access to immune cells in the oral cavity such as Langerhans cells that are thought to be protolerogenic in nature [33]. More practically, the advantages of SLIT include its ease of administration and potential for improved safety owing to the smaller doses that are allowed by its efficient absorption. One early case report by Mempel described a 29 year old woman with 3 episodes of anaphylactic shock after kiwi ingestion who underwent successful SLIT with subsequent maintenance of tolerance for 4 months off therapy [34, 35]. Enrique conducted the first double-blind, placebo-controlled study of SLIT on 29 adults with hazelnut allergy [36]. Significant increases in threshold were achieved but with half of the subjects diagnosed with oral allergy syndrome, its direct applicability to type 1 food allergy was not clear. Recently, the results of a double-blind, placebo-controlled study of SLIT in peanut allergic children were published by our group [37]. Children receiving 12 months of peanut SLIT therapy not only demonstrated an increased threshold to peanut ingestion but also changes in the immune response including basophils, mast cells, peanut specific IgE and IgG4, and cytokines. Similar to the OIT studies, this suggests not only successful desensitization but also the potential for the induction of long-term tolerance.

Safety

As there are no treatments currently available for food allergy and the risk of accidental exposure remains high, the success of these recent studies on OIT and SLIT has increased the pressure to bring these treatments to market sooner. However, there are a number of reasons to exercise patience. In a paper by Hofmann analyzing the safety of peanut OIT, 93% of children experienced symptoms during the initial dosing day including 15% of which required epinephrine [38]. Subsequent home dosing was safer but 2 subjects required epinephrine for reactions. Although rare this remains important in that, as stated previously, the majority of doses in current OIT and SLIT protocol as administered at home without

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medical supervision. In a letter to the editor, Varshney described the development of symptoms during OIT with episodes of fever, during exercise, when taken on an empty stomach, and during menses in children who had previously tolerated the eliciting dose [39]. Similar patterns of reactions have also been reported during cow's milk and egg OIT [27]. Continued study to further understand these patterns of reactions and to identify additional triggers is necessary to assure patient safety. Another reason for patience is the variable but significant drop out rates with current OIT protocols. Blumchen's study of peanut OIT reported a 35% drop out rate with children withdrawing because of adverse reactions or poor compliance [32]. Administration of OIT can be difficult with the patient's natural aversion to the food allergen and the likelihood of reactions. With dosing recommended as daily and potentially lifelong, concerns for the efficacy and safety of OIT in noncompliant patients must be addressed. Although the ease of administration and safety profile of SLIT make it an attractive alternative to OIT, the initial change in threshold reported during peanut SLIT, while significant, remains inferior to that of peanut OIT. The clinical significance of this lower reaction threshold remains to be studied as well as the long term risks and benefits of SLIT.

Overall, immunotherapy in the form of OIT and SLIT for food allergy has advanced significantly in recent years with more progress expected in the near future. With ample evidence of successful desensitization, ongoing studies of OIT have been focusing on blinding to more precisely describe safety and overall efficacy, as well as on immunological parameters to predict the likelihood of long-term tolerance. OIT is also being studied in conjunction with omalizumab anti-IgE therapy (ClincalTrials.gov #NCT00932282). Regarding SLIT, an ongoing study through the Consortium of Food Allergy Researchers (CoFAR) has been investigating the use of SLIT in adults with peanut allergy (ClinicalTrials.gov #NCT00580606). Lastly, in contrast to prior studies focused on either OIT or SLIT, investigators at Johns Hopkins University have been studying the use of both OIT and SLIT modalities in tandem for the treatment of cow's milk allergy (ClinicalTrials.gov #NCT00732654) and more recently for peanut allergy (ClinicalTrials.gov #NCT01084174).

Conclusions

In summary, food allergy is an IgE-mediated immediate type hypersensitivity that is thought to be a result of a breakdown in the normal process of oral tolerance. Although the prevalence of food allergy continues to rise, avoidance remains the standard of care as no disease modifying treatments are readily available. A large body of evidence has accumulated demonstrating the successful induction of desensitization by OIT. In addition, early evidence indicates successful desensitization by SLIT as well. Although questions regarding the safety of the treatments and the potential for the development of long-term immunological tolerance remain, OIT and SLIT offers some hope for the future treatment of food allergy.

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Table I

Results of Recent Prospective Studies of Oral (OIT) and Sublingual (SLIT) Immunotherapy for Food Allergy (excluding individual case reports).

Year	Author	Food Allergen	Type	Age	Blinded	Total Subjects	Completed Treatment	Completed Food Challenge	Immunoglobulin changes
1984	Patriarca	Milk, Egg, Other	OIT		No	19	15/19	14/15	n/a
2003	Patriarca	Milk, Egg, Other	OIT	3–55	No	59	38/59	n/a	↓IgE, ↑IgG4
2004	Meglio	Milk	OIT	5–10	No	21	15/21	n/a	IgE no change
2007	Buchanan	Egg	OIT	1–7	No	7	7/7	4/7	↓IgE, ↑IgG
2007	Staden	Milk, Egg	OIT	1–13	No	25	16/25	9/16	↓IgE
2008	Longo	Milk	OIT	5–17	No	30	27/30	11/27	↓IgE
2008	Skripak	Milk	OIT	6–17	Yes	13	12/13	4/12	IgE no change, ↑IgG4
2008	Staden	Milk	OIT	3–14	No	9	6/9	n/a	n/a
2008	Zapatero	Milk	OIT	4–8	No	18	16/18	n/a	IgE no change
2009	Clark	Peanut	OIT	9–13	No	4	4/4	3/4	n/a
2009	Jones	Peanut	OIT	1–16	No	39	29/39	27/29	↓IgE, ↑IgG4
2010	Blumchen	Peanut	OIT	3–14	No	23	14/23	3/14	IgE no change, ↑IgG4
2010	Itoh	Egg	OIT	7–12	No	6	6/6	3/6	↓IgE, ↑IgG4
2005	Enrique	Hazelnut	SLIT	19–53	Yes	12	11/12	5/11	IgE no change, ↑IgG4
2011	Kim (In Press)	Peanut	SLIT	1–11	Yes	11	11/11	0	↓IgE, ↑IgG4