Approaches to maintenance dosing during oral immunotherapy

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ABSTRACT

Long term daily dosing for patients and families may be challenging due to food aversions, dosing protocols, and age of the patient. The few long term studies suggest that low quantity daily dosing is associated with passing higher dose challenges over the long term, whereas high dose maintenance may protect for longer avoidance intervals. We review the data for peanut and suggest several strategies for your patients.

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It is an exciting day for families when they reach their maintenance dose. However, the longer they administer the daily dose, the more difficult it becomes to maintain strict dosing protocols, especially for older children and for busy families. The specter of graduating from school and leaving home also creates unique challenges for patients as they try to maintain daily dosing that may be unsustainable without a family to provide support. Many teenagers in our early patient cohort had trouble maintaining daily dosing, especially because families were no longer tied to the updose cycle and constant reminders by staff and providers. Many children who have had severe allergic reactions to foods already have strong aversions to the smell and taste of those foods. Oral immunotherapy (OIT) with daily dosing can exacerbate that aversion and make long-term daily dosing unsustainable.[1]

In one long-term study of patients treated with peanut OIT, 30% of the patients were no longer ingesting the food after 2 years.[2] For these reasons, it is critical that outcomes, expectations, and long-term strategies for maintenance be discussed before the patient begins OIT.[3] This requires an honest and open discussion with the patient and his or her family. The treatment goals may vary for a toddler, school age child, or soon to be college student or adult. Also, if the patient is undergoing multiple food OIT, is the goal the same for each food? S.R. Inamdar and B. Mandal participated equally in data review, writing, and editing.

COMMON GOALS

Some commonly reported colloquial goals for therapy may range from "bite proof" to "free eating." "Bite proof" suggests that a patient would be able to experience most (*e.g.*, 95%) accidental ingestions without reactions, which thereby allows the patient increased freedom to visit restaurants, to travel, and to work. However, "bite proof" does not define a consistent protein amount, and the definition of what constitutes a "bite" may vary among patients and OIT prescribers. This is a gray area and should be openly discussed with regard to treatment goals. "Free eating" suggests eating as much of the food protein as frequently as a patient would like without lifestyle accommodations.

The type of food also influences the final treatment goals. For example, ubiquitous foods, such as milk and egg, may be chosen for "free-eating" compared with less commonly encountered nuts, such as peanut or walnut. Although a cure for food allergy is not a reasonable expectation, "sustained unresponsiveness," defined as being able to tolerate the allergen weeks or months after stopping ingestion, may be a reasonable goal for some patients. The growing body of research in peanut, milk, and egg allergy can guide decisions for providers and families for those allergens but it is unclear how well those data reflect outcomes in less-studied foods, such as shellfish, fish, or tree nuts.

When starting a patient on OIT, many questions need to be answered. What is the appropriate goal

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dose? How often does the allergen need to be consumed to confer long-term protection? Must the patient maintain strict dosing protocols in the maintenance phase and for how long? Determining the minimum quantity of food necessary to meet the patient's dietary goals, along with the lowest frequency of dosing that will maintain efficacy, will facilitate real-world, long-term adherence. Clinicians should expect to revisit these questions periodically as patient needs evolve after months or years of treatment.

FORMS OF FOOD

The form of the food used is also important. The spectrum of allergenic proteins present in different foods can also complicate maintenance. Egg, for example, requires dosing with uncooked egg proteins to ensure adequate exposure to raw egg that may be present in ice cream, salad dressings and other foods. The literature on egg OIT reports a variety of different egg sources such as egg powder,[4] raw egg,[5] undercooked egg,[6] along with different maintenance doses, which range from 194 mg of egg protein[7] to 3600 mg[2] and may reflect our evolving understanding of long-term pitfalls in treatment.[4] Similarly, with peanut, families often request alternatives to dosing with whole peanuts. Analysis of peanut butter and peanut flour shows differences in allergen content from brand to brand and from batch to batch.[8] AraH1 content in peanut butters varied from 991 to 21,406 μg/g. Peanut flours ranged in content from 787 to 14,631 μg/g in AraH2 content. For this reason, if transitioning from whole peanuts to peanut butter or peanut flour, we recommend that families start with a half equivalent protein dose and advance up rapidly in case there is a significant difference in allergenic protein. Many clinicians will transition these patients to different food forms of allergen in the office.

ONGOING MONITORING

Methods to follow an individual's food allergies over time could include blood tests such as food specific immunoglobulin E (IgE) levels, allergen-specific component testing, allergen specific IgG4 testing, or basophil activation tests. As the data evolves, having threshold values for biomarkers may help guide treatment decisions. Tsai *et al.*,[9] by using the data from The Peanut Oral Immunotherapy Study: Safety, Efficacy and Discovery (POISED)[15] study, showed that, in patients who became reactive after being off peanut OIT had higher peanut-induced basophil activation; higher serum IgE to peanut, AraH1, AraH2, AraH3; and lower serum IgG4 to peanut. Oral challenges under a variety of extreme conditions or with large amounts of food may also be beneficial, but again, this may be traumatic to patients and may not be helpful.[10] The discussion with patients and parents should include the possibility that a patient may initially be able to tolerate a defined amount of the allergenic food and be "bite proof" but that, within a few years, the patient may be able to "free eat"; however, long-term data supporting that notion are scarce.

POTENTIAL STRATEGIES

Approaches to attaining "free-eating" or "*ad-libitum*" consumption of the allergenic food include "escalation target dosing," in which individuals continue to updose regularly to high target doses with the expectation that they will eat that high dose amount daily. Unpublished strategies for peanut include aiming for the highest dose possible of daily eating. For example, if a peanut butter sandwich has an estimated 2 tablespoons of peanut butter in it (~6 g of peanut protein), then the clinician may set a goal dose of 4 g of peanut protein (16 g of whole peanut). Once well established at 4 g of peanut protein for several months, challenge to 24 g of whole peanut would demonstrate that a threshold for tolerance is reached. Two tablespoons of peanut butter, or ~24 peanuts, could then be consumed daily as food rather than as a "dose." Long-term safety and tolerability has not been published for this strategy but provides a guide for rapid escalation.

Another strategy is to use lower daily dosing for longer periods of time. In patients with egg allergy and who were on a maintenance dose of 2 g of egg white protein (~1/3 of an egg), only 55% passed 5 g of egg protein (one full egg) challenge after 10 months. After 22 months at the 2-g dose, 75% of the patients were able to pass 10-g egg challenge.[11] The patients in this study were not eating large amounts of egg *ad libitum* but continued to eat a small and sustainable amount of egg over years. This study highlighted the benefits of cumulative dosing over time to increase threshold dose tolerance.

CLINICAL TRIAL DATA

Regardless of the dose and the length of treatment, patients are likely to need to eat the food with some regularity because clinical tolerance diminishes with discontinuation of the food. One long-term follow-up study of peanut OIT started with a goal maintenance dose of 1800 mg of peanut protein daily and increased the goal maintenance dose to 4 g of peanut protein daily in eligible participants. They were then asked to stop eating peanut for 1 month and were subsequently challenged to 5000 mg of peanut protein; 50% of patients were able to pass the challenge after 1 month of avoidance.[12]

The AR101 Oral Immunotherapy for Peanut Allergy[13] trial and second-year open-label follow-up study give excellent information for dosing strategies in patients on

300 mg of peanut protein. Results of this study suggest that patients maintained on 300 mg of peanut (~1/4 tsp of peanut butter) dosing daily for 2 years resulted in higher dose tolerability and reduced adverse effects.[14] Some patients were randomized to every other day dosing for 4 weeks and twice weekly dosing for 24 weeks. Other cohorts were randomized to every other day dosing for 24 weeks and then every other week dosing for 24 weeks. At the end, each cohort went through double-blind placebo controlled food challenge to determine their dose tolerance after these dosing regimens. Eighty percent of those who were dosed at 300 mg of peanut protein daily for a total of 56 weeks were able to tolerate 1000 mg of peanut protein compared with 30% of those who dosed twice weekly for 24 weeks. Analysis of these data suggests that, at the 300-mg peanut protein dose, patients who want to have a high tolerance if they accidently ingest peanut should expect to dose daily for at least 2 years after reaching maintenance.

The POISED study aimed for a higher maintenance dose,[15] of 4 g of peanut protein daily (~3.3 tsp peanut butter), and, once that was achieved, reduced half of their participants to 300 mg and the other half to avoidance. They showed that once a patient had been successfully treated and was on maintenance of 4 g of peanut protein, the patient had a similar double-blind placebo controlled food challenge threshold dose (900 mg) after avoiding the allergen at 3 months as did those who had stayed on a 300-mg dose.[15] This suggests that higher maintenance doses might allow for less-frequent dosing regimens.

REACTIONS

An important question an OIT clinician should ask is, "What is our tolerance for reactions?" Risk factors for reactions during maintenance in patients with milk allergy in one study included the presence of asthma, pre-OIT reaction severity, lower tolerated dose, and epinephrine-requiring reactions during OIT treatment.[16] With that in mind, how do you "prove" protection from accidental ingestion or cross-contamination. Similarly, how do you know that, under the least ideal of circumstances, an individual who is free eating is "safe?" In one study, almost half of patients with milk allergy (21/43) and half of those with wheat allergy (21/43) who were treated with OIT, had failed exercise provocation tests after achieving maintenance. No difference in patient characteristics were seen between those who passed and those who did not. This suggests that some (many?) patients will have a lifelong need for exercise restriction with OIT dosing for these foods.[10]

In our program, attrition rates in our early cohort prompted a change in maintenance options. Once a child reached his or her peanut, tree nut, fish, or shellfish maintenance dose, we asked that the child maintain that dose for 3 months. Based on the published data, we aim for the highest maintenance doses possible, depending on patient tolerability and adherence. We then order food allergy blood tests with components, along with total serum lgE levels. If the patient has a 20% reduction in total food-specific lgE levels and/or reduction of pertinent components, or a 20% reduction in the serum-specific IgE to total IgE ratio, we schedule a high-dose food challenge. If the patient passes his or her high-dose challenge, then the patient is allowed to reduce the dosing frequency from daily dosing to three times a week dosing. Patients are also followed up with annual blood tests. If they continue to have an ongoing reduction in their serum lgE levels or components, then they are reduced to twice a week dosing for a year and, with continued reductions in their annual blood tests, they eventually will progress to once a week dosing. The expectation is that once a week dosing with higher doses maintains a minimum exposure and gives clear guidelines to families to ensure that they do not forget to eat the food. It also provides a sustainable strategy for college age or adult patients. Data from this approach have not been subjected to peer review.

CONCLUSION

Analysis of the nascent data offers several strategies for long-term dosing based on patient preferences and lifestyle. Some patients may prefer lower dosing daily to maintain consistency and predictability, whereas others may opt for higher dosing but with "days off." Other patients cannot get to the desired maintenance dose due to gastrointestinal symptoms, taste aversion, or other adverse effects. Occasionally, families have found that lower, more frequent doses are easier to maintain in their busy lives. They hope that low but more frequent dosing will improve tolerance over time and reduce variability of reactions. However, in our experience, overwhelmingly, most families and children prefer reducing the frequency of dosing. These strategies have not been studied long term in those children who may start OIT as toddlers, in whom volume of food is a bigger concern. Although some data exist for egg, milk, and peanut, we do not know if these strategies apply to other foods such as fish, shellfish, tree nuts, and seeds. Balancing long-term adherence with concerns for the frequency of mild reactions, severe reactions, and improved quality of life is the essence of the art and science of being an OIT provider.

CLINICAL PEARLS

- Discussion for maintenance dosing should begin before a patient starts OIT

- Higher protein maintenance doses may confer greater tolerance for the food
- Lower protein daily maintenance dosing may be easier and provides a measure of protection
- Reducing dosing frequency but with higher quantity dosing may improve adherence but more follow up is needed.

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