Oral Immunotherapy for Food Allergy

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Current Allergy and Asthma Reports 2009, 9:43–49
Current Medicine Group LLC ISSN 1529-7322
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Current management of food allergy involves strict avoidance, education on recognizing and managing allergic reactions, and carrying an adrenaline autoinjector. This approach is burdensome and associated with reduced quality of life. Patients with food allergy would benefit greatly from a treatment that could achieve desensitization or long-term tolerance. Recent studies have shown that oral immunotherapy (OIT) can induce desensitization and modulate allergen-specific immune responses; however, it remains uncertain whether OIT can induce long-term tolerance. Nevertheless, successful desensitization provides a major advance in management by reducing the risk of reaction to low amounts of allergen. Allergic reactions during OIT are common, although severe reactions are less common. Therefore, OIT should be performed in specialist centers under close medical supervision and would ideally be conducted as part of ongoing research studies. OIT holds promise as a novel approach to managing food allergy.

Introduction

Rates of allergic disease have risen exponentially in the past three decades. Although the prevalence of asthma has stabilized and the rise in prevalence of eczema and allergic rhinitis appears to be slowing, the prevalence of food allergy and anaphylaxis continues to rise [1,2]. In the United Kingdom, hospital admissions for food allergy and anaphylaxis increased 500% and 700%, respectively, between 1991 and 2005 [1]. Similar trends have been reported in Australia for anaphylaxis admissions between 1993–1994 and 2004–2005, with food anaphylaxis in children 0 to 4 years old accounting for most of this rise [3]. In particular, the prevalence of peanut allergy increased approximately threefold over a 5-year period in the United Kingdom (1989 to 1994–1996) and the United States (1997–2002) [4,5]. Food allergy is now estimated to affect 3% to 6% of children and 2% of adults [6,7], and the cumulative incidence of peanut allergy was estimated to be 1.8% by the age of 4 to 5 years for children born in the United Kingdom in 1999 and 2000 [8].

Allergic reactions to foods can range in severity from mild to severe; however, foods are the most common triggers of anaphylaxis [9] and the second most common cause of death from anaphylaxis [10]. Among the common food allergens, peanuts and tree nuts are especially significant in that allergies to these foods generally persist into adulthood, reactions are often severe, and allergy to these foods is a strong risk factor for death from food anaphylaxis. Whereas most cases of allergy to milk and egg resolve by later childhood, allergies to peanut, tree nut, fish, and shellfish usually persist. Only 18% [11] to 21% [12] of children outgrow their peanut allergy (spontaneous development of tolerance), and there are no reliable predictors for resolution [5,13]. Peanut allergy is the most common cause of food anaphylaxis [14], and 42% of reactions to peanut involve respiratory symptoms [15]. Accidental ingestion of peanut in children with peanut allergy is also common (50% within 1 year, 75% within 5 years) [13], and most reactions from accidental peanut ingestion are severe [16]. Furthermore, nuts (peanut or tree nuts) were reported to cause 81% and 38% of deaths from food-induced anaphylaxis in recent US and UK series, respectively [10,17]. Therefore, children who fail to outgrow their food allergy often have peanut or tree nut allergy and are at greatest risk for severe allergic reactions and fatal anaphylaxis. Consistent with this, adolescents with peanut or tree nut allergy are overrepresented among food-induced anaphylaxis fatalities, with the incidence of fatal anaphylaxis among 15- to 24-year-olds with nut allergy in the United Kingdom estimated to be 10 times higher than the overall population rate of fatal anaphylaxis (2.3 cases per 100,000 population vs 1–3 cases per 1 million population) [18]. A treatment that could modify the natural history of food allergy by inducing long-term tolerance (ability to tolerate any quantity of allergen in the absence of ongoing regular administration) would be of
great benefit to individuals who fail to outgrow their food allergy in childhood.

Current Management of Food Allergy
There is currently no effective long-term treatment for food allergy. Management involves avoiding the food in question, recognizing symptoms of an allergic reaction early, and initiating appropriate emergency treatment of allergic reactions (particularly anaphylaxis) [18••]. This approach is fraught with difficulties, and the burden of living with food allergy and its management is significant. For example, children with peanut allergy are reported by their parents to have a poorer quality of life than children with rheumatologic conditions [19].

Avoiding food allergens is difficult, particularly with commercially prepared foods. Accidental exposures to food allergens occur in 58% of patients within 5 years and 75% within 10 years [16]. Furthermore, in reports of fatal food-induced anaphylaxis, most patients knew that they were allergic to the food in question but were not aware that the allergen was present within the food ingested, and approximately 40% of deaths involved ingestion of foods catered or prepared outside the home [10••,17••].

Adrenaline is the first-line therapy for anaphylaxis. Several available self-injectable devices can be administered if accidental exposure to a food allergen results in a severe reaction (anaphylaxis). The use of an EpiPen epinephrine autoinjector (DEY, Napa, CA) is not intuitive and requires specific training [20]. Most patients who were prescribed an EpiPen failed to use it at the time of a severe allergic reaction. In one study, only 71% of patients prescribed an EpiPen had it with them, 10% of these had expired, and only 32% could demonstrate its correct use [21]. Inadequate education and failure to use an adrenaline autoinjector even when prescribed were prominent among cases of fatal anaphylaxis, with 10 of 19 fatalities involving failure to carry or use the device correctly [10••]. Patients with anaphylaxis generally are reluctant to seek medical attention, and physicians seem similarly reluctant to administer adrenaline for severe symptoms. In a survey of Food Allergy & Anaphylaxis Network conference participants, only 35% of patients with severe symptoms sought medical attention, and only 6% received prehospital adrenaline [22]. Even for repeat severe episodes, although 73% of patients sought medical attention, only 33% received prehospital adrenaline [22]. Adrenaline may not always be sufficient to prevent death, as early and repeated administration of adrenaline failed to prevent death in 12% to 14% of anaphylaxis fatalities [10••,17••].

The many limitations of current management of food allergy highlight the need for treatment options that can induce long-term tolerance.

Failure of Oral Tolerance as a Cause of Food Allergy
The mechanisms leading to the development of food allergy remain poorly understood. Food allergy is considered to be caused by a failure or loss of oral tolerance [23••]. Oral tolerance can be induced by a single high-dose exposure or by repeated low-dose exposures to antigen. High-dose tolerance involves Fas-mediated apoptosis or anergy, whereas low-dose tolerance is mediated by T regulatory cells (Tregs). Recent studies suggest that anergy and induction of Tregs may not be distinct mechanisms for tolerance, and most studies now focus on the role of Tregs [24••]. Several Treg subsets have been identified, including T-helper type 3 (Th3) cells, Tr1 cells, and CD4+CD25+ Tregs. Th3 cells produce transforming growth factor-β (TGF-β) and variable amounts of interleukin (IL)-4 and IL-10 [25]. Tr1 cells secrete IL-10 [26]. CD4+CD25+ Tregs express the transcription factor forkhead box P3 and mediate their suppressive effects in part by cell surface–bound TGF-β and, to a lesser extent, IL-10 [27]. CD4+CD25+ Tregs arise predominantly in the thymus but also may develop in mesenteric lymph nodes, Peyer’s patches, and peripheral lymph nodes, where they play a role in mucosal tolerance [27].

Tregs TGF-β and IL-10 have been shown to play important roles in oral tolerance induction and food allergy. In a murine model of food allergy, mice tolerized to β-lactoglobulin had higher numbers of antigen–specific IgA-secreting cells in Peyer’s patches and higher levels of fecal IgA, as well as increased TGF-β and IL-10 production by Peyer’s patch T cells, compared with sensitized mice [28]. Children with food allergy have fewer TGF-β+ lymphocytes in the duodenal epithelium and lamina propria [29] and show reduced TGF-β expression by milk-specific duodenal lymphocytes [30]. Similar findings have been reported for patients with non–IgE-mediated food allergies (food protein–induced enterocolitis) [31]. In patients with cow’s milk allergy, resolution of allergy was associated with increased numbers of CD4+CD25+ T cells and reduced β-lactoglobulin–induced proliferation compared with those with ongoing allergy [32]. In vitro depletion of these CD4+CD25+ cells led to increased β-lactoglobulin–induced proliferation, suggesting that oral tolerance induction was related to increased CD4+CD25+ cells [32]. Oral tolerance is also associated with Th1-skewed responses, whereas food allergy is associated with Th2-skewed responses [33]. Comparison of peanut-specific immune responses in normal children, children with peanut allergy, and peanut-allergic children who had outgrown their allergy showed Th2-skewed responses in children with peanut allergy and Th1-skewed responses in oral tolerance (healthy children without food allergy and children who outgrew their peanut allergy) [33]. These findings suggest that food allergy is associated with failure or loss of tolerance, reduced Tregs and TGF-β, and reduced Th1 and increased Th2 responses.