

Induction of Tolerance Through Early Weaning and Oral Immunotherapy

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Abstract

Purpose of review The increase in IgE-mediated food allergy in the world with prevalence of egg, milk, peanut, and wheat allergies presenting and coexisting as multiple food allergies in young children.

Recent findings Earlier initiation in weaning and timing of exposure of specific food allergens to an atopic infant appears to affect the trajectory and progression of acquiring tolerance in these children for specific foods. In this review, the allergen-specific strategies for increasing tolerance (desensitization) and hastening the resolution of food allergy (SU) are reviewed for treatment of food allergy.

Summary Phenotypic complexity of the individual (eczema, asthma, rhinitis), age of the child at presentation and severity of food reactions, alongside skin test size and IgE levels can determine adopting a strategy for low-dose oral immunotherapy versus conventional oral immunotherapy to complete an immunotherapy program with the least adverse events.

Introduction

The past decade has seen a paradigm change in the management of food allergy in young children. Food allergy is often the prelude to the allergic march, frequently coexisting with atopic dermatitis with an increased association with asthma and anaphylaxis [1]. The natural history of food allergy varies

widely depending on the populations from different geographic regions studied. Acquisition of tolerance in young children is dependant upon different causative food allergens and appears to be affected by patient's complexity of atopic phenotype (eczema, rhinitis, asthma). The presence of multiple food sensitizations and history of food-specific anaphylaxis, as well as the trajectory of decreasing trend in antigen-specific IgE or skin test to the specific allergens over the initial years of a child's life often determines the rate and likelihood of acquiring tolerance to the specific antigen. Instead of avoiding potentially allergenic foods for allergy

prevention in children at risk of food allergy, evidence is accumulating that deliberate exposure in the correct form is beneficial in the majority of infants for specific food allergens. Egg allergy is one of the commonest forms of food allergy, with cow's milk, wheat, and peanut sensitization and allergy being frequently documented as the top allergens in most countries. Recent findings from observational studies indicate that contrary to dogma of delay and avoidance of specific allergenic foods, the early introduction of allergenic foods in the appropriate form appears to decrease the incidence of food allergy [2–5].

Incidence and natural history: acquisition of tolerance for cow milk

Cow's milk allergy (CMA) is a spectrum encompassing IgE-mediated, non-IgE-mediated, and mixed IgE/non-IgE reactions to cow's milk which makes it challenging to document the true incidence of CMA. In IgE-mediated CMA, the incidence in a pan European birth cohort ($n = 12,049$ enrolled) showed that the incidence of CMA differed between nine countries ranging from 0 to 1.3%, with a mean incidence of challenge-positive CMA to be 0.54%. In this cohort, 57% of children tolerated cow's milk by 2 years old and 69% of children with CMA tolerated cow's milk by 30 months old [6]. In Israel, a prospective population-based study demonstrated 57% of children with CMA achieved cow's milk tolerance by 5 years old [7]. In previous studies, the incidence of developing tolerance to cow's milk at 2 years ranged from 25% to 77% with 19–82% outgrowing CMA by 4 years old [8–10]. This wide range in age of acquiring tolerance to cow's milk maybe a referral bias, as tertiary referral centers often have a significantly higher population of patients with multiple food allergies who show a different trajectory in outgrowing CMA. Skripak et al., in a retrospective review of CMA, reported resolutions rates of 19% by age 4 years old, 42% by 8 years old, 64% by 12 years old, and 79% by 16 years old [11].

Observational studies suggest that the timing of exposure to cow's milk in an infant is important for the development of CMA. Almost two decades ago, a birth cohort with early introduction of formula feeding within the first month of life, had a significant increase in their risk of developing CMA/intolerance [12]. In a retrospective, observational case-controlled study, it has been observed that isolated doses of formula feeding in hospital (FFH) with periods of exclusive breast-feeding predispose and increase the risk of IgE-mediated CMA in infants. Interestingly, FFH was a risk factor (OR 4.94) especially for infants delivered by

cesarean delivery (OR 11.82), and prematurity (OR 0.29) was a protective factor for the development of CMA [13].

Incidence and natural history: acquisition of tolerance for egg

Hen's egg is often the second most prevalent allergen during infancy and early childhood in European countries [6, 14], but in Japan, China, and Australia, egg is the most prevalent food allergy with prevalence ranging from 1.3 to 10.1% [15–18]. The mean incidence of egg allergy at the age of 2 years of life is about 1.23% on average in the EuroPrevall birth cohort surveillance of nine countries, with 49% of children becoming egg tolerant by 2 years old [19]. In the HealthNuts study following a birth cohort in Australia ($n = 5276$), egg allergy resolved in 47% infants by 2 years of age (although raw egg challenge was used) [18]. In a multicenter observational cohort in the USA with egg allergy, 49.3% achieved egg tolerance by 6 years old [20].

Incidence and natural history: acquisition of tolerance for peanut

The HealthNuts birth cohort prospectively followed up peanut-sensitized children. Twenty-two percent of children with challenge-confirmed peanut tolerance at 1 year old were peanut tolerant by 4 years old [21]. Similarly, retrospective studies in Australia [22] and USA [23, 24] have found that approximately 20% of their peanut-sensitized populations are tolerant to peanut by 5 years old.

Incidence and natural history: acquisition of tolerance for wheat

The natural history of wheat allergy differs from observation trials of different cohorts. Keet et al. showed that in a western cohort, the median age of acquiring tolerance through oral food challenge to wheat appears to be 29% by 4 years old and 69% by 10 years old. Up to 35% remained wheat allergic in their teenage years [25]. Similarly, in Japan, Koike et al. demonstrated tolerance acquisition was 20.5% at 3 years old, 54.2% at 5 years old, and 66.3% at 6 years of age. A history of anaphylaxis to all foods including wheat and/or a high level of wheat- or ω -5 gliadin-specific IgE antibodies was identified as risk factors for persistent wheat allergy [26]. Conversely, Ikematsu et al. estimated that the rate of wheat tolerance was 60% in their cohort of children with wheat allergy at 3 years of age [27].

Hastening the resolution of egg allergy

The early introduction of egg powder as well as baked egg in high-risk infants (with moderate to severe eczema and/or food allergy) affects the threshold of tolerance for egg in most and resolution of egg allergy in some individuals. Prevention of egg allergy in high-risk infants with eczema (PETIT) was carried out in Japan using heated 50-mg egg white powder. Infants were introduced to

the egg powder at introduction from 6 to 9 months followed by a step up to 250 mg from 9 to 12 months old resulting in a significant reduction in egg allergy in those offered egg white powder daily as compared to those in the avoidance arm (9% vs 38% in the placebo group, RR 0.22 $p < 0.0001$) [28]. Furthermore, two randomized controlled trials investigated the effect of raw egg powder introduction at 4–6 months of age and did not show any protection with early raw egg powder introduction in unselected infants in the absence of eczema [29] or with moderate to severe eczema by 12 months of age [30]. These studies may support lower starting doses in the right form (e.g., heated egg powder instead of raw egg powder) to reduce reactions of early introduction of egg during weaning and acquiring oral tolerance in high-risk infant with eczema.

A more practical approach is the initiation of baked egg immunotherapy to accelerate acquisition to egg tolerance with minimal adverse events, although it is reported that up to 9.4–22% of baked egg reactors develop anaphylaxis during baked egg challenge [31, 32•]. As seen in a population-based cohort study, almost 76% of egg-allergic children were tolerant to baked egg at age 1 year with the rate of development of egg tolerance being 3.5 times faster with frequent ingestion of baked egg ($\geq$ five times per month) compared with infrequent ingestion (0–4 times per month) [18]. Novel strategies include baked egg immunotherapy trials achieving varying target levels of 3-g, 2.2-g, or 1-g egg protein in baked egg matrix to initiate baked egg immunotherapy in majority (66–84%) of egg reactive patients with minimal adverse reactions, although this remains to be investigated in future trials [33–37].

Hastening the resolution of milk allergy

The introduction of cow milk (CM) as well as baked milk has been shown to improve the threshold of milk tolerance in children. Milk oral immunotherapy (OIT) was effective in desensitizing 90% versus 23% of placebo-treated children [38]. In an earlier milk OIT trial involving severe CM-allergic children, 35% treated versus 5% untreated children were able to tolerate a dose of 150 mL of CM after 1 year of OIT. However, 54% could only take limited amounts of milk (5–150 mL) [39].

Baked milk is tolerated by the majority (75%) of children with CM allergy [40]. CM proteins coupled in a wheat matrix and exposed to high temperature for an extended period, result in proteins which are modified, known as the "matrix effect". When milk is exposed to higher temperatures for a longer period of time, its allergenicity is reduced [12, 41]. Baked milk at 1.3 g and 0.5 g of milk protein was successfully introduced in 69–83% of milk-allergic individuals [40, 42, 43]. In recent trials for children with severe CM allergy (anaphylaxis with/high specific IgE), the use of lower dose baked milk (102 mg) OIT appears to be tolerated by 42% of children. In those with CM IgE > 100 kU/L, 71.6% failed the low-dose CM OFC [44].

Hastening the resolution of peanut allergy

The early introduction of peanuts in high-risk infants in the LEAP study revealed that early introduction of peanuts in infancy (less than 1 year old) reduced peanut allergy at 5 years of age (17.2% in the avoidance group vs 3.2% in the

early introduction group) [45]. In this early introduction of peanut infancy cohort, stopping peanut ingestion for more than a year (after 5 years old of POIT) did not result in an increase in percentage of children who failed an open challenge to peanuts [46••]. In preschool children below 3 years old, early peanut OIT with 300-mg maintenance dose of peanut protein had comparable efficacy and improved safety compared with OIT with 3000-mg maintenance dose with a 19-fold likelihood of introducing dietary peanut than matched standard care control subjects, in whom the peanut-specific IgE levels increased significantly [47•]. The study of induction of tolerance of oral peanut (STOP) II trial is a randomized controlled crossover trial demonstrating desensitization with an increase in tolerance to 1400 mg of peanut protein was achievable in 6 months [48]. Interestingly, another study using adjunctive anti-IgE therapy with peanut OIT [49], rapid desensitization was performed safely within 16 weeks [50].

Hastening the resolution of wheat allergy

The spectrum of wheat allergy includes IgE-mediated wheat allergy and wheat anaphylaxis with or without exercise. There is paucity of clinical trials on the OIT for wheat-allergic patients with scattered case reports [51–54] of wheat OIT undertaken. In a case series in Japan, wheat OIT maintained at 5.2-g wheat protein for wheat-induced anaphylaxis increased the threshold dose of symptoms and achieved desensitization and tolerance in 60% of subjects at 2 years of age [55]. The current trend for attaining a lower threshold maintenance OIT for high-risk patients with high-antigen-specific IgE values or a history of previous anaphylactic symptoms with wheat OIT was demonstrated in a study by Noruyuki et al [44]. In this study, the frequency of the induced symptoms from OIT is lower as compared with the frequency induced by conventional OIT. Low-dose maintenance on 2 g of udon noodles after 1 year was able to achieve a tolerance of 15 g of udon noodles in 56% of patients.

Conclusion

The current shift in early weaning and introduction of peanuts to high-risk infants with moderate to severe eczema as well as stratified food OIT (low-dose versus high-dose OIT) and baked foods presents unique opportunities to achieve desensitization safely with minimal adverse reactions in most patients. It is imperative that in most individuals, continual exposure to the allergen is adhered to achieve oral tolerance. However, in some cases, exceeding threshold doses, or the presence of illness, exercise, menstrual periods, and even seasonal peak pollen seasons, may result in inadvertent reactions during the up-dosing schedules or maintenance schedules on OIT. In a subset of patients completing their immunotherapy programs, we can achieve sustained unresponsiveness (SU) with varying degrees of success for specific allergens after a period of OIT as defined as 4 to 12 weeks of allergen avoidance with no reaction on ad lib reintroduction of the allergen. In peanut OIT studies, 25–50% of school-aged children demonstrate SU to peanuts for 4–

8 weeks of avoidance [56, 57]. For egg OIT, 28–50% achieved SU after 8–12 weeks of avoidance [58, 59]. Studies have not been conducted to look at SU in most allergens.

A recent study demonstrating that preschool children are just as likely to achieve oral tolerance at a lower dose peanut OIT with possibly a higher percentage of young children achieving SU to peanut OIT presents us with an earlier window to intervene [47]. The strategies available for hastening the resolution of food allergy need to be safe and efficacious. OIT reactions associated with introduction of the allergen are reported to be higher than accidental reactions to the allergen although most of the reactions are mild with more reactions reported during the built-up phase as opposed to the maintenance phase. Published studies report ranges from 0.8 to 45% of daily doses with 0.4% dosing days experiencing multiple system reactions, 0.1–3.4% moderate reactions. Gastrointestinal symptoms predominant in up to 2.5–9% of doses, lower respiratory symptoms in 0.4–7% of doses [60–62]. A 3-year prospective study of accidental allergic reactions in an observational cohort of 512 young children who were to have milk or egg allergy found an annualized reaction rate of 0.81 per year to milk, egg, and peanut [63]. In contrast, OIT reaction rate was over 400% higher, at 3.5 per year [62]. In comparison, these data suggest that OIT-induced allergic reactions to the index food may occur more commonly than accidental reactions during avoidance.

OIT has been shown to desensitize milk-, egg-, wheat-, and peanut-allergic children using increasing amounts of the allergen protein. However, dropout rates from studies have been as high as 25% with poor adherence to OIT over time 20% of patients, mostly due to frequent, primarily mild reactions especially abdominal discomfort. A risk of return of clinical reactivity upon discontinuation of treatment has been reported in a subgroup of subjects [64]. The growing body of experience demonstrates that peanut OIT is associated with frequent adverse events, with rates of reactions declining over time, and most graded mild. However, systemic reactions and intolerable gastrointestinal adverse events do occur and are significantly associated with allergic rhinitis (especially seasonal) and peanut SPT wheal size, respectively [62]. These validated predictors may allow risk stratification of individuals and identify those at risk of persistence of gastrointestinal symptoms, which accounts for up to 10% of patients who may withdraw from OIT programs. Moreover, recent literature has shown 2.7% of individuals have developed eosinophilic esophagitis from iatrogenic food-induced OIT [65].

In summary, OIT is a treatment algorithm that is allergen-specific and carries considerable risk of adverse events during the desensitization process. In our patient selection, unique phenotypic features and biomarkers are helpful in delineating individuals who may benefit from OIT will minimize adverse events.

Compliance with Ethical Standards

Conflict of Interest

The author declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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