

Editorial

Food OIT



What do we know, what don't we know, and what do we need to know?

Oral immunotherapy (OIT) is a form of desensitization proposed as a treatment for food allergy (FA). Oral immunotherapy involves feeding with increasing amounts of an allergen until a small portion is regularly tolerated. The OIT goals range from “bite safe” to induction of tolerance.^{1,2}

In this issue of *Annals*, the Food Allergy Support Team (FAST) reports the minutes from its annual meeting of allergists who offer OIT in their practices.³ This report reflects the collective experiences of 109 clinicians representing 80 practices who have treated more than 7800 patients. It outlines factors that are important in the shared decision of starting OIT: protocol development, including types of foods and maintenance dosing, as well as adverse event management. This voluntary contribution by a large number of allergists primarily self-funding their travel is remarkable and nearly unprecedented. Ongoing reporting of the outcomes and adverse events in the FAST registry will provide valuable insights into OIT and with time can generate hypotheses to test in clinical trials.

Several seminal studies demonstrated OIT safety and efficacy. In 2012, Burks et al² reported a double-blind, randomized, placebo-controlled study of OIT in 55 egg-allergic children.² After 10 months of OIT with up to 2 g of egg-white protein (approximately one third of an egg), 55% of those treated with egg-OIT tolerated a cumulative 5 g of egg-white protein at oral food challenge (OFC) compared with no children in placebo-OIT. After 22 months, 75% of those receiving egg-OIT passed an OFC with a cumulative 10 g of egg-white protein. No severe adverse events occurred, but 78% of children reported oral or pharyngeal discomfort (20% placebo). In 2018, the PALISADE group reported a phase 3 clinical trial of peanut-OIT.¹ After 12 months, 67.2% of those treated with AR101 (300 mg peanut protein) tolerated 600 mg or more (approximately 2 peanut kernels) on OFC compared with 4% treated with placebo. Fourteen percent of AR101-treated group experienced a systemic allergic reaction compared with 3% in the placebo-treated group; all but 1 reaction were mild to moderate in severity. In addition, 52.2% of children in the peanut-OIT group developed abdominal pain compared with 24% in the placebo group.

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Despite the promise of OIT, questions remain about optimal protocols, maintenance dose, dosing interval, age at initiation, predictors of response, and the risk factors for eosinophilic esophagitis that should be answered before large-scale adoption into practice.^{4–6} Although our ability to phenotype FA is currently limited, age, reactivity, immunologic markers (including food-specific and total immunoglobulin E [IgE], specific IgG4, and component-resolved testing), comorbidities, maintenance dose, and length of maintenance dosing likely all influence the outcome of OIT. We hypothesize that younger children with a high-threshold, low food-specific IgE and no history of anaphylaxis are more likely to achieve tolerance. In contrast, in older patients with a low threshold, higher food-specific IgE, and history of anaphylaxis, a realistic goal may be prolonged, daily dosing to be “bite safe” (Fig 1). If the latter is the primary goal, patients must understand that OIT may be a life-long therapy. This phenotypic diversity likely accounts for differences in the reported outcomes and safety profiles from different patient populations and explains the different success rates and favorable safety profile alluded to by Wasserman et al³ when compared with clinical trials.

Another consideration is selection of patients capable of following the protocols, which require 2 exercise-free hours after daily dosing as well as frequent office visits. Allergists are accustomed to screening patients who can adhere to immunotherapy; however, the stakes are raised in OIT, in which most doses are unmonitored and nonadherence could result in anaphylaxis outside of an allergist's office. Newly published trials hint, though, that in certain carefully selected cases, even home up-dosing may be safe and effective.⁷

A recent meta-analysis of 12 peanut-OIT studies demonstrated with high-level evidence that peanut-OIT is associated with increased risk of systemic allergic reactions compared with untreated patients or placebo-OIT, with an overall estimated risk of anaphylaxis with peanut-OIT 22% compared with a baseline risk of 7%.⁸ This risk was attenuated in trials that did not confirm peanut allergy by baseline OFC, arguing that phenotypic differences may explain this difference as most trials required low threshold doses for inclusion, and therefore selected a more severe phenotype. This meta-analysis invigorated the discussion about OIT risk/benefit ratio and highlighted the need for strategies to improve safety and better understand the evolution of risks during the OIT maintenance phase.

The OIT schedule individualization, not permitted under research protocols, may mitigate adverse events. Novel strategies to minimize the risk, maximize efficacy, and increase the potential for achieving tolerance are desirable. Several biologic therapies (omalizumab, dupilumab) as well as probiotic lactobacillus

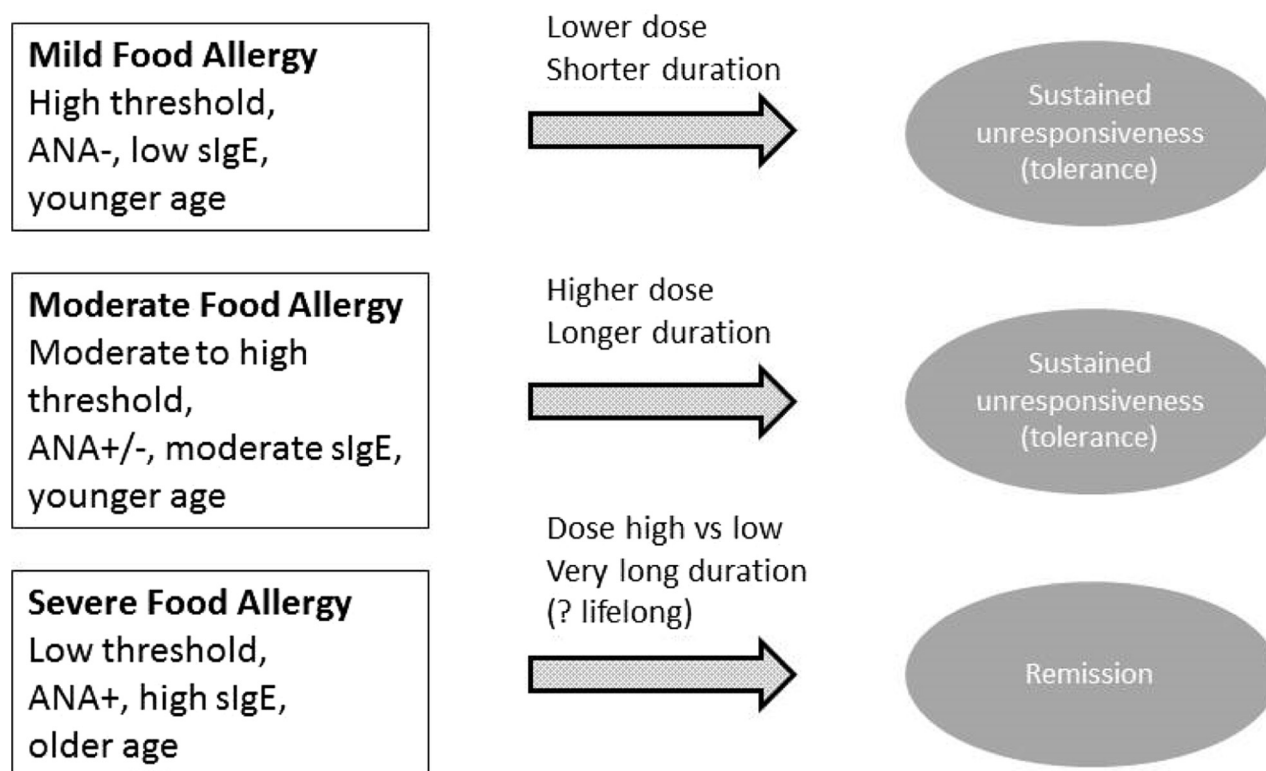


Figure 1. Food 1 OIT outcomes vs phenotype.

rhannosus are under investigation as OIT adjuncts with potential to decrease side effects.^{9–11}

Barriers exist, however, in restricting OIT to research. Many OIT trials were limited to a small number of sites in large cities. The commute can be expensive, time-consuming, and limiting participation to those who are affluent and highly motivated. The inclusion criteria requiring low thresholds for reactivity preselect for the highly allergic individuals, which limits the generalizability of these studies. However, expansion is difficult with the limited funding from the National Institutes of Health for FA compared with human immunodeficiency virus, cancer, and asthma. Advocacy by all stakeholders is necessary to increase funding for FA. Additionally, current protocols require OFC to prove reactivity at baseline and assess response. Because OIT is becoming increasingly available in off-research protocols, potential subjects are becoming reluctant to participate in trials that require the risk of OFC. If OIT protocols are to be optimized through rigorous trials, a strong unified position from the leaders in FA is needed as to what could reasonably replace baseline OFC. Proof of reactivity at baseline may not be necessary if the goal of treatment is, for example, significant improvement in quality of life.

Allergists care deeply about patients with FA and are eager to offer a safe and effective OIT. Although agreement does not yet exist, intense efforts are being directed toward reaching consensus to benefit patients.

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