

Correspondence

Reply

To the Editor:

We appreciate the perspectives of Katz et al¹ and Wasserman et al² in reference to our publication in the July 2010 issue of the *Journal* in which we discussed the issues precluding oral immunotherapy (OIT) from application in clinical practice at this time. OIT in clinical trials is performed in highly controlled settings, with all dose increases administered by trained professionals experienced in food allergy trials. According to Wasserman et al,² we commented on limiting OIT to academic centers. This interpretation of our statement is inaccurate. We believe that OIT should be limited to clinical trials in which there is proper oversight by a data safety monitoring board and the US Food and Drug Administration with an Investigational New Drug application. Many clinical trials are not executed in academic centers, but they still have the third-party oversight of safety profiles and adverse events that are crucial for the development of new therapies.

These safety concerns are and should be paramount. Despite intensive oversight, adrenaline administration and visits to emergency care facilities have been required with a small number of home doses.³ Katz et al¹ assert that patients experiencing OIT failures (ie, disabling allergic side effects to relatively small doses of OIT) are not “in any danger of death,” and conclude that OIT itself does not carry significant risk. It is correct that there have been no fatalities in the studies of OIT up to the present time, but this is due to primarily investigator-implemented safety measures required by institutional review boards and the US Food and Drug Administration. In addition, strict enrollment criteria have carefully excluded patients at high risk for life-threatening anaphylaxis. This fact, combined with a small total number of subjects, greatly limits the ability to generalize the published studies to date because in clinical practice these high-risk patients might be the most likely to desire treatment. This limitation is further compounded by the inability of clinical allergy testing to predict which patients are at risk for anaphylaxis, a common source of confusion and misinterpretation by physicians. Indeed, in an office-based desensitization to peanut, adverse reactions requiring epinephrine occurred in 7 (43%) of 16 patients, and overall, 9 (32%) of 28 patients with food allergy were unable to continue.⁴ These rates are significantly higher than those reported in research-based trials.

Moreover, we must bear in mind adverse outcomes other than death. Further investigation must address the less common but potentially more disabling consequences of OIT, such as eosinophilic esophagitis and other delayed-type reactions.⁵ This class of adverse effects has not been described with subcutaneous immunotherapy (SCIT)⁶ and therefore warrants further study. Potential OIT recipients will derive no benefit in health-related quality of life should they undergo peanut desensitization only to have eosinophilic esophagitis.

Both authors compare OIT with SCIT; however, in contrast to OIT, SCIT is a parenteral therapy that uses several log-fold lower doses to treat a condition that does not itself cause anaphylaxis. Yet practice parameters call for SCIT to be administered in a medical facility with personnel and equipment immediately available for treatment of reactions.⁶ The fact that the majority of OIT doses are given at home confers significant risk that must be addressed. In our experience dosing reactions have

occurred at home after tolerating the same OIT dose on the research unit. Further study is needed to refine recommendations for home dosing and to better understand the long-term efficacy of OIT. For example, if desensitization wanes after treatment with SCIT, there is no risk of resulting fatalities. In contrast, loss of the desensitized state after OIT can lead to severe adverse reactions caused by accidental ingestion. This might occur because of nonadherence to an indefinite daily medication, complacency about dietary elimination and epinephrine availability, or even risk-taking behavior, all of which could be expected in patients with this chronic disease. Until more is known about the proper dose and length of treatment and duration of the treatment effect, patients might falsely assume they are “cured.”

In addition to its potential health consequences, we concur that food allergy poses significant emotional and social morbidity. We agree that a treatment for food allergy cannot come soon enough, but the premature application of this investigational treatment is risky, and we disagree that keeping it in a research setting is unethical. A state of equipoise exists when there is reasonable uncertainty about which of 2 treatment approaches is superior, allowing the ethical assignment of study subjects into either group. Although early uncontrolled pilot data suggest that OIT might be effective in a small number of highly selected subjects, the long-term risks are still unknown and might be greater than allergen avoidance. Therefore we believe equipoise still exists and continued investigative work is warranted. This is especially important given the systematically overestimated treatment effects and bias often reported by clinical trials, especially small trials, when they are halted early because of perceived benefit.⁷

Formal guidelines need to be established before the dissemination of OIT in the clinical setting to establish OIT as an evidence-based practice. A recent meta-analysis noted the significant lack of food allergy studies with strong research designs.⁸ It is our hope that data derived from ongoing placebo-controlled studies will provide the high-quality evidence needed to formulate such recommendations. Data-driven recommendations for food allergy treatment are especially important because families volunteering for OIT trials are far more likely to express anxiety about fatal reactions⁹; the potential for coercion and conflict of interest must be handled judiciously. Additionally, information gleaned from trials will aid in the design of safe postdesensitization strategies. It is also possible that alternate routes of allergen administration currently under investigation (sublingual and epicutaneous) could confer protective effects with more favorable safety profiles.

We have hope that an evidenced-based food allergy treatment strategy will be available for all patients soon. However, now is definitely not the right time.

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