



Does clinical protection persist after food allergen oral immunotherapy?

“...design limitations common to early phase clinical trials prevent confident conclusions about oral immunotherapy’s ability to produce long-lasting changes.”

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Food allergy is an increasingly important public health problem resulting in high physical, emotional and economic costs. It is the leading cause of anaphylaxis in US children and can be fatal [1]. Although mortality from food anaphylaxis is rare, due in large part to the effectiveness of self-administered auto-injectable epinephrine, it is perceived by affected families and patients as a constant threat. Difficulties in allergen avoidance lead to frequent and unpredictable reactions [2] that must be immediately managed by a caregiver or the patient, a situation that contributes directly to a profound impairment in health-related quality of life [3]. A safe treatment that could modify the clinical course of the disease by preventing or mitigating accidental anaphylaxis is an urgent and unmet clinical need.

Over the past decade, academic and industry research teams around the world have made substantial progress in addressing this need. Currently, several investigational allergen-specific immunotherapy (IT) products are in Phase II studies [4], and at least two companies have plans to commercialize IT products for the treatment of food-allergic patients if successful in Phase III. These advanced programs offer near-term potential for a change in clinical care by focusing on desensitization, which can be operationally defined as an alteration in reactivity to allergen(s) initiated by, and dependent upon, regular exposure to the allergen(s). Current standard of care treatment guidelines recommend strict dietary avoidance of food allergens [5], such that the immunologic systems of food-allergic patients are not regularly exposed to allergens in their native or

unmodified forms. Despite avoidance, robust immunologic and clinical tolerance develops in many patients, especially those allergic to certain common food allergens like wheat, soy and to a lesser extent milk and egg; whereas in contrast, allergies to other foods like peanut, tree nuts and crustacea tend to persist. Patients who develop tolerance experience an attenuation of their allergic immune responses and can resume symptom-free consumption of the previously allergenic food without limitation. This resolution is considered a durable change to a nonallergic state, and such individuals are said to have ‘outgrown’ their allergy. Notably, this is antigen specific and occurs despite strict avoidance, suggesting that ongoing stimulation of immunologic cells is not required for the onset of disease resolution.

In contrast, desensitization is the desired end result of a deliberate interventional strategy designed to lessen clinical responsiveness among individuals who are currently still allergic. In this approach, the progressive daily exposure of allergen(s) works through mechanisms that are still not entirely clear but which result in the hyporesponsiveness of allergic effector cells (i.e., mast cells [MCs] and basophils) [6]. Although trial protocols vary widely [7], desensitization procedures start with doses that are too low to elicit MC activation and then gradually escalate the dose at intervals ranging from days to weeks. Low-dose steady exposures of this type tend initially to drive production of IgE, the effector antibody isotype in allergic individuals. Yet at the same time, the MCs and basophils that are sensitized with IgE bound to their membranes become paradoxically less



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reactive over the course of weeks to months, suggesting that tonic exposure induces regulation of cellular behavior through cell-intrinsic changes [8]. Long before there was any mechanistic understanding of the effect, clinicians in the early 1900s began to treat allergic respiratory disease with controlled allergen exposure, and their clinical observations of improvement were later supported by large well-designed clinical trials.

“Immune ‘tolerance’ is a term with many different meanings, depending on the immunologic context.”

Recently, a number of small but rigorously conducted prospective, institutional review board (IRB)-approved clinical trials have convincingly demonstrated in intent-to-treat analyses that desensitization is also achievable with oral IT (OIT) for many if not most food-allergic patients [9–15]. It is important to note that the approach to OIT is not harmonized, and as a result, there are some critical differences between studies in the per-protocol definitions of key study variables, such as the constitution and dose of the study product, the length of therapy and the method of determining whether desensitization itself has occurred. In addition, OIT is associated with intolerable study-limiting side effects, primarily involving the GI tract, in 10–20% of study subjects. Finally, most but not all studies assess desensitization by performing oral food challenges (OFC) intended to provoke clinical reactions, and these are not standardized either. However, despite these limitations, rates of per-protocol desensitization after active OIT in the published literature range from 50 to over 90% depending on the study, with minimal responses in placebo-treated subjects. In addition, the magnitude of the desensitization effect is generally large, as shown by 20-fold or greater improvement in OFC performance from baseline to when the target maintenance dose is reached [12,15].

The question to be considered here is, then: among responders, does this clinical protection persist after OIT? The answer to this question has vital implications. If desensitization can be achieved but requires ongoing exposure to be maintained, then OIT must be continued indefinitely to remain effective, calling into question the long-term feasibility of this approach. On the other hand, if OIT is truly a disease-modifying treatment, then it could be discontinued with the expectation of continued clinical benefit. There have been several trials that have investigated this question by discontinuing OIT in those participants who fully pass their provocation OFC after a period of treatment; for example, who consume several grams of allergenic material without symptoms and are considered desensitized. These studies require participants to stop therapy and resume allergen avoid-

ance for some interval before returning to the research unit to repeat the OFC off of therapy. In this way the durability of desensitization is formally tested.

Every published study that has addressed this issue has shown that the proportion of participants passing the final OFC is lower than the proportion passing the OFC at end of treatment [10,13,14,16,17]. Interestingly, this appears to be a time-dependent event, which supports the idea that clinical protection decays kinetically after stopping OIT. For example, Tang *et al.* observed that 20% had lost their desensitization at 2 weeks after stopping OIT, Vickery *et al.* observed 50% at 4 weeks and Burks *et al.* observed 67% at 8 weeks. Mechanistic studies performed in these post-OIT settings support these clinical observations, and have demonstrated the loss of MC/basophil suppression once OIT is halted, with MC and basophil activation returning to prestudy levels in those subjects who become clinically reactive again [8,17]. Taken together, these data suggest that the clinical benefit of OIT is ultimately transient, ‘wearing off’ in many or even most participants once allergen exposure ceases; and that this process is time dependent. Though longer intervals of avoidance increase the likelihood of relapse, it is important to note that it has been reported to occur within days, even among participants considered to be per-protocol successes [18].

However, a number of studies have demonstrated that this decay in clinical and cellular protection after OIT is not universal. A minority of participants in OIT trials have been shown capable of fully passing an OFC after a post-OIT avoidance period of as much as 3 months [10,13,14,17,18], and are then able to consume the previously allergenic food in the diet regularly without symptoms. Following a landmark egg OIT study by the Consortium of Food Allergy Research [10], the term ‘sustained unresponsiveness (SU)’ entered the lexicon to describe this phenomenon. However, the ultimate immunologic disposition of such individuals, and whether or not the OIT was directly responsible, is a subject of much current debate in the field. Immune ‘tolerance’ is a term with many different meanings, depending on the immunologic context. In the food allergy context, it is still not at all clear whether therapeutic immune ‘tolerance’ is even possible with OIT; and if it is, whether or not it is the same thing as SU. Long-term, appropriately controlled studies will be required to address this question.

Unfortunately most long-term OIT studies do not have a control group. For reasons related primarily to safety and ethics, few of the randomized controlled OIT studies have evaluated the subjects in the active and control arms in the exact same way. For example, several controlled OIT studies [9,11,12] have had a planned interim OFC analysis that unblinds the study; and then the control participants have switched to the

active treatment arm, such that key end-of-study end points are measured without a control referent. The previously mentioned landmark egg study returned nonresponders at the interim OFC back to allergen avoidance and only conditionally evaluated the control group for desensitization/SU [10]. The reason that this is important is that some participants achieving SU after OIT may have simply outgrown their allergy naturally while being treated, as has been shown to occur in rigorously controlled randomized studies of OIT and sublingual peanut IT [14,19–20]. Until controlled trials address primary end points uniformly in all randomized arms, the occurrence of spontaneous resolution will obscure the effect of OIT in producing desired long-term outcomes. Another critical knowledge gap that must be addressed with future study is whether SU (i.e., therapeutic ‘tolerance’) bears clinical and mechanistic resemblance to true immune tolerance (i.e., ‘outgrowing’ an allergy).

In summary, design limitations common to early phase clinical trials prevent confident conclusions about OIT’s ability to produce long-lasting changes. The available clinical and mechanistic data support the view that OIT can create clinically meaningful desensitization in most subjects that can tolerate the exposures. Ultimately, the improvement appears to be transient and dependent upon ongoing exposure, emphasizing the need for more definitive long-term solutions to what is often a life-long, life-threatening condition.

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