



Pro/Con Debates

Food oral immunotherapy is superior to food avoidance-PRO



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Over the last decade much attention has focused on the possibility of using oral immunotherapy (OIT) as a therapeutic approach for treatment of immunoglobulin (Ig) E-mediated food allergies, a disease without a Food and Drug Administration (FDA)–approved disease-modifying therapy. Peanut allergy has been a particular concern because of its persistent nature and association with potentially life-threatening reactions. The OIT literature has been criticized for heterogeneity in trial design with disparities in identification of allergic individuals by double blind placebo-controlled food challenges, differences in desensitization approaches and maintenance doses of allergen, absence of a standardized product, inconsistency in the primary endpoint (eg, desensitization vs sustained unresponsiveness (SU)), a paucity of data on long-term effects on quality of life (QOL) and sustainability of therapy, and unproven benefits of therapeutic intervention over avoidance. In 2014, Wood and Sampson¹ identified many of these factors in their editorial piece in response to whether OIT was ready for clinical practice and argued that peanut OIT existed in a state of equipoise without clear evidence that the benefits of therapeutic intervention with OIT outweighed the burden of avoidance of allergen.¹

Allergists now face more questions from their food-allergic patients regarding whether the patient should or should not undergo a therapeutic intervention such as OIT. Although currently no FDA-approved therapy exists for OIT, this procedure is available in many clinical practices, and with the anticipated arrival of an FDA-approved peanut OIT product, most allergy practices may be offering OIT to some extent in the coming years. As a disclaimer, I

do not currently offer off-label OIT in my clinical practice, for several reasons, including that I believe waiting for FDA approval and grade A evidence is in the best interests of patients and allergists. Food and Drug Administration approval will insure that a safety label is on the product and the risks vs benefits of therapy will be transparent for all patients. In addition, I believe that charges to patients with compensation for allergists' time and effort need to be standardized. My following argument in favor of OIT over avoidance assumes FDA approval is in place and focuses primarily on peanut OIT, because this will likely be the first FDA-approved OIT product on the market. Here I outline how my thinking has evolved and the questions I would consider when talking with families deciding whether peanut OIT is indeed superior to avoidance for their child. As stronger evidence is gathered for other food allergens, conceivably the argument could be generalized.

How Has the Evidence Changed to Weigh in Favor of Peanut OIT?

In 2012, a Cochrane review of peanut OIT stated that peanut OIT could not be recommended because of a lack of randomized controlled trials establishing the efficacy and safety of peanut OIT.² Since 2012, more rigorously designed trials have been performed using peanut OIT.^{3,4} Bird et al³ reported results from a phase 2 trial using AR101 (Aimmune Therapeutics), showing 79% of subjects receiving therapy were able to safely ingest 300 mg or more of peanut protein after therapy.³ A phase 3 trial using AR101 and enrolling nearly 500 peanut-allergic subjects has been completed, with publication pending. Because the phase 3 results have not been peer reviewed and published, they cannot fairly be used to support the argument in favor of OIT; however, a well-designed phase 3 trial should answer several important questions regarding broad implementation of peanut OIT.

Many of the arguments for or against OIT as outlined in the opening paragraph will be answered with a phase 3 trial. If the phase 3 results are favorable, they would yield grade A evidence to support the use of a regulated product for treatment of peanut allergy with a standard buildup protocol, a common maintenance

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dose, and evidence that a peanut-allergic individual may significantly augment their threshold of reactivity to peanut compared with a treatment-naïve subject. If AR101 receives FDA approval, then allergists will have a product for peanut-allergic patients manufactured to US Pharmacopeia specifications that is easy to use, has associated costs that are reimbursable through insurance, and for which medicolegal concerns (eg, potential dosing errors or product contamination associated with product preparation and dispensation from an individual practice) are mitigated. If the results of the phase 3 trial do not support the safety and efficacy of AR101, then the argument in support of peanut OIT should be reconsidered.

What Are the Expectations of the Family or Patient?

Available evidence has shown that OIT increases the threshold of reactivity to the allergen for most individuals on therapy.^{3,4} Baumert et al⁵ have demonstrated through exposure risk modeling that elevating the threshold of reactivity from 100 mg or less of peanut protein to 300 mg reduces the risk of a reaction to peanut by greater than 95%, assuming accidental ingestion of allergen in high-risk foods and situations.⁵ For a patient with sensitivity to small amounts of peanut seeking a decrease in risk from potential cross-contamination, peanut OIT offers assured dosing of an amount greater than is typically encountered with accidental ingestion.

If the family is seeking a long-term “cure,” then OIT or any other therapy currently under investigation may not be the fix they are seeking. Studies have shown that protection from OIT may be lost with brief periods of avoidance.¹ Sustained unresponsiveness (SU) refers to absence of an allergic response on exposure to the allergenic food after a prolonged period of avoidance. Sustained unresponsiveness has been understudied and is not uniformly defined, with particular disagreement regarding how long of a period of avoidance is necessary to define the development of a fixed protective benefit of therapy. Reports suggest that approximately 30% to 80% of subjects may achieve SU, although factors such as age at study entry, length of time on therapy, inconsistency in maintenance dosing, and variability in the period of abstinence from therapy to SU challenge make clear conclusions regarding development of SU uncertain.⁴

The argument in favor of OIT relies heavily on expected desensitization benefit while on therapy and potential improvement in QOL during the first year of therapy that may induce meaningful change in the patient's perception of disease and ability to self-manage their allergy more effectively.⁴ A recent study supports the notion that the most benefit in QOL is experienced by those with worse initial QOL scores, and it may improve significantly after 6 months of maintenance therapy⁶; however, QOL data must be interpreted in light of the fact that no studies have looked at long-term effects of OIT on QOL.

Does the Patient Have Other Food Allergies?

The literature in support of OIT has primarily focused on the ability to desensitize the allergic patient, but the value in OIT as assessed by the individuals undergoing OIT appears to be related to their perception of a fatal food-induced reaction, regardless of whether this fear is valid, and the second most common reason being “to reduce the hassle of strict avoidance.”⁷ If the patient is allergic to only 1 food, then desensitization to that food alone may significantly reduce the “hassle of strict avoidance.” For example, allowing food-allergic patients to gain confidence with ingestion of foods with precautionary labeling (eg, “may contain,” “made in a factory that contains”) will reduce a significant burden of the disease. If the patient has multiple food allergies, then the advantage to treating 1 allergy may be less meaningful. This is not always the

case, because some individuals are frequently in situations with high-risk exposures to the allergen, or the particular allergen causes a higher burden of anxiety on the patient's QOL because of perception of risk.

What Are Lifestyle Considerations for the Patient and Family?

Most OIT protocols have required up-dosing every 2 weeks in the office until achieving maintenance doses of allergen, daily dosing after a snack or meal, and abstinence from exercise or activity that may elevate the patient's body temperature (eg, taking a hot shower) within 2 hours of dosing. These limitations in daily life are easily accepted by some and not achieved easily by others. When talking with families, consideration is given to whether the child is cared for in more than 1 household, and if the child's living arrangements are shared, ensuring that all family members are supportive and willing to maintain therapy is necessary.

Why Not Tip the Scale in Favor of OIT for All Foods?

The evidence outlined weighs in favor of the ability of peanut OIT to induce clinical desensitization for peanut allergy. Heterogeneity in trial design including differences in populations, interventions, outcomes, and protocol diversity with other allergens limits broad interpretability of other studies of allergen OIT.^{8,9} The question is asked of whether grade A evidence is necessary for every allergen to acknowledge its utility in clinical practice, but the reasoning for each allergen is more complex than answering the simple question of whether clinical desensitization may be induced.

If we assume that product standardization with FDA approval is required to assure quality and safety of the product, precision and consistency in dosing, and mitigation of medicolegal concerns for the allergist, then we must wait for a manufacturer to produce additional allergens; however, the utility of OIT for other foods requires consideration of other factors. Limited diagnostic tools accurately predict whether a child will or will not outgrow any food allergy, although most children will develop a natural tolerance to allergens other than peanut, tree nuts, fish, shellfish, and seeds.¹⁰ If a child is going to develop natural tolerance, is the risk of reacting with therapy unnecessarily greater than standard avoidance? For those with more persistent disease, preliminary evidence suggests that OIT may cause significant adverse effects and may not be sustainable for many patients.^{2,4} Introduction of allergens with OIT early in the life of an allergic child may be safer and more effective than waiting until the child is older (eg, more than 5 years),⁴ but these considerations are mostly hypothetical at this time. Data are lacking regarding the efficacy and safety of introduction of baked milk or baked egg in the younger population compared with standard OIT with unmodified allergen.⁴ In addition, evidence is especially limited regarding efficacy of OIT for foods other than peanut, milk, and egg.⁴

Conclusion

Is food OIT superior to food avoidance? The answer is likely to be yes for some patients with some food allergies. It is still premature to confidently generalize the data regarding peanut OIT to all other food allergens and all patients, for the reasons outlined. We are closer to stating that peanut OIT may be superior to avoidance for some individuals, and we are waiting for an FDA-approved product before implementation into clinical practice benefits patients and allergists.

Identification of the best patient for OIT will require an open dialogue between the allergist and patient, with shared decision-making regarding what is likely to be most beneficial for the patient, and when treating a child, what will achieve the family's goals for their allergic child. An honest discussion will include the potential increased risk of reactivity on therapy and the potential loss of protection when OIT is stopped for a prolonged period. The long-awaited results from a phase 3 trial are expected to provide

strong evidence that peanut OIT induces clinical desensitization and will further elucidate safety considerations for our patients. Product standardization with FDA oversight is best for both patients and allergists, and I anticipate that the near future will bring necessary information to tip the balance for or against the equipoise that still exists for OIT with foods other than peanut.

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