REVIEW

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Oral immunotherapy: The answer to peanut allergy?

ABSTRACT

Peanut and tree-nut allergies have increased dramatically in prevalence, especially in children. Historically, children with food allergies have been treated through strict avoidance of the allergen. Recently, an oral preparation of peanut allergen (Palforzia) was approved for immunotherapy (ie, desensitization) in children 4 to 17 years old. This article reviews oral immunotherapy and its role in children with peanut allergies.

KEY POINTS

Peanut allergy is the most common food allergy in children.

A peanut-allergen powder is the first product approved by the US Food and Drug Administration for the treatment of childhood peanut allergy.

This product is given in a 3-phase oral protocol that gradually increases the dose to desensitize the patient to peanuts.

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Food allergies affect 32 million Americans, including roughly 1 in 13 children or 2 in every average-size American classroom.[1,2] In a recent survey,[3] approximately 38% of 4,075 respondents, both children and adults, reported having at least 1 food-related allergic reaction per year.

Many food allergies are first diagnosed when the patient is a young child. The most common food allergy in children is peanut and tree-nut allergy, estimated to affect 1 million children, and its prevalence more than tripled between 1997 and 2008.[4] Peanut allergy is also the most common cause of severe food-associated anaphylaxis.

Risk factors for peanut allergy include severe atopic dermatitis, egg allergy in infancy, a family history of peanut allergy, and a personal or family history of atopy.[5,6] The higher risk of familial peanut allergy may be in part related to delayed and reluctant introduction of peanuts to siblings of peanut-allergic children. Recent research suggests that delayed introduction of peanut into the diet is linked to higher rates of peanut allergies.[4,7] The Learning Early About Peanut Allergy trial showed that introducing peanuts to children at age 4 to 11 months decreased the risk of developing a peanut allergy in children at high risk.[8] Once patients develop peanut allergy, only 20% to 25% develop tolerance; most maintain their allergy for life.[9]

A NEW TREATMENT OPTION

Treatment of peanut allergy has been largely limited to educating patients and families about ingredient labeling and recommending complete avoidance of peanuts. Anaphylaxis caused by exposure to an allergen requires im-

TABLE 1

Protocol for the peanut-derived oral immunotherapy agent

Phase	Duration	Dosage
Dose-escalation	Single day	5 levels: 0.5, 1, 1.5, 3, and 6 mg; increasing doses every 20–30 minutes
Up-dosing	Months	11 levels: 3, 6, 12, 20, 40, 80, 120, 160, 200, 240, and 300 mg daily; increasing doses at visits every 2 weeks
Maintenance	Months to years	300 mg daily

Adapted from information in reference 15.

mediate treatment with epinephrine.

Oral immunotherapy is an emerging option offered by a limited number of allergists and immunologists. Although this therapy has shown some efficacy for food allergy desensitization, it has been criticized for lacking established protocols, having high rates of adverse reactions, and using grocery store products that may contain variable amounts of the allergenic proteins.[10,11]

In January 2020, the US Food and Drug Administration (FDA) approved a novel peanut-derived oral immunotherapy product for treating childhood peanut allergy: Palforzia (peanut *Arachis hypogaea* allergen powder-dnfp). Containing a powder derived from roasted peanuts packaged in capsules or sachets at varying doses, it is indicated for use in children 4 to 17 years old. The capsule or sachet is not swallowed. Instead, it is opened, and the powder is mixed with applesauce, pudding, or something similar. It is given in dosing phases according to an oral immunotherapy protocol.

GRADUALLY INCREASING DOSES

Oral immunotherapy is based on the concept of desensitization, exposing the patient to gradually increasing doses of a specific allergen to induce tolerance and raise the threshold that triggers a reaction. Over time, this process desensitizes the immune system to the allergen so that the symptoms that occur on exposure are less severe or cease altogether.

Whereas oral immunotherapy uses oral ingestion of antigenic proteins to promote physiologic changes that suppress an allergic response to the antigen, desensitization to other allergens is done by various other routes, including the subcutaneous (the most common example being environmental allergen immunotherapy or "allergy shots"), sublingual, and epicutaneous routes.

Although its mechanisms are not completely understood, oral immunotherapy works primarily through allergen activation of dendritic cells in the gut mucosa, resulting in effector cell modulation. This inhibits immunoglobulin E-dependent mast cell and basophil activation, mitigating the ability of an allergen to elicit an allergic response. During desensitization, T-regulatory cell function is increased while antigen-specific T-helper 2 (Th2) cells become apoptotic and anergic.[12]

A 3-phase protocol

A typical oral immunotherapy protocol[13–15] proceeds in 3 phases: initial dose escalation, up-dosing or buildup, and maintenance **(Table 1)**.[15] Some protocols also use an oral food challenge at the beginning and end of the study, sometimes after a period of avoidance of the study drug.

Treatment of peanut allergy has consisted of education, avoidance, and epinephrine

The dose-escalation phase typically lasts 1 day and starts at a very small, subthreshold dose of the allergen. This dose is increased to the goal dose for that day or the highest dose tolerated without symptoms. Labeling recommendations for the peanut immunotherapy agent are to begin at 0.5 mg and increase the dose every 20 to 30 minutes up to 6 mg **(Table 1)**.[15] This phase requires close patient monitoring in a healthcare facility by a practitioner trained to manage potentially severe allergic reactions, including anaphylaxis. Patients need to be observed for at least 60 minutes after the last dose.

Up-dosing phase. After the dose-escalation phase, patients continue to take the high-

est dose that they achieved, at home, once a day, until the first up-dosing phase appointment. For the peanut-allergen product, this needs to be within 4 days.

At each up-dosing appointment, the patient receives a higher dose and is then observed for reactions. If all goes well, the patient continues to take the higher dose every day at home until the next appointment, typically at 2-week intervals, until the goal dose or the highest tolerated dose is reached. This is the maintenance dose. At this dose, the patient has achieved desensitization and can maintain allergen hyporesponsiveness during regular ingestion of food.

Of importance: patients need to take their medicine every day. Even brief dosing interruptions—just a few days—can result in loss of desensitization, and patients can have a hypersensitivity reaction to a previously tolerated dose of the allergen.

For the peanut oral immunotherapy agent, the up-dosing phase has 11 levels, starting at 3 mg/day and increasing every 2 weeks until the patient reaches 300 mg/day. Each new dose level is administered under supervision at a healthcare facility.

Oral immunotherapy is not a cure for food allergies—it reduces reactivity to peanut

The maintenance phase can go on for months to years, during which the patient continues to take the established maintenance dose every day. The recommended dosage for the peanut-allergen product is 300 mg/day.

Adding a food challenge

If the patient has been in the maintenance phase for a long time and is doing well, a food desensitization challenge may be performed using an age-appropriate, full serving of food. (The gold standard for diagnosing food allergy is a double-blind, placebo-controlled food challenge, but this is rarely done.)

In some protocols, if the patient completes a food challenge without symptoms, the daily maintenance dose is discontinued for 4 to 12 weeks, and another food challenge is performed. If the patient can ingest the food without an adverse reaction, then sustained unresponsiveness has been achieved, meaning the desensitized state is maintained without the need for regular allergen ingestion. The duration of sustained unresponsiveness achieved using the FDA-approved peanut powder product has not been established in clinical trials.

Some patients experience symptoms of a hypersensitivity reaction during the food challenge: eg, they had been tolerating the controlled doses of allergen, but had a reaction to a full meal. These patients are often deemed "bite-proof," meaning they are unlikely to have an allergic reaction to 1 bite of a peanut product or a product contaminated by peanut, but unlike patients who have sustained unresponsiveness, they need to continue their maintenance dosing to sustain their hyporesponsiveness, and they should avoid peanuts in their diet.

WHAT ARE THE EFFICACY AND SAFETY CONCERNS OF ORAL IMMUNOTHERAPY?

Safety and efficacy data for the peanut-allergen agent come from clinical trials that enrolled more than 700 patients who were allergic to peanuts.

In a phase 3 trial,[16] 551 patients ages 4 to 55 with allergic dose-limiting symptoms at 100 mg or less of peanut protein (approximately one-third of a peanut kernel) were randomly assigned to receive the study drug or placebo in an escalating-dose protocol. Most patients (n = 496) were between ages 4 and 17, which reflects the FDA-approved age range.

Once participants reached the final study dose, they underwent a peanut challenge. The study drug recipients could ingest higher doses of peanut protein without dose-limiting symptoms than placebo recipients. The most common adverse reactions during treatment (incidence > 5%) were gastrointestinal, respiratory, and skin symptoms and anaphylactic reactions.[16]

This peanut-derived oral immunotherapy agent, like other forms of oral immunotherapy (which are not FDA-approved), is not appropriate for patients with uncontrolled asthma, eosinophilic esophagitis, or other eosinophilic gastrointestinal disease.

Adverse reactions are a leading reason for stopping oral immunotherapy. In the randomized controlled trial of peanut allergen,[16] 43 (11.6%) of the 362 patients assigned to the active treatment group withdrew because of adverse events. Gastrointestinal disorders

accounted for most of the adverse reaction-related discontinuations. Most discontinuations occur during the escalation or up-dosing phases, with only a few patients withdrawing during the maintenance phase.[15,16]

For those experiencing adverse reactions, the onset was typically rapid (median time 4 minutes after the dose), and symptoms resolved relatively quickly (median time 37 minutes).[15] Thus, careful patient monitoring is crucial during the first hour after dosing. Additionally, dose escalation and up-dosing must be done in a medical setting with medical personnel experienced with oral immunotherapy and treatment of allergic reactions.

Patients should be cautioned that the FDA-approved oral immunotherapy product is not a cure for food allergies; instead, it is intended to reduce their reactivity to peanut. In the initial clinical trials, an exit challenge was included to approximate a real-life scenario of accidental ingestion.

Daily dosing important

Longitudinal studies are under way, with 2-year data from an open-label follow-up study that suggest long-term efficacy of daily treatment with the peanut-derived oral immunotherapy agent.[17] Patients who received daily doses in the study showed greater immunomodulation and higher rates of desensitization that increased over time compared with patients given nondaily dosing. Furthermore, most patients in the daily-dosing groups had lower adverse event rates than those in the nondaily dosing groups.

All forms of oral immunotherapy carry the risk of life-threatening anaphylaxis. Oral immunotherapy has not been studied in pregnant women, and the risks to a fetus are unknown. Anaphylactic reactions could lead to hypotension and potential fetal demise.

Counseling needed

Patients and families must be carefully counseled on the signs and symptoms of anaphylaxis and carry auto-injectable epinephrine at all times. Strict avoidance of allergens, aside from daily oral immunotherapy dosing, is imperative. Illness, physical exertion around dosing, and recent dental work or tooth loss may increase the risk of a reaction.

When identifying candidates for oral immunotherapy, consideration should be given to the capacity of the patient and family to adhere to the safety precautions and dosing regimens. This requires careful discussion of medication compliance, family support, and ability to attend regularly scheduled appointments before initiating treatment. Patients with families who are not highly motivated to incorporate the necessary lifestyle modifications are unlikely to be ideal candidates for therapy.

IMPLEMENTING A PROGRAM: COST, TRAINING, RISKS, LIMITATIONS

Incorporating oral immunotherapy into a clinical practice requires significant resources dedicated to staffing, training, and physical space. Due to the extended course of treatment, a practice interested in implementing oral immunotherapy would need to ensure that adequate clinical support staff are available for preparing materials, administering doses, monitoring, and treating reactions if they occur.

The initial dose-escalation visit can last 5 to 6 hours. During this time, doses are given every 20 minutes, and clinicians monitor and assess the patient's vital signs, making it a time-intensive first day.

Dosing interruptions of only a few days can result in loss of desensitization

Subsequent visits in the up-dosing phase involve preparing materials, administering 1 dose, and monitoring for a minimum of 1 hour. As a clinical practice with oral immunotherapy grows, these subsequent visits would require a structure similar to the established practice of incorporating allergen inhalant immunotherapy in allergy practices, but more allergic reactions are expected with oral immunotherapy.

Providers and clinical support staff should have appropriate training for administering oral immunotherapy and managing allergic reactions. Practices must be equipped with medications needed to treat anaphylaxis, oxygen, and basic resuscitation supplies.

Clinicians who prescribe the FDA-approved product and pharmacies that dispense it are required to register with the FDA Risk Evaluation and Mitigation Strategy program.[18] This ensures that clinical practices admin-

istering oral immunotherapy are adequately prepared to monitor, identify, and treat anaphylaxis.

Given the intensive process, duration, and lifestyle restrictions associated with oral immunotherapy, patients and their families need extensive education before starting treatment. Adequate time is needed for consultations with providers to counsel on the risks, benefits, and limitations of oral immunotherapy. This is a crucial part of optimizing success and safety with oral immunotherapy.

Thus, the cost of oral immunotherapy will include both the fees associated with supplies (ie, drug and materials used for dosing) and the cost of additional provider time, clinical support staff, and physical space to accommodate the frequency and duration of office visits. The list price for Palforzia is about $890 per month ($11,000/year), although the manufacturer has various patient assistance and copay savings programs. This is much more expensive than purchasing grocery store products and using them in published protocols. A cost-effectiveness analysis found that the new product may be cost-effective only under some assumptions.[19]

While peanut-derived oral immunotherapy has been shown to be effective for mitigating allergic reactions to peanut, there are limitations that play a role in determining ideal candidates for treatment. Notably, not all patients may be able to achieve tolerance. Additionally, individuals undergoing oral immunotherapy must continue a daily maintenance dose to maintain hyporesponsiveness, as the duration needed to achieve uniform sustained tolerance is not yet known.

The risk of reactions during oral immunotherapy must also be carefully considered. A recent meta-analysis of 12 oral immunotherapy trials showed a higher frequency of reactions and epinephrine use while undergoing oral immunotherapy compared with food avoidance alone.[11] But this does not take into account the protective effect and better quality of life associated with oral immunotherapy once maintenance dosing has been achieved.[20] Providers, patients, and families must seriously consider the level of resources and commitment required for the success of oral immunotherapy before undertaking this treatment.

AN EXCITING TIME OF EMERGING OPTIONS

Oral immunotherapy with this new product for peanut allergy has challenges and limitations and therefore requires careful consideration from patients, families, and prescribers. However, its approval ushers in an exciting time of emerging therapeutic options for patients with food allergy.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Gupta RS, Warren CM, Smith BM, et al**. The public health impact of parent-reported childhood food allergies in the United States. Pediatrics 2018; 142(6):e20181235. doi:10.1542/peds.2018-1235
2. **Food Allergy Research & Education (FARE)**. Facts and statistics: key information to help better understand food allergies and anaphylaxis. Accessed January 21, 2021. https://www.foodallergy.org/resources/facts-and-statistics.
3. **Fierstein JL, Brown D, Gupta R, Bilaver L**. Understanding food-related allergic reactions through a US national patient registry. J Allergy Clin Immunol Pract 2020; S2213–S2198(20)30827-8. doi:10.1016/j.jaip.2020.08.011
4. **Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA**. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010; 125(6):1322–1326. doi:10.1016/j.jaci.2010.03.029
5. **Hourihane JO, Dean TP, Warner JO**. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. BMJ 1996; 313(7056):518–521. doi:10.1136/bmj.313.7056.518
6. **Lack G**. Update on risk factors for food allergy. J Allergy Clin Immunol 2012; 129(5):1187–1197. doi:10.1016/j.jaci.2012.02.036
7. **Gupta RS, Walkner MM, Greenhawt M, et al**. Food allergy sensitization and presentation in siblings of food allergic children. J Allergy Clin Immunol Pract 2016; 4(5):956–962. doi:10.1016/j.jaip.2016.04.009
8. **Du Toit G, Roberts G, Sayre PH, et al**. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015; 372(9):803–813. doi:10.1056/NEJMoa1414850
9. **Hourihane JO, Roberts SA, Warner JO**. Resolution of peanut allergy: case-control study. BMJ 1998; 316(7140):1271–1275. doi:10.1136/bmj.316.7140.1271
10. **Wasserman RL, Jones DH, Windom HH**. Oral immunotherapy for food allergy: the FAST perspective. Ann Allergy Asthma Immunol 2018; 121(3):272–275. doi:10.1016/j.anai.2018.06.011
11. **Chu DK, Wood RA, French S, et al**. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet 2019; 393(10187):2222–2232. doi:10.1016/S0140-6736(19)30420-9
12. **Yu W, Freeland DMH, Nadeau KC**. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol 2016; 16(12):751–765. doi:10.1038/nri.2016.111
13. **Feuille E, Nowak-Węgrzyn A**. Oral immunotherapy for food allergies. Ann Nutr Metab 2016; 68(suppl 1):19–31. doi:10.1159/000445391

14. **Freeland DMH, Manohar M, Andorf S, Hobson BD, Zhang W, Nadeau KC**. Oral immunotherapy for food allergy. Semin Immunol 2017; 30:36-44. doi:10.1016/j.smim.2017.08.008
15. **Palforzia**. Prescribing information. Aimmune Therapeutics; 2020. Accessed January 21, 2021. https://www.fda.gov/media/134838/download.
16. **PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, et al**. AR101 oral immunotherapy for peanut allergy. N Engl J Med 2018; 379(21):1991–2001. doi:10.1056/NEJMoa1812856
17. **Aimmune Therapeutics**. Press release: new two-year Palforzia™ data show on-going safety and efficacy and continued immunomodulation in patients with peanut allergy. June 8, 2020. Accessed January 21, 2021. https://ir.aimmune.com/news-releases/news-release-details/new-two-year-palforziatm-data-show-going-safety-and-efficacy-and.
18. **US Food and Drug Administration**. Approved risk evaluation and mitigation strategies (REMS): Palforzia (peanut (*Arachis hypogaea*) allergen powder-dnfp). Accessed January 21, 2021. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=398.
19. **Shaker M, Greenhawt M**. Estimation of health and economic benefits of commercial peanut immunotherapy products: a cost-effectiveness analysis. JAMA Netw Open 2019; 2(5):e193242. doi:10.1001/jamanetworkopen.2019.3242
20. **Epstein-Rigbi N, Goldberg MR, Levy MB, Nachshon L, Elizur A**. Quality of life of food-allergic patients before, during, and after oral immunotherapy. J Allergy Clin Immunol Pract 2019; 7(2):429–436.e2. doi:10.1016/j.jaip.2018.06.016

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