

# Peanut Oral Immunotherapy: Is the Second Year the Charm?



Joan H. Dunlop, MD, MHS, and Robert A. Wood, MD *Baltimore, Md*

Compared with the extensive experience with immunotherapy for environmental allergens and venoms, oral immunotherapy (OIT) for the treatment of food allergy has a relatively short history.<sup>1</sup> Peanut became a prime target for OIT as it is less likely to be outgrown and more likely to cause severe reactions than most other foods. Studies of peanut OIT culminated in FDA approval of a peanut OIT product in early 2020.<sup>2</sup> As currently labeled, this product requires an initial in-office dose escalation, gradual up dosing at office visits every 2 weeks, followed by indefinite maintenance dosing of 300 mg daily. Previous phase 3 studies (PALISADE<sup>3</sup> and ARTEMIS<sup>4</sup>) have only reported results up to the 1-year end point. The article from Vickery et al in this issue<sup>5</sup> chronicles the efficacy, adverse event, immunologic, and desensitization profile of study subjects carried over from the PALISADE trial for a second year of OIT to provide some insight into the 2-year performance characteristics of Peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH, formerly AR101).

Many questions arise when counseling patients and families regarding the pros and cons of peanut OIT. The most common concern relates to the risk of allergic reactions to PTAH compared with simply following a peanut-free diet. Embedded in this concern is the question as to whether reactions will decline or even disappear on a constant maintenance dose beyond the first year of therapy. Additional key questions include whether efficacy improves with prolonged dosing, whether daily dosing is truly necessary, and whether any protection will persist if treatment is stopped. This study addresses a few of these crucial questions.

With regard to the risks of treatment, mild dose-related symptoms remained common and systemic allergic reactions occurred among 6.4% and 16.1% of participants in the 2 daily dosing cohorts during their second year of therapy. Most were mild or moderate, but 2 were severe and epinephrine use was common. These rates were slightly lower than the rates of

systemic allergic reaction seen in the first year of therapy in the PALISADE trial and in the PTAH-naïve group in this trial, where 17% (n = 17/100) of participants experienced systemic allergic reactions. Two key points should be noted to put these data into further context. First, it is likely that most PALISADE participants with a higher predilection for significant allergic reactions never made it to this trial. In fact, 21% of actively treated participants in PALISADE discontinued treatment, over half due to adverse events. Second, although the numbers are small, it appears that the rate of systemic allergic reactions in the second year of OIT remains far higher than that of patients practicing avoidance alone. Although estimates vary, 1 large study reported a peanut reaction rate of 4.7% per year, with only one-third classified as severe and less than one-quarter treated with epinephrine.<sup>6</sup> Although further study is clearly needed, from a clinical perspective, these results support that the concerns raised by 2 recent meta-analyses, that OIT actually increases the likelihood of allergic reactions, carry into the second year of treatment, long after the risks associated with dose increases have passed.<sup>7,8</sup>

The Vickery study also sought to address the critical questions regarding the need for daily versus less frequent dosing. Although attempts to decrease dosing frequency might have increased treatment adherence in the every other day dosing group, subjects in the non-daily dosing groups experienced greater frequency and severity of adverse events as well as a lesser degree of desensitization compared with subjects in the daily dosing groups. More importantly, non-daily dosing was abandoned in 18 of the 111 subjects because of treatment-related adverse events, with 1 subject discontinuing treatment because of ongoing treatment-related adverse events even after reversion to daily dosing. It is likely that a subset of patients could do well with less than daily dosing, but at this juncture, it is not clear what distinguishes those who can and cannot tolerate non-daily dosing. Therefore, daily OIT dosing will remain the standard for the foreseeable future.

This requirement for daily, long-term dosing raises significant concerns about the feasibility of this therapy. Dosing fatigue is common with all therapies and may be even more common when adverse reactions are possible, and in this case actually frequent. For example, in addition to the systemic reactions noted above, other dose-related symptoms were reported in about half of participants on daily dosing in the second year of treatment. In our clinical experience and long-term follow-up studies of OIT,<sup>9,10</sup> patients frequently elect to return to strict avoidance rather than have to take a daily treatment with the potential for adverse reactions. This concern is exemplified in this trial, with only 80% of those in the PTAH-continuing groups completing the second year of OIT and even more remarkably with only 51% of those who were PTAH-naïve on entry to

Division of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, Md

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Corresponding author: Joan H. Dunlop, MD, MHS, Division of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, 600 N. Wolfe St., CMSC 1102, Baltimore, MD 21287. E-mail: [jdunlop7@jhmi.edu](mailto:jdunlop7@jhmi.edu).

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ARC004 completing the year-long study period, a dropout rate more than double that reported in PALISADE. We therefore need to recognize that dosing fatigue, nonadherence, and dropout will be critical issues in the real-world application of this treatment, even beyond completion of the first year of daily therapy.

Finally, in terms of efficacy, the results of the exit food challenges suggested modest increases in challenge thresholds with an additional year of daily treatment. Although the clinical importance of this finding is unclear among patients who are unlikely to be consuming peanut as part of their diets, any added buffer from reactions should be of some value. However, this added protection may come with unexpected risks, as demonstrated by the high rate of adverse reactions to peanut and other food allergens in those on PTAH treatment, raising concern that patients on peanut OIT will become more lax in peanut avoidance as well as avoidance of other foods.

It is important to understand that quality of life is also an important end point, and some studies do suggest that food allergy-related quality of life may improve with OIT.<sup>11</sup> Unfortunately, this study did not address quality of life measures. Therefore, at this point, the decision to start peanut OIT needs to be shared between the patient, the family, and the provider, considering all available data. For some families peanut OIT makes perfect sense, whereas for other the downsides outweigh the upsides. If further studies do demonstrate improvements in safety and efficacy with prolonged treatment, the balance may shift to a greater acceptance of treatment.

This is indeed an exciting time in the world of food allergy. For OIT the second year may not be the charm, but it may be an important step forward. Over the coming decade we will learn more about the long-term benefits, risks, and feasibility of OIT for peanut and other foods. In addition, there is real promise that new and potentially better treatments will emerge, some food specific and others more focused on the patient with multiple

food allergies. In spite of the downsides, it is fantastic that we finally have a treatment to offer our patients with peanut allergy and we can look forward to the day when we have multiple safe and effective treatment options to discuss with our patients based on science and precision.

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