Peanut oral immunotherapy is not ready for clinical use

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Hippocrates wrote that "The physician must . . . have two special objects in view with regard to disease, namely, to do good or to do no harm" (Hippocratic Corpus, *Epidemics,* Bk I, Sect 5). As physicians, we are continually challenged with the task of weighing the possible risks and benefits of treatment against those of taking no action. Similarly, we pursue clinical investigation when existing evidence is in a state of equipoise, or uncertainty regarding the comparative therapeutic merits of a particular treatment.[1] Only once we demonstrate that action (eg, experimental treatment) is superior to nonaction (or the current standard of care) can we then recommend it with confidence that our practices uphold the principle of *primum non nocere*—"first, do no harm."

In the United States, 3.9% of children are affected by food allergy, with an increase in prevalence of 18% from 1997 to 2007.[2] Peanut allergy, in particular, affects over 1% of the general population in Westernized countries.[3-5] The current standard of care includes appropriate diagnosis, avoidance of the food, and education of the patient and family. Because treatment options are limited, there is a vital need for new therapeutic modalities. Several groups have studied potential therapies for peanut allergy, including various forms of antigen-specific and nonspecific treatments.[6] Peanut oral immunotherapy (OIT) in an open-label study has been shown to raise the threshold dose of reaction to ingested allergen, resulting in clinical desensitization for the majority of subjects.[7] Peanut OIT is also associated with decreased peanut skin prick test size, antigen-specific basophil activation, and allergen-specific IgE as well as increased allergen-specific IgG_4, regulatory T-cell number, and associated cytokine levels while on therapy. Nevertheless, numerous unanswered questions surrounding this investigational treatment remain, with the foremost being the risks of OIT compared with food avoidance (ie, incidence of accidental ingestion). Additional unanswered questions include issues associated with dosing regimens, patient selection, postdesensitization strategy, allocation of clinical resources, and reimbursement.

With current forms of OIT, as with other forms of immunotherapy, up to 18% of patients undergoing treatment will not be able to endure the associated side effects.[7-12] In addition, accidental ingestions do pose a threat, with events occurring in about 15% of children with peanut and tree nut allergy over a 4-year period.[13,14] The major issue to address is whether the likelihood of patients experiencing accidental food reactions over a given period is more or less than the percentage of patients who cannot tolerate OIT.

In initial studies, peanut OIT has been generally safe but not without risk. In an earlier open-label peanut OIT protocol, the risks of reaction during the initial escalation day, build-up phase, and home dosing were 93%, 46%, and 3.5%, respectively.[15] In a more recent study of open-label peanut OIT during the 1-week rush immunotherapy phase, 17 of 22 subjects could not reach the 500-mg dose of peanuts.[12] In fact, 18% of subjects in this protocol dropped out secondary to side effects from peanut OIT. Unlike subcutaneous immunotherapy for inhalant allergens, OIT is administered daily, with the majority of OIT doses given at home. Despite the infrequent incidence of allergic reactions with home dosing (<4% of doses), certain factors may be associated with an increased likelihood of reacting with a home dose, including (1) dosing during concurrent illness, (2) suboptimally controlled asthma, (3) timing of dose administration after food ingestion, (4) physical exertion after dosing, and (5) dosing during menses.[16] Because OIT continues to be studied in research settings, other patterns may emerge, providing important information to characterize its safety profile further.

It is also important to recognize that OIT to other foods has been associated with adverse reaction rates equal to or even exceeding those seen with peanut OIT. In fact, in a double-blind study of milk OIT, reactions were seen in nearly half of all doses, with over 10% requiring treatment.[8] Further, other less common but potentially more important adverse consequences of OIT, such as eosinophilic esophagitis, clearly deserve further study.[11]

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Oral immunotherapy protocols currently under investigation use different dosing schedules and varying durations of treatment. The selection criterion for these protocols excludes individuals with a history of anaphylaxis with hypotension, which may represent many patients seeking this treatment in the clinical setting. Specific patient selection characteristics need further refinement because it has not yet been shown who may benefit most from the protection conferred by OIT treatment. "Desensitization" in this context refers to increasing the threshold of food needed to cause an allergic reaction, while on ongoing therapy, whereas "tolerance" is defined as resolution of allergy without ongoing treatment.[17] Individual patients and their families may have differing goals of therapy with respect to desensitization versus tolerance. The protective effects that are seen while still on therapy include a significant change in the family's perception of their quality of life,[18] but we do not know what happens once therapy has been discontinued. Current protocols are investigating whether treatment with higher OIT doses leads to an increased chance of inducing tolerance, but this strategy may come with increased risk. These factors must be elucidated in the research setting before widespread use.

Additional work is needed in designing a postdesensitization strategy for patients who demonstrate effective desensitization with OIT treatment. How much peanut should desensitized subjects ingest to maintain their state of protection? How often? Although there is evidence of increasing the threshold dose,[7,19] the ability to incorporate peanut freely into the diet is still in question. Without further investigation, clinicians will be unable to provide advice on the basis of objective data. In addition, this treatment may create a false sense of security leading to lax behavior in terms of access to self-injectable epinephrine and/or inappropriate emergency facility treatment with ingestion.

On a pragmatic note, current OIT protocols are time- intensive and labor-intensive, with dedicated study personnel available for observation of subjects postdosing, preparation and administration of doses, monitoring, and ongoing communication with patients and families. Space for initial desensitization, observed dose escalation visits, and challenges is also a concern. Because third-party reimbursement for such services has not yet been established, such personnel and spatial requirements may be difficult to implement. Assessing compliance is imperative given the potential for reactions if doses are missed.[20] Modification of checkpoints used in the research setting (pharmacy dose pack inspections, home diaries, and so forth) may need to be carried out.

Oral immunotherapy represents a promising therapeutic intervention for food allergy, but we remain at a state of equipoise with many unanswered questions to be studied, including the risks of OIT compared with avoidance, dosing regimen issues, patient selection, postdesensitization strategy, allocation of clinical resources, and reimbursement. Studies of OIT using other food allergens (eg, milk, egg) are associated with similar side effects and issues as those surrounding peanut OIT.[8,9] Therefore, OIT to neither peanut nor other foods is ready for clinical use.

Although everyone involved in patient care and in novel therapeutic research would like a treatment option to offer individuals with food allergy, now is not the right time. Further studies are needed to address these outstanding issues to determine whether this type of therapy is appropriate for clinical use.

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