

Oral Immunotherapy for Food Allergy

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Food allergy is an increasingly prevalent disorder with potentially life-threatening complications that requires life-altering changes in dietary habits and psychosocial interactions. The standard of care presently includes strict dietary elimination of the implicated allergen and ready access to injectable epinephrine; however, no active, definitive therapeutic options exist for food-allergic patients. Although the detailed immunologic mechanisms underlying the development of food allergy are still being fully defined, food allergy appears to be the direct result of a breakdown in oral tolerance. Thus, current therapeutic approaches to food allergy are focused on modulating the immunologic response to food proteins to promote induction of oral tolerance. In this review, we examine gastrointestinal mucosal immunity and the mechanisms of oral tolerance, as well as the breakdown in oral tolerance that promotes food allergy, and we also explore novel therapeutic interventions for treatment of food allergy.

Introduction

Over the past two decades, the prevalence of food allergy has increased, resulting in heightened public awareness of this potentially life-threatening disorder and recognition of the need for definitive therapeutic interventions. Current estimates suggest that food allergy affects 6% of children younger than 3 years of age and approximately 4% of adults in the United States [1,2••]. The prevalence of peanut allergy in particular doubled from 1997 to 2002 [3]. Food-induced anaphylaxis is the most common cause of anaphylaxis treated in hospital emergency departments [4,5], with peanuts and tree nuts accounting for the vast majority of life-threatening or fatal reactions to foods [6•]. At present, the standard treatment for food allergy includes strict avoidance of implicated food allergens and ready access to self-injectable epinephrine

[1,2••]. Strict avoidance diets are challenging for patients and families because of the difficulty in interpreting labels [7] and the presence of undeclared or hidden allergens in commercially prepared foods [8,9]. As a result, accidental ingestions are common, and up to 50% of food-allergic patients have an allergic reaction during a given 2-year period [10]. Because of the need for strict avoidance diets, the high incidence of accidental exposures, and the risk of severe or fatal reactions, a diagnosis of food allergy can be life altering for patients and families, resulting in significant anxiety, psychosocial stressors, and reduced health-related quality of life [11,12,13•].

Food allergy appears to result from aberrations in the normal induction of oral tolerance, resulting in a T-helper (Th) type 2-predominant CD4⁺ T-cell immune response and elevated levels of food allergen-specific IgE. Thus, recent work has focused on altering the food-allergic response through induction of oral tolerance to promote development of T-regulatory cells (Tregs) and immunologic skewing of the immune response toward a Th1 response. In this article, we review gastrointestinal (GI) mucosal immunity and oral tolerance and explore novel immunomodulatory therapies for food allergy, including oral immunotherapy (OIT) and sublingual immunotherapy (SLIT).

GI Mucosal Immunity

The GI tract is the largest immunologic organ in the body with an epithelial surface continuously exposed to the external environment [14,15]. The GI mucosal immune system has evolved innate and adaptive components that are adept at inhibiting responses to harmless antigens such as food proteins and commensal bacteria while mounting immunoprotective responses against pathogenic organisms in an effort to maintain the primary physiologic function of nutrient absorption. Dietary proteins represent a large antigenic load, with current estimates suggesting that in the average US diet, 130 to 190 g of protein are absorbed daily [14,15]. Despite the increasing prevalence of food allergy, adverse immunologic responses to foods are remarkably rare considering the myriad antigens encountered by the GI mucosal immune system on a daily basis and the complex nature of the gut-associated mucosal immune response, in which tolerance of dietary antigens is the standard.

After ingestion, dietary proteins are processed by gastric acids and luminal digestive enzymes that destroy

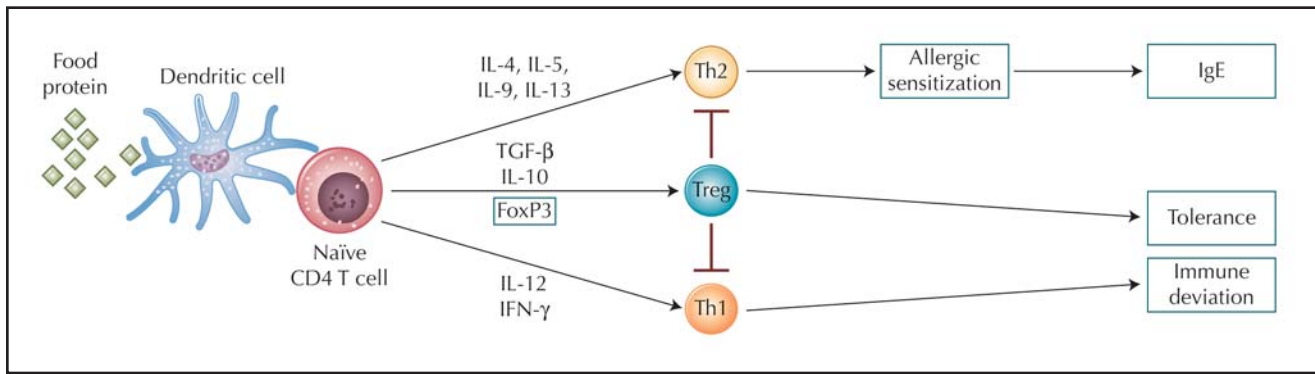


Figure 1. Food antigen exposure in the gastrointestinal mucosal immune system can result in oral tolerance induction or allergic sensitization, depending on multiple factors (eg, antigen dose and processing, timing of the exposure, and host susceptibility to atopic disease).

FoxP3—forkhead box P3; IFN—interferon; IL—interleukin; TGF—transforming growth factor; Th—T-helper cell; Treg—T-regulatory cell.

conformational epitopes, putatively reducing the immunogenicity of the protein. In animal models, factors that disrupt normal digestion and antigen processing have been shown to result in a breakdown in oral tolerance induction [16,17]. The GI tract is lined by a single layer of epithelium that covers a stroma of loose connective tissue populated by lymphocytes. Dietary antigens are taken up at different sites in the GI tract, including the dendritic cell, microfold cell (M cell), and epithelial cell routes [14,15]. GI dendritic cells sample the lumen of the GI tract, presenting and processing the antigen to gut-associated lymphatic tissues. A specialized population of epithelial cells called M cells overlay the Peyer's patches and allow for efficient delivery to subepithelial antigen-presenting cells to activate Tregs, usually resulting in suppression of immune response. Dietary proteins that escape proteolysis in the gut can be taken up by intestinal epithelial cells. The epithelial cells may act as nonprofessional antigen-presenting cells given that they constitutively express major histocompatibility complex class II molecules on their basolateral membranes [18] and can present antigen to primed T cells.

Oral antigen exposure generally results in one of the following outcomes: 1) local, noninflammatory secretory IgA production at the GI mucosal surface; 2) priming of the systemic immune response to protect against the antigen upon re-exposure; or 3) induction of local and systemic immunologic tolerance to prevent adverse immunologic responses and collateral tissue damage upon antigen re-encounter. Food proteins present in the normal diet also play a critical role in stimulating maturation of the immune system. Mice raised on a balanced but protein-free diet have poorly developed gut-associated lymphoid tissue [19]. Such mice also have low numbers of lymphocytes and reduced levels of circulating IgG and IgA, as well as cytokine production consistent with Th2 responses.

Mechanisms of Oral Tolerance

Oral tolerance is defined as the specific suppression of cellular or humoral immune responses to an antigen by

prior oral administration of the antigen [14,15,20]. This response likely evolved as an analogue of self-tolerance to prevent hypersensitivity reactions to food proteins and commensal bacterial antigens. Mechanisms of oral tolerance induction include clonal anergy or deletion or active suppression (Fig. 1). The antigen dose is a primary factor in determining the method of oral tolerance induction, with high doses of antigen favoring anergy-driven oral tolerance and low doses of antigen promoting Treg induction [14,21]. Besides the antigen dose, other factors important in oral tolerance induction include the age and genetic susceptibility of the host, host commensal flora, route of antigen exposure, and antigen composition, with soluble antigens being more tolerogenic than particulate antigens [22]. The potential roles of gastric acid blockers, as well as dietary lipids, antioxidants, and vitamins in the modulation of allergen processing and immune cell activation in relation to oral tolerance induction are also intriguing [23••].

Lymphocyte anergy results from T-cell receptor ligation in the absence of costimulatory markers, such as interleukin (IL)-2, or CD28, CD80, and CD86 counterreceptors, whereas mechanisms of induced deletion include Fas (CD95)-mediated apoptosis or cytokine blockade. Low doses of antigen promote immunosuppression mediated by suppressor CD8⁺ T cells and Tregs through production of IL-10 and transforming growth factor (TGF)-β [14].

Antigen-specific Tregs suppress immune responses in lymphoid tissues, in which they inhibit generation of effector T cells, and in target organs through cytokine production. Although this is still the subject of some debate, at least one class of Tregs, the natural Tregs (nTregs), develop intrathymically, whereas growing evidence suggests another population, called adaptive Tregs (aTregs), develop from naïve CD4⁺ T-cell precursors in the periphery. At least two types of aTregs have been described: Tr1 cells are characterized by high levels of IL-10 production and do not express the transcription factor forkhead box P3 (FoxP3) [24,25], while another group of aTregs is induced by TGF-β, expresses FoxP3, and displays suppressive activities identical to those of

nTregs even though they develop extrathymically [26]. Original reports of the phenotypic and functional characteristics of Tregs by Sakaguchi [27,28] identified Tregs on the basis of stable expression of the high-affinity component of the IL-2 receptor, CD25.

Further work then identified FoxP3 as the “master regulator” of nTreg and aTreg lineages in mice and humans. Enforced expression of FoxP3 in CD4⁺CD25⁺ T cells has shown induction of Treg function and phenotypic features, while TGF- β treatment has promoted the expression of FoxP3 in CD4⁺CD25⁺ naïve T cells [29,30]. TGF- β recently garnered much attention because of its emerging roles in the differentiation of both inducible FoxP3⁺ Tregs and ROR γ ⁺ Th17 cells, with IL-2 and IL-6 serving as switch factors between Tregs and Th17 cells, respectively [31,32]. At present, little is known about the role, if one exists, of the Th17 response in food allergy, but work in other models suggests counterregulation between the Th17 and Treg responses [31].

Food hypersensitivity likely results from a failure to establish oral tolerance or a breakdown in existing tolerance. Current data suggest that defective regulatory T-cell development plays a central role in development of food allergy. Mutations in human FoxP3 are associated with immune dysregulation polyendocrinopathy enteropathy X-linked disorder, a fatal X-linked disorder characterized by profound immune dysregulation, severe enteropathy, food allergy, and endocrinopathy [33]. Beyer and colleagues [34] have shown that in children with non-IgE-mediated milk allergy, active GI disease is associated with high Th2- and low Treg-associated cytokines compared with controls.

Induction of tolerance in infants and toddlers may be important for preventing the development of food allergies. Interestingly, children in countries that have peanut snacks that are safe for infants to consume have relatively low rates of peanut allergies [35]. Randomized, controlled trials are under way to evaluate whether high doses of peanut protein in high-risk infants are more effective at preventing peanut allergy than avoidance therapy. The LEAP Study (Learning Early About Peanut Allergy, <http://www.leapstudy.co.uk>) is enrolling 480 children 4 to 10 months old who have eczema and are allergic to egg (such children have a 20% chance of developing peanut allergy). Each child will be randomly assigned to avoid consumption of peanuts or fed an age-appropriate peanut snack 3 times per week (~ 6 g of peanut per week). The rates of development of peanut allergy by age 5 years will be compared.

Proposed Therapeutic Modalities for Food Allergy

Because food allergy is believed to result from a breakdown of normal oral tolerance induction [14], novel immunotherapeutic strategies designed to alter the immune system's response to food allergens are under

investigation (Table 1). When discussing mucosal immunomodulatory therapies for food allergy, two relevant definitions must be clarified. *Desensitization* refers to protection from life-threatening anaphylaxis that can be short term or prolonged with ongoing therapy. Possible mechanisms of desensitization include increased IgG and reduced IgE antibodies, as well as decreased mast cell and basophil activation and release of inflammatory mediators. In contrast, *tolerance* refers to active modulation of the immune response to promote Treg development and immunologic skewing away from a Th2 response. Traditional injection immunotherapy has been effective for allergic rhinoconjunctivitis and asthma through induction of cellular and humoral mechanisms that results in disease modulation. In a recent study of grass pollen subcutaneous immunotherapy in adults with severe allergic rhinitis, clear clinical efficacy was associated with significant production of the anti-inflammatory cytokine IL-10, elevation of specific IgG4 and IgA, and induction of inhibitory antibody activity for histamine release and IgE-facilitated allergen binding to B cells [36]. Although it may have shown some benefit previously, food allergen subcutaneous immunotherapy is impractical and unsafe for use in routine clinical settings because of an unacceptably high rate of severe systemic reactions [37,38].

At present, alternatives to antigen injection—including injection with engineered antigen or ingestion of antigen via the GI route—are being evaluated. Immunization with engineered or mutated peanut protein allergens that have altered IgE epitope binding sites has shown promising results in murine models. Through recombinant genetic techniques, Li et al. [39,40] altered single amino acids within epitope-binding regions of Ara h 1, -2, and -3 peanut proteins. The recombinant proteins were administered rectally to C3H/HeJ mice. During a food challenge with peanut 10 weeks later, mice that received the recombinant proteins were protected from anaphylactic symptoms. In mice that received the highest dose of protein, IL-4, IL-13, IL-5, and IL-10 production were significantly decreased, and interferon- γ and TGF- β production were significantly increased. Other novel approaches to food allergen immunotherapy include use of peptide immunotherapy, DNA immunization, and immunostimulatory sequences to promote immune deviation from Th2 to a Th1 response [39,40]. Other therapies are in various stages of development and testing for food allergy. These therapies are designed to modulate nonspecifically the immune response and include Chinese herbal therapy, monoclonal IgE antibody therapy, and cytokine-specific therapy (eg, anti-IL-5).

Sublingual and Oral Immunotherapy

SLIT and OIT are therapeutic strategies that are being evaluated for their ability to induce desensitization and tolerance in patients with food allergy. SLIT uses a liquid

Table 1. Proposed therapies for treatment and prevention of food allergy and induction of oral tolerance

Therapy	Application	Research stage	Proposed immunologic mechanism
Allergen-specific therapies			
Mutated protein immunotherapy	IgE-mediated peanut allergy	Preclinical	Modified IgE-binding epitopes prevent activation of IgE but maintain T-cell responses; possibly switch from Th2 to Th1
Overlapping peptide vaccine	IgE-mediated peanut allergy	Preclinical	Small peptides cannot cross-link IgE bound to high-affinity receptors and induce mast cell degranulation; T-cell responses maintained
Plasmid DNA encoded vaccines	IgE-mediated peanut allergy	Preclinical	Induction of tolerance by endogenous production of allergen; murine models suggest strain-specific responses
Allergen-conjugated immunostimulatory sequences	IgE-mediated peanut allergy	Preclinical	Augment Th1 response via innate immune pathways (TLR9); studies in allergic rhinitis suggest clinical efficacy
High dose of allergen in at-risk infants (LEAP Study)	IgE-mediated peanut allergy	Clinical	Early induction of Th1 responses and oral tolerance
Sublingual immunotherapy	Oral allergy syndrome (hazelnut), IgE-mediated food allergy	Clinical	Possible switch from Th2 to Th1 and promotion of T-regulatory cell response
Oral immunotherapy	IgE-mediated milk, egg, and peanut allergy	Clinical	Possible switch from Th2 to Th1 and promotion of T-regulatory cell response
Generalized downregulation of the allergic response (not allergen specific)			
Chinese herbal medicine	IgE-mediated peanut allergy	Preclinical	Unknown
Humanized monoclonal anti-IgE antibodies	IgE-mediated peanut allergy; pilot studies in eosinophilic gastrointestinal disorders	Clinical	Inactivates IgE and prevents binding of IgE to high-affinity receptor (FcεRI) and subsequent mast cell activation
Immunomodulatory cytokine therapy (eg, anti-interleukin-5)	Eosinophilic esophagitis	Clinical	Modulates immune response by disrupting proinflammatory signals that promote eosinophil development
LEAP—Learning Early About Peanut Allergy; Th—T-helper cell; TLR—Toll-like receptor.			

extract that is administered under the tongue, whereas OIT generally involves the use of a protein powder that is often mixed in a vehicle food and consumed orally. Both interventions generally involve administering small yet increasing doses of antigen in a controlled setting, followed by regular home dosing of a maximum tolerated amount of antigen. Treatment is followed by an open or blind food challenge with antigen or placebo. In a study of SLIT for hazelnut allergy, 23 patients who primarily had symptoms consistent with oral allergy syndrome received hazelnut extract or placebo for 8 to 12 weeks [41]. In the subsequent food challenge, the mean hazelnut quantity that provoked symptoms increased 9 g from baseline in the hazelnut group versus 0.6 g in the placebo group ($P < 0.05$). Individuals in the hazelnut group also experienced significant increases in IgG4 and IL-10, although none were seen in the placebo group. SLIT was also used in a single case for treatment of

life-threatening kiwi allergy. Kiwi extract was used for SLIT, starting at an initial concentration of 100 mL of a 1-mg/mL stock, with maintenance therapy consisting of a 1-cm³ kiwi cube administered sublingually and then swallowed. After 5 years, kiwi SLIT was discontinued for 4 months because of a prolonged illness. A repeat skin test was smaller (5 mm vs 10 mm before SLIT), and labial application of kiwi fruit was negative, as was oral provocation with a 1-cm³ cube of kiwi [42,43]. This study case provides evidence to support prolonged desensitization after SLIT.

In a standardized OIT protocol for treatment of a variety of food allergies, Patriarca and colleagues [44] induced desensitization in 77% of participants. The most common food allergy was milk, followed by egg and fish. In comparison with age-matched food-allergic controls, individuals receiving OIT experienced a significant decrease in food-specific IgE and an increase

in specific IgG4. Using a 6-month OIT protocol in children with proven IgE-mediated hypersensitivity to milk, Meglio and colleagues [45] fully desensitized 15 of 21 children and partially desensitized three children. Even partial desensitization dramatically reduced the risk of severe reactions after unintentional ingestion of small quantities of cow's milk. Recently, seven individuals with egg allergy completed a 24-month protocol for egg oral immunotherapy [46••]. Four of the seven passed a double-blind, placebo-controlled food challenge to 10 g of egg at the conclusion of the therapy. Although three participants did not tolerate the 10-g dose of egg protein, each tolerated higher doses of egg protein than noted at entry into the study.

Although both SLIT and OIT have shown promising results, most studies reported to date have lacked control groups, and it has been suggested that the success of the therapy may be due to spontaneous resolution of the allergies that can occur with age, particularly in milk and egg allergies, which are generally "outgrown" in childhood. In 2005, Rolinck-Werninghaus and colleagues [47] reported data from three patients enrolled in a randomized, placebo-controlled study of oral tolerance induction therapy for cow's milk or egg allergy. Home daily dosing was conducted until patients achieved tolerance to 250 mL of milk or 4.5 g of egg protein, which happened after 37 to 52 weeks. Daily dosing was followed by an elimination diet for 2 months and then a double-blind, placebo-controlled food challenge. The two patients who underwent the final food challenge experienced moderate systemic allergic reactions similar to their symptoms before therapy. A subsequent study published in 2007 using the same protocol included 45 patients [48••]. At the follow-up food challenge, 9 of 25 children (36%) showed permanent tolerance in the tolerance induction group, compared with 7 of 20 (35%) in the elimination diet control group. The results suggest that oral tolerance induction therapy may not alter the natural course of tolerance development. However, in the tolerance induction group, seven children were considered partial responders or responders when they had regular antigen intake, boosting the rate of any response to 64%. Allergen-specific IgE decreased significantly in children who developed natural tolerance during the elimination diet and in those who received induction therapy. Even though partially tolerant patients would need a regular intake of allergen to maintain desensitization, this could protect patients against severe reactions or reactions resulting from accidental exposure to antigen.

A further controlled study of rush oral tolerance therapy for children with severe allergy to cow's milk found significant differences between those in the treatment group and those who followed an elimination diet [49]. Sixty children 5 years of age or older with a history of severe allergic reactions and significantly elevated IgE levels to cow's milk protein were divided into the follow-

ing groups: 1) specific oral tolerance induction to cow's milk and 2) milk-free elimination diet. After 1 year, 36% of children in the treatment group were completely tolerant to milk (≥ 150 mL/d), 54% could tolerate 5 to 150 mL of milk daily, and 10% did not complete the protocol because of persistent respiratory or abdominal complaints. Tolerance was confirmed in an open feeding observed by investigators. In contrast, in the group that maintained an elimination diet, all 30 patients failed a double-blind, placebo-controlled food challenge after 1 year. Half of the patients in the treatment group had significant decreases in IgE specific to cow's milk at 6 and 12 months. In the control group, milk-specific IgE levels remained essentially unchanged, and none of the children spontaneously acquired tolerance. In a recent study using rush oral immunotherapy for persistent cow's milk allergy, similar results were noted among nine children undergoing therapy. Six of nine participants reached the maximal dose of 120 mL of milk with only mild to moderate symptoms. Unlike the Longo et al. [49] study, no patient required oral corticosteroids or injectable epinephrine [50•]. A recently published randomized, placebo-controlled study of milk-allergic children who were treated with OIT also showed promising results. Nineteen children between 6 and 17 years of age received milk OIT (12 participants) or placebo (seven participants). After milk OIT, the median milk threshold dosing required to elicit symptoms increased from 40 mg to 5140 mg in the OIT group, whereas all individuals in the placebo group showed no change in their threshold dose. Although milk-specific IgE levels did not change significantly during treatment, milk-specific IgG4 levels were significantly increased in the treatment group. The most common reactions included oral pruritus and abdominal pain, with all patients on active therapy experiencing at least one adverse reaction; however, 90% of reactions were transient and required no treatment, suggesting that in controlled, highly supervised settings, milk OIT is a safe therapy that is effective for desensitization to milk protein. Future studies will evaluate whether long-term tolerance is induced [51••].

In our ongoing study of children with peanut allergy, which is rarely outgrown, we are experiencing similarly encouraging results with peanut OIT. Twenty-nine children have been enrolled in a protocol that ends with an open food challenge to 3.9 g of peanut protein. Presently, 93% of participants have ingested 3.9 g of peanut protein during the challenge while receiving OIT. During the study, participants have experienced typical allergic symptoms, primarily in the initial phases of therapy. Peanut-specific IgE increased initially but then decreased at 12 and 18 months, whereas peanut-specific IgG4 increased significantly throughout the study. After 6 months on therapy, titrated skin prick tests and basophil activation were significantly decreased, whereas peanut-specific FoxP3⁺ Tregs increased. The initial results suggest that peanut OIT can safely establish desensitiza-

tion in peanut-allergic children. Studies are ongoing to determine the possibility of clinical tolerance induction subsequent to OIT.

Conclusions

Despite improved food allergy diagnostic techniques and advances in the biochemical characterization of food allergens, definitive therapy for food allergy has remained elusive. Recent work evaluating induction of tolerance by OIT and SLIT, as well as other novel therapeutic approaches has generated renewed optimism that a definitive therapy for food allergy is on the horizon. To date, therapy aimed at inducing tolerance has been safe and well tolerated, with allergic reactions controlled by antihistamines, steroids, or epinephrine. However, treatment protocols have been initiated in highly supervised research settings and with small numbers of patients. Because these interventions place patients at risk for severe systemic reactions, induction of tolerance is not appropriate for broad implementation in clinical practice settings at this time. Although the progress made toward a definitive therapy has been substantial, many unanswered questions about food allergy remain, including the role of primary prevention strategies, natural history of food allergy, maternal diet during pregnancy and lactation, and food allergen exposure in infants and toddlers. Furthermore, an improved understanding of the GI mucosal immune response and the molecular mechanisms of oral tolerance induction is necessary to develop informed treatment strategies and identify future therapeutic targets. Still, safe, affordable, and easily administered immunomodulatory therapy for food allergy is an emerging reality, providing hope and optimism for patients with food allergy and expanding the future therapeutic armamentarium to improve the care and quality of life of patients with food allergy.

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Disclosure

Dr. Burks serves as a consultant for Novartis, McNeil Nutritionals, and Mead Johnson Nutritionals; is a minority stockholder in Allertein Therapeutics and MastCell; serves on the advisory board for Dannon Co. Probiotics; serves on the speakers' bureau for EpiPen/Dey; serves on the data monitoring committee for Genentech; serves on an expert panel for Nutricia; and has received grants from Gerber and Mead Johnson Nutritionals.

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This placebo-controlled study demonstrated that milk OIT is effective in desensitizing patients and increasing the threshold dose to elicit symptoms and has an acceptable safety profile when performed in a highly supervised setting. Additional studies are necessary to determine whether oral tolerance is induced and to further examine the side effects of therapy in a larger cohort.