Integrating oral immunotherapy into clinical practice

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Date of Original Release: January 2021. Credit may be obtained for these courses until December 31, 2021.

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1.00 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: Stephanie A. Leonard, MD, Susan Laubach, MD, and Julie Wang, MD (authors); Zuhair K. Ballas, MD (editor)

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: S. A. Leonard and S. Laubach receive research support from Aimmune Therapeutics and DBV Technologies. They have no financial disclosures pertaining to this article. S. A. Leonard is a Medical Advisory Board member for the International FPIES Association. J. Wang receives research support from the National Institute of Allergy and Infectious Diseases, Aimmune, DBV Technologies, and Regeneron, and has received consultancy fees from ALK Abello, DBV Technologies, and Genentech. Z. K. Ballas (editor) disclosed no relevant financial relationships.

Activity Objectives:

1. To summarize recent data on food allergy treatments and develop ways to optimize integration of oral immunotherapy (OIT) into clinical practice.
2. To determine which patients are good candidates for allergen oral immunotherapy and to describe the overall schedule of OIT dosing.
3. To identify and manage the most common adverse effects of OIT.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Tina Banzon, MD, Brenna LaBere, MD, Elsa Treffeisen, MD, and Lynda C. Schneider, MD.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The examination authors declare no relevant conflicts of interest.

In 2020, the first food allergy treatment, an oral immunotherapy (OIT) product for peanut allergy, was approved by the Food and Drug Administration, and a peanut epicutaneous immunotherapy patch was under review. As food allergy therapies become available and widespread, allergy offices will need to adjust practices to be able to offer their patients these new treatments. OIT is an intensive therapy that requires commitment from patients and their families, and open communication with the practice is paramount. OIT may not be the right therapy for every patient, and although identifying good candidates is still an area rich for research opportunity, experience from cohorts and clinical trials provides some insight. It is important to understand the scope of practice for each member of the OIT team based on state regulations for a particular location. Staffing and space will likely dictate how many patients at an individual office could be on active OIT at one time. Emergency medications, supplies, and protocols must be in place. Screening, scheduling, visit procedures, monitoring, home dosing, dose modifications, safety precautions, adverse reactions, and maintenance will be addressed in this article. Finally, adjunct therapies under investigation will be reviewed. (J Allergy Clin Immunol 2021;147:1-13.)

Key words: *Oral immunotherapy, food allergy treatment, sublingual immunotherapy, epicutaneous immunotherapy*

Food allergies affect up to 6% to 8% of children younger than 18 years.[1] Without a current cure, management of food allergy has relied on strict avoidance and treating allergic reactions when they occur. Desensitizing food-allergic patients with the food allergen as a form of immunotherapy has been a focus of

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Received for publication July 7, 2020; revised November 4, 2020; accepted for publication November 16, 2020.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.11.011

Abbreviations used

AHP: Allied health professional
EGD: Esophagogastroduodenoscopy
EMS: Emergency medical services
EoE: Eosinophilic esophagitis
FDA: Food and Drug Administration
GI: Gastrointestinal
OFC: Oral food challenge
OIT: Oral immunotherapy
ODK: Office Dose Kit
PALISADE: Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization
QOL: Quality of life
SCIT: Subcutaneous immunotherapy
sIgE: Serum-specific IgE
SU: Sustained unresponsiveness

investigation over the past 2 decades, starting with reports in the 1980s to proof-of-concept studies in mid-2000s.[2] The clinical use of allergen immunotherapy, of course, has been around since the early 1900s, and in fact, a case of oral egg desensitization was described in 1908.[3] Oral immunotherapy (OIT) trials have primarily focused on peanut, cow's milk, and egg; however, wheat, tree nuts, and sesame OIT trials have been conducted, as well as multiallergen OIT.[2,4-11] Only in 2020 was the first food allergy treatment, a peanut OIT drug called Palforzia (Aimmune Therapeutics, Brisbane, Calif), approved by the Food and Drug Administration (FDA). A peanut epicutaneous immunotherapy patch, Viaskin Peanut (DBV Technologies, Montrouge, France), was under FDA review.

As food allergy treatments become available and widespread, allergy offices will need to adjust practices to be able to provide their patients these new treatments. Food allergy immunotherapy guidelines have been published by the European Academy of Allergy and Clinical Immunology and the Canadian Society of Allergy and Clinical Immunology, as well as a US consensus report from the Food Allergy Research and Education Oral Immunotherapy for Food Allergy Summit.[12-14] In this review, we will summarize recent data on food allergy treatments in the context of outlining a practical guide to administering OIT in the office.

BACKGROUND

OIT for food allergy has been administered clinically in some allergy practices using non–FDA-approved food products.[15,16] Without a standard protocol, there has been a wide variety of approaches to administering OIT in the office as well as in clinical trials. See Table I[15-17] for a summary of select OIT publications.

Net health benefit of OIT

There continues to be debate about the net health benefit of OIT. From a medical standpoint, the benefit of OIT is to protect food-allergic individuals from reacting to accidental ingestions of their allergen and/or lessen the severity of a reaction if one were to develop. Accidental reactions are common as evidenced by a study in which 72% of preschoolers with known food allergy reported an allergic reaction over a median follow-up of 36 months, and 53% had more than 1 reaction.[18] Although the severity of accidental ingestions is unpredictable, 30% to 50% of food reactions are classified as severe.[19]

Adverse effects from OIT are frequent, and although most are mild, systemic reactions have been reported in both placebo-controlled and retrospective community-based studies on peanut OIT (Table I). Two systematic reviews and meta-analyses concluded that although OIT effectively induces desensitization, it is associated with increased risk of systemic reactions, including anaphylaxis, and increased use of epinephrine compared with placebo or avoidance.[20,21]

There is currently a lack of evidence that OIT leads to the development of immune tolerance when therapy is discontinued, and therefore cannot be considered curative. Studies continue to assess the achievability of sustained unresponsiveness (SU), or persistent desensitization after OIT is discontinued for a period of time, in different populations and on different protocols. In 2019, The Institute for Clinical and Economic Review assessed both Palforzia and Viaskin and came to the conclusion that the long-term benefits of desensitization did not outweigh the short-term risks.[22] Families, allergist/immunologists with OIT experience, and advocacy groups have highlighted that this conclusion suffered from lack of data on quality of life (QOL) and protection from real-world accidental ingestions.[23] Methodology of QOL studies in OIT has varied in regard to comparison with controls and whether the QOL measurement was disease-specific versus general. Three studies that used the validated Food Allergy Quality of Life Questionnaire and included controls reported improvement in scores pre- and postactive OIT in children and/or their parents.[11,24,25] Further study into the effect of OIT on QOL will facilitate the discussion of long-term benefits of this treatment.

Patient advocacy groups have been supporting the push toward expanding access to treatment. Food allergy is a chronic condition that is associated with increased anxiety and decreased QOL.[26] Until now, the care of patients with food allergy has largely placed the burden of safety on the individual and family.[13] Based on the principles of beneficence and patient autonomy, the patient and family have the right to decide whether or not the potential outcomes (ie, desensitization) are worth pursuing.[13] Proactively protecting children from accidental ingestions that are mostly inevitable can be life-changing, and it is evident to providers of OIT that most patients on such therapies and their families experience gratitude and relief.[11,25]

Patient advocacy groups, such as Food Allergy Research and Education, invested start-up funds into new companies that would be able to translate emerging data from small clinical trials done at academic centers into phase II and III clinical studies that could lead to an FDA-approved product for clinical use. On its website, Aimmune Therapeutics credits its formation "to a united call to action by leading stakeholders in food allergy."[27] Food Allergy Research and Education has since divested its stock in Aimmune Therapeutics. As these products start to become available, management of food allergy will change drastically.

Now that the United States has an FDA-approved OIT product to treat peanut allergy, more allergist/immunologists will likely offer OIT as a treatment. As a specialty, we can benefit from the experience of those who ran the controlled clinical trials and those who have been practicing OIT using non–FDA-approved food products in the community. This report offers practical ways to integrate OIT into clinical practice and reviews adjunct therapies under investigation.

TABLE I. Summary of select community-based and phase 3 OIT studies

Characteristic	Afinogenova et al[15]	Wasserman et al[16]	PALISADE[17]
Type of study	Retrospective cohort from single community practice	Retrospective cohort from single community practice	Phase 3 randomized, double-blind, placebo-controlled
Type of immunotherapy	Peanut OIT	Peanut OIT	Peanut OIT
No. of participants	783	270	413 (active)
Age (y)	Mean, 9.7 (range, 3.5-48.3)	Mean, 8.1	90% <18 y, 58% <12 y
Sex: female, %	38	40	44
Baseline OIT allergen testing			
SPT wheal (mm)	13.1 (range, 0-40)*	NA	Median, 11 (range, 9-14)
sIgE (kU/L)	53.1 (range, 0->100)*	Median, 24.1 (range, 0.25- 100)	Median, 69 (range, 19-194)
Comorbidities, %			
Asthma	53	43	53
Other food allergies	65	NA	65
Past anaphylaxis to OIT allergen	25	70.7	66
Dosing			
Starting dose (mg protein)	0.1	0.0025	0.5
Maintenance dose (mg protein)	Median, ~1800 mg† (range, 750-4500)	3000 mg (n = 3; 2000 mg)	300 mg
Time in build-up (d)	Mean, 230.5 (range, 1-697)	Median, 180.6 (105-2576)	~168 d
Products used			
	Byrd Mill 12% light roast peanut flour (for doses < 400 mg), then whole peanuts, powder, butter, M&M's, or Reese's PB cup	Peanut flour suspended in Kool-Aid, then peanuts, peanut flour (28%), powder, butter, M&M's, Bamba, or Reese's pieces	AR101 (Palforzia) characterized peanut protein product
Outcomes, %			
Reached maintenance	89 (697 of 783)	79 (214 of 270)	83 (310 of 372)
Systemic reactions, %			
Build-up	10 (78 of 783)	23 (63 of 270)	8.5 (31 of 372)
Maintenance	18.8 (131 of 697)	13 (28 of 214)	8.7 (27 of 310)
Withdrawals, %			
Total	14 (108 of 783)	39 (106 of 270)	21.5 (80 of 372)
Build-up	11 (86 of 783)	18 (48 of 270)	NA
Maintenance	3 (22 of 697)	27 (58 of 214)	NA
Reason for withdrawal			
Gastrointestinal symptoms	40 (43 of 108)	23 (24 of 106)	6.5 (24 of 80)
Inconvenience/taste/other	19 (20 of 108)	23 (24 of 106)	46.3 (37 of 80)
Systemic reactions	9 (10 of 108)	18 (19 of 106)	8.8 (7 of 80)
Unknown/lost to follow-up	22 (24 of 108)	37 (39 of 106)	0

NA, Not applicable/available; *SPT*, skin prick testing.
*Median or mean not indicated.
†Reported as peanuts; 1 peanut = ~300 mg peanut protein.

OFFICE PREPAREDNESS FOR OIT

Developing standard operating protocols is a helpful reference. Some examples of protocols for OIT may include those for administering the intervention itself, managing allergic reactions in the office, providing after-hours patient support, and navigating insurance authorization. Preparing protocols is a useful exercise in thinking through each step, ensuring resources are available, and having a plan for situational responses.

When available, an electronic health record may be leveraged to standardize protocols and monitor patient progress. For instance, an electronic health record registry of patients on OIT will help keep track of patients, improve adherence to treatment, and identify trends in the clinical course of OIT. Data from the electronic health record can also be mined to help identify patient characteristics that predict successful desensitization or that may be associated with premature discontinuation of therapy.

Staffing and resources

Having staff well-trained in managing allergic reactions is key in administering OIT to patients. For example, registered nurses (RNs) or licensed vocational nurses (LVNs) who participate in conducting clinic oral food challenges (OFCs) would be valuable on an OIT team. If resources allow, other valuable members of an OIT team would include a dietician, a psychologist, a child life specialist, and a nurse educator.

It is important to understand the scope of practice for each member of the OIT team based on state regulations for a particular office location. For instance, a licensed vocational nurse may be able to measure and administer specific doses of OIT and assess whether or not a new sign or symptoms develop but may not be allowed to follow a treatment protocol that an RN may be licensed to do. Some programs may reasonably be run by a skilled and experienced allied health professional (AHP), such as a nurse practitioner or physician assistant, with close oversight by a supervising physician. All OIT office dosing visits should have a physician or AHP on-site to evaluate and treat within minutes if a reaction occurs.

Staffing and space will likely dictate how many patients at an individual office could be on active OIT at one time. Ideally, an OIT patient would remain in a private treatment room for the duration of dosing and observation, but if transitioned to the waiting room after 30 minutes of close observation, a treatment

room should be readily available in case a reaction occurs. Besides physical space, experience of staff may determine how many OIT visits could be performed simultaneously.

The office will need to decide whether all physicians in a practice will act in a supervising capacity for OIT patients, or only specialized core members, and who will field after-hours calls. Families should be counseled about when to call the office after hours. If a family is unsure about whether or not to give a dose and it is after hours, the patient should hold the dose and call the next morning during regular business hours. Missing 1 to 2 doses is typically well tolerated and does not require dose modification. Physicians should advise erring on the side of caution and holding the dose. This should have the dual effect of enhancing safety and minimizing staff impact after hours. Decisions on dose modifications or overall OIT treatment course can be reserved for particular physicians or AHPs who are familiar with the protocol and individual patients. Further discussion on dose modifications can be found in the *Home Dosing* section below. Urgent calls regarding allergic symptoms can be handled by any allergist/immunologist on call.

Safety considerations

The updated American Academy of Allergy, Asthma & Immunology Work Group Report on *Conducting an Oral Food Challenge* contains details on emergency preparedness for life-threatening allergic reactions, which can be applied to OIT administration in the office.[28] The report includes overview of emergency medications, necessary equipment, and a standard protocol for managing anaphylaxis in an office.

Intramuscular epinephrine is the first-line treatment for anaphylaxis. If available, stocking epinephrine autoinjectors in the office can be beneficial in improving response time and OIT safety. Although vials of 1:1000 epinephrine may be a more economic option, data suggest that errors are often made with multiuse vials, even by trained nurses and physicians.[29] If multidose vials are used, the patient weight–based dose should be precalculated before the OIT dose administration in the office. Antihistamines should also be available for milder symptoms. Oral/intramuscular diphenhydramine has the most data supporting its use in acute allergic reactions to food, but oral cetirizine is less sedating and has a similar time to onset of action.[30] Additional emergency medications include albuterol and supplemental oxygen with supplies, H2 antihistamines, steroids, and intravenous fluids with supplies. Each patient should have a medication sheet with precalculated doses that is immediately available.

Emergency supplies including bag-valve-mask should also be available. Intubation equipment, oro- or nasopharyngeal airways, and other supraglottic airways could be stocked with the caveat that providers should have proper training in advanced airways management.[31] Endotracheal intubation by inexperienced providers has been shown to increase complications, particularly in an edematous airway as may be present during anaphylaxis.[32] Vasopressors require monitoring and could be stocked in offices that are part of a medical facility.

At a minimum, the physicians, AHP, and staff conducting OIT should have current cardiopulmonary resuscitation certification. Pediatric advanced life support and advanced cardiovascular life support certifications provide practitioners with advanced skills in the rare occurrence of cardiovascular collapse. If the practice is part of a medical facility, collaboration with the emergency department and code blue team on emergency protocols can be beneficial. An anaphylaxis mock code is useful in sorting out roles and practicalities. If the office does not have close access to the emergency department or a code team, a protocol for when to activate emergency medical services (EMS) should be implemented. The threshold for calling may depend on how quickly EMS can respond and how far from an emergency department the clinic is located. In general, EMS should be activated if a patient experiences a severe allergic reaction that is poorly responsive to epinephrine, requires more than 1 dose of epinephrine, has signs or symptoms of impending cardiorespiratory failure, or has prolonged symptoms requiring additional monitoring beyond the capacity of the clinic.[31]

Reimbursement and billing

Little is known about how practices have been reimbursed for OIT up to this point. FDA-approved products allow for insurance reimbursement and will likely increase access to OIT. It remains to be seen over the next few years to what extent insurance companies will authorize and reimburse for food allergy treatments. Pharmaceutical company assistance programs may help patients with high co-pays, without insurance, or those with insurances that do not cover food allergy treatments.

Current Procedural Terminology codes have not yet been developed for OIT or any food allergy treatment. It is unclear whether appropriate codes may be included in the expected 2021 Medicare Evaluation/Management and Current Procedural Terminology changes. The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma, and Immunology have recommendations for coding on their website in the interim.[33]

Hospital-based clinics

For academic allergy practices and those located within a hospital-based setting, additional opportunities and challenges may arise. Because many of the early clinical studies occurred in academic medical centers, the research staff may have advanced knowledge and experience using OIT and can help train and prepare the clinical staff. Advocating for adequate staff and space can be a challenge, but at one institution, for example, the financial analysis supported hiring 1 full-time equivalent nurse practitioner and 2 full-time equivalent LVNs to see 2 new and 8 return OIT patients per day (Susan Laubach, verbal communication, 2020).

The maker of Palforzia supplies an Office Dose Kit (ODK) with 10 individual doses of each escalation dose in the OIT treatment protocol, which are to be used as the in-office test dose. In response to the Sunshine Act and evidence that pharmaceutical companies can influence prescribing habits of physicians, many academic medical centers limit free samples for patients and contact with sales representatives on their premises. Many institutions will not allow samples due to their interpretation of regulations about dispensing and labeling medications for patients. Some hospitals may regard this ODK as a “free sample” because there is no charge currently for these doses. Although samples that may influence prescribing habits should be viewed scrupulously, the Palforzia ODK is used only after the treatment decision has already been made, and therefore is not an incentive in the Sunshine Act sense. In addition, there is no therapeutic

alternative to Palforzia; therefore, having the ODK on-site does not favor one manufacturer or product over another. The ODK allows flexibility of on-site dosing, which increases the safety and convenience for patients and providers. Hospital administrators may be reassured that this is a standard of practice for this new medication and can help operationalize the use of the ODK in a way that maintains the integrity of medication dispensing.

In a hospital-based clinic, close communication and coordination with the pharmacy will help with purchasing and storage of the ODKs and OIT home dose kits. The maker of Palforzia has contracted with a limited number of outpatient specialty pharmacies to deliver the drug overnight. The home dose kits can be directly shipped to the patient after they have tolerated the dose in the office under supervision; alternatively, the kit can be shipped to the hospital pharmacy and then provided to the patient by the physician.

Consenting

The office should consider having patients or guardians sign a consent form for OIT treatment per local institutional guidance that outlines risks and safety precautions, expected benefits and limitations of OIT, and alternatives, including avoidance. Although not required by law, age-appropriate assent should also be considered because OIT is not an essential treatment. Children as young as age 7 years should be able to participate in decision making about their medical care in a developmentally appropriate way.[34] Parents and patients should understand that OIT is not a cure. Daily commitment is required, and treatment could be indefinite. Avoidance of the allergen in the diet should be maintained, and the patient must always carry an epinephrine autoinjector; having 2 devices available at all times is recommended.[31,35] There should be clear communication with the patient and family about indications for discontinuing therapy, including concerning adverse effects and nonadherence. Both parents/guardians, if available, should give informed consent. Having both parents/guardians on board can be beneficial in ensuring the treatment plan is followed no matter which parent/guardian is present, particularly when there are 2 households.

The FDA has required use of a Risk Evaluation and Mitigation Strategy program where patients, providers, and clinics must be registered to receive/administer Palforzia. Because the approved drug will be widely available, this FDA requirement is primarily to ensure that offices administering the drug are familiar with the risks of OIT and ways to mitigate them and are equipped to handle life-threatening allergic reactions.

Patient education

OIT is an intensive therapy that requires commitment from patients and their families, and open communication with the practice is paramount. Patient education regarding OIT can be time-consuming, and offices may consider online resources and/or in-person or recorded informational sessions to educate groups of patients at the same time. Having information on the clinic's website with an overview of the potential benefits and risks of OIT, office procedures and policies, home dosing instructions, and Frequently Asked Questions can be a helpful resource for both potential and existing patients. Individualized questions can then be answered at a screening or consultation visit.

TABLE II. Considerations for initiating OIT

High-risk factors
History of life-threatening anaphylaxis* to OIT allergen
Uncontrolled asthma
Pregnancy (initiation or build-up phase)
Moderate risk factors
Eosinophilic gastrointestinal disorders
Chronic urticaria
Mastocytosis/mast cell disorder
Beta-blocker therapy
ACE-inhibitor therapy
Certain chronic conditions†
Nonmedical[13]
Excessive anxiety in patient or parent
Taste aversion
Unreliable adherence to protocol
Reluctance to use epinephrine
Excessive distance from the patient's home to an emergency facility
Language barrier
Noncollaborative family dynamics
Lack of schedule flexibility
Lack of commitment from patient or parents/guardians
Not contraindications
Controlled asthma
History of mild to moderate anaphylaxis to OIT allergen
Multiple food allergies

ACE, Angiotensin-converting enzyme.
*Reactions including hypoxia, hypotension, and/or need for mechanical ventilation.
†This includes conditions that may lower the threshold for an allergic reaction, or interfere with symptom assessment and/or treatment of allergic reactions.

OIT patients need to be educated to recognize signs of an allergic reaction and treat symptoms on the basis of their personalized allergy and anaphylaxis emergency plan. It should be emphasized that epinephrine is safe, fast, and effective and that it should be given early if indicated. Patients should be counseled on indications for activating EMS, typically immediately following the administration of epinephrine. These actions will help to avoid delays in critical treatment of allergic symptoms. In extraordinary circumstances, such as during a pandemic, adjustments to management of anaphylaxis may occur.[36]

CLINICAL OIT PROCEDURES

Identification of OIT candidates

The question of which patients with food allergy are good candidates for OIT is still an area rich for research opportunity. The Canadian Society of Allergy and Clinical Immunology guidelines outline the clinical, economic, and organizational considerations for OIT, but also discuss the sociopolitical, ethical, and populational implications of OIT for patients with food allergy. Patient-centered outcomes must be considered at both population and individual levels.[13] At a population level, access to the diagnosis and treatment of food allergy should be available to all patients. The rise of telemedicine ushered in by the coronavirus disease 2019 pandemic may increase individual access to expert food allergy care for many patients. However, access to OIT, which requires frequent in-person visits during the updosing phase, may still be inequitable.

At an individual level, candidates for OIT must have an IgE-mediated food allergy without high-risk factors (Table II), and a realistic understanding of the risks, benefits, and goals of OIT.

Moderate risk factors and nonmedical considerations should be discussed with the patient and family in the context of net health benefit (Table II). Package inserts of FDA-approved OIT products such as Palforzia will contain details on contraindications, warnings, and precautions that should be followed.

Candidates for OIT should have a physician-diagnosed IgE-mediated food allergy to the specific allergen. This diagnosis generally includes a history of a clinical reaction to the food confirmed by positive serum-specific IgE (sIgE) and/or skin prick testing, or highly predictive testing.[37] Patients who are monosensitized to Ara h8 via commercially available peanut component testing and who have only experienced mild oropharyngeal symptoms after ingestion of peanut have a clinical picture consistent with oral allergy syndrome. These patients may find the time investment and cost of OIT not to be of value because they are at low risk for anaphylaxis. If the diagnosis is in doubt, a supervised OFC should be considered before initiating a food allergy treatment. OIT is not indicated to prevent food allergy at this time, nor is it indicated for food intolerances or non–IgE-mediated adverse food reactions.

OIT may not be suitable for every patient, and a shared decision-making strategy involving the patient, family, and physician is necessary.[14] Identifying the goals of the patient and family in undertaking treatment can help start the conversation. Most patients and families seeking food allergy treatment do not want the allergen to be eaten freely. In 1 study, the most commonly selected primary goal for OIT chosen by respondents was "reducing the risk of a fatal food reaction" (62%) and "reducing the hassle of strict avoidance" (10.6%).[38] Only 9% chose "being able to incorporate the food into the diet normally." Most participants agreed that successful OIT was "avoiding the food but having a lower rate of reaction than prior to treatment." Strict avoidance of peanut ingestion is still recommended while on OIT. Restrictions may be eased while on maintenance OIT with regard to eating products with precautionary labeling and eating at restaurants where cross-contact may occur.

Patients with a history of life-threatening anaphylaxis to the OIT food allergen, including hypoxia, hypotension, and/or the need for mechanical ventilation, may not currently be good candidates for OIT. Although protecting such patients from allergic reactions is desirable, the risks of OIT may outweigh the benefits, especially because it is not curative. Studies investigating methods of making the OIT product less allergenic but still immunogenic could allow for OIT treatment in higher risk patients.[39]

Assessment of psychological concerns and family support is important in considering OIT for a patient. Anxiety in particular can affect dose administration and may give rise to subjective symptoms that hinder evaluation of symptoms, assessment of dose tolerance, and ultimately dose escalation. Adherence may also be affected by health care and financial resources. Patients receiving OIT to date have mostly been white, male, and from higher socioeconomic and educational backgrounds. Programs to assist families from various racial and socioeconomic backgrounds with access to OIT will be vital in achieving equity in food allergy care.

Initiating OIT early in immune development may improve long-term results, and data suggest that OIT may be more effective in younger age groups. Palforzia is currently approved for children aged 4 to 17 years, and a phase III trial is underway studying this treatment for children ages 1 to 3 years (NCT03736447). OIT results in adults have not been shown to be statistically significant, likely due to low numbers and high rate of withdrawals from treatment.[17] Wasserman et al[16] reported that for each year increase in patient age there was a 17% decrease in odds ratios of reaching the maintenance dose ($P < .001$). OIT in preschoolers appears to be effective with an acceptable safety profile, although systemic reactions and epinephrine treatment still occur.[40,41] In Vickery et al,[41] 91% of per-protocol subjects age 9 to 36 months on 300 or 3000 mg peanut protein maintenance dose OIT achieved 4-week SU, and were 19 times more likely to be able to consume dietary peanut versus standard-care controls. A 2017 workgroup report from the American Academy of Allergy, Asthma & Immunology provides guidance to allergist/immunologists conducting OFC to peanut in infants.[42] Insights from this report can be extrapolated to administering OIT to infants and toddlers.

Screening

A screening visit should be performed by a physician or AHP specializing in allergy and include a full medical history focusing on atopic diseases and other chronic conditions that may be pertinent. A social history may be relevant for practicalities of therapy such as the distance a family has to travel to the clinic for visits and how far away they live from an emergency facility in the event of a reaction at home. Availability of adult supervision and ability to adhere to safety considerations with home dosing should also be explicitly discussed. A family history is important to consider if there is more than 1 family member with a food allergy in the home, particularly if a sibling also wants to initiate OIT or how to safely administer OIT if the parent or another sibling is allergic to the OIT food allergen.

A complete physical examination should be performed to document baseline status. Skin prick testing and sIgE testing are recommended to determine allergy status and for baseline measurements. A baseline pulmonary function test is also suggested in those with a history of asthma.

Scheduling

A typical visit schedule for OIT requires patients to return to clinic every 2 weeks for monitored updosing. For peanut OIT, increasing the dose every 2 weeks would take approximately 6 months to reach a maintenance dose of 300 mg peanut protein. Although in practice there can be flexibility in scheduling, it is not recommended to escalate the dose within 1 week of the last dose increase. Extending the time period a patient is on a single dose may be prudent depending on wellness of the patient or adverse effects, or may simply be a reflection of scheduling interruptions including school timetables, vacations, clinic staffing, and of recent, pandemics.

Once at maintenance dose, it is important for patients to return periodically for observed doses to document tolerability and reinforce adherence. Patients may develop treatment fatigue and parents may monitor doses less closely as children get older. If the doses are not taken consistently, the risk of reactions to the treatment increases. Consistent periodic office visits for observed dosing can help identify patients who have become inconsistent and motivate patients to continue taking their daily OIT doses. Visits may space out while on maintenance, for example, to every 2 to 3 months, and may have a shorter monitoring time (eg, 30

minutes) similar to that after subcutaneous immunotherapy (SCIT) as long as no symptoms develop.

Dosing visit procedures

Patients should be free from active wheezing, clinically significant flares of atopic dermatitis, allergic rhinitis, and urticaria, and other active illnesses. Previsit screening communication is useful; however, patients should be reassessed in the clinic before dosing.

Suggested dosing visit procedures include home-dose symptom and medication review, and physical examinations predose, predischarge, and as needed. Baseline and as-needed vital signs should include blood pressure, pulse, and body temperature. Periodic weight checks for emergency medication dosing should be done on the basis of age, with younger children being weighed more frequently than adolescents. Consider pulmonary function tests or peak flow in patients with asthma as needed, for example, to determine whether asthma is stable enough to dose or to evaluate lung function in the presence of respiratory symptoms.

If an OIT patient is on a daily antihistamine or other medications to treat other atopic diseases (eczema, allergic rhinitis, asthma, etc), it is suggested that patients remain on these medications to maintain control and/or prevent flares. Patients should withhold their daily home OIT dose on in-clinic dosing days but should take all other prescribed medications as scheduled to ensure optimal control of their other allergic and/or nonallergic disorders.

Premedication with antihistamines is a common practice in SCIT. The difference between SCIT and OIT is that OIT doses are taken every day at home, whereas SCIT doses are administered in clinic once per time period. If an antihistamine is used as premedication for an OIT dose escalation in clinic but not at home, it is not known whether the patient may have symptoms the next day with the home dose. There could be 2 strategies: (1) No premedication for dose escalation and treat as needed only to get a clearer evaluation of potential symptoms. (2) With patients experiencing persistent mild symptoms at the beginning of each dose escalation but who eventually tolerate the dose, plan for premedication and use of antihistamines for the first few days of each dose period.

In practice, offices administering OIT monitor between 30 minutes and 2 hours, usually when no to mild symptoms are present. Palforzia instructions include 1 hour of monitoring in the office after dose administration. Monitoring for up to 4 hours or longer may be required if symptoms are moderate to severe. If a patient requires prolonged monitoring and/or treatment, they may need to be transferred to an emergency department or admitted to an inpatient floor.

HOME DOSING

Patients and families need to be educated at each visit about important home dosing instructions meant to decrease adverse effects and increase safety (Box 1). Patients should take OIT doses at the same time every day to avoid ingesting too much cumulatively and increasing the risk of adverse effects. Taking the dose around the same time ± 30 minutes is acceptable, but doses should not be taken within 8 to 12 hours of each other (unless split dosing is advised by the physician). Having a designated time to take the dose every day increases safety by increasing adherence and decreasing missed doses. Missed doses on previous days has been a patient-reported factor in systemic reactions to OIT and a break of even 1 to 2 days has been reported to result in a loss of desensitization.[15,44,45] All caregivers of the patient need to understand the dosing instructions and the importance of uninterrupted dosing. Parents of older children and adolescents may want them to become more independent; however, these age groups still need close supervision while taking their doses to ensure they adhere to timing of the doses and all precautions. Keeping a daily dose log can help engage older patients and give them a sense of accountability.

Box 1. General instructions for OIT home dosing

- Take dose around the same time *every day* with a meal*
- Observe patient for at least 1-2 h after dose*
- Avoid exercise and heat exposure (hot showers, baths, etc) right before and 3 h after dose*
- Contact physician for dosing instructions if doses are missed*
- Monitor patient closely during menstrual cycle, especially if exercise or illness factors are present[43]
- Avoid taking NSAIDs or consuming alcohol around the time of dose
- Hold dose and contact physician if:
  - >2 doses have been missed
  - Patient has a fever or signs of a viral illness or infection
  - Asthma flares or is not under control
  - More than mild environmental/seasonal allergy symptoms are not under control
  - A significant medical event (surgery, hospitalization, etc) or a traumatic life event has occurred

NSAID, Nonsteroidal anti-inflammatory drug.
*These recommendations are included in Palforzia dosing instructions.

Augmenting factors of allergic reactions can lower the threshold for reactions, increase severity, and reverse acquired tolerance (or desensitization in the case of OIT).[46] Common factors include increased basal metabolic rate caused by exercise, acute infections, or fever, and other factors such as menstruation, nonsteroidal anti-inflammatory drugs, alcohol, and stress.[46] Suboptimal control of asthma and pollen allergy can also be augmenting factors in OIT, as in SCIT.[43,44,47] One augmenting factor unique to OIT is fasting, or taking doses on an empty stomach.[43] Although OIT doses are typically mixed with food before being ingested, eating a meal or snack around the same time can help decrease the risk of adverse effects. It is important to note that reactions to OIT can occur without an identifiable cofactor.

In studies, exercise within 2 hours and acute illness were most commonly associated with adverse effects of previously well-tolerated OIT doses.[15,16,43,44,48,49] Some families find it helpful to take OIT doses at dinner, after the day's activities and long enough before bedtime to allow for at least 1 to 2 hours of monitoring. An alternative would be dosing in the morning with breakfast if patients have too many sport activities in the evening, with enough time to monitor before the child goes off to school.

Families and patients must be educated about the augmenting factors discussed above and commit to following the precautions to decrease the risk of adverse effects. They should be instructed to hold the OIT dose if they are unsure whether or not to give it and contact the OIT staff during clinic hours to discuss

how to proceed. Doses should be temporarily held or decreased for fever and vomiting, as well as for other concerning symptoms in the setting of acute illness at the discretion of the physician. Doses may be continued for milder symptoms, such as nasal congestion or sneezing, if the doses had been well tolerated thus far. If the patient improves and only 1 to 2 doses were held or decreased, most often full doses resumed at home are tolerated. See the following section on dose modifications for more detail.

Most OIT protocols that use doses made of powder or flour, including Palforzia, provide instructions to mix doses into a semisolid food (such as pudding or applesauce) before consuming. The food should not be heated to avoid altering the properties of the OIT doses and should not contain any of the patient's other allergens. Mixing OIT doses that are powders or flours into liquids is not a good option because they do not fully incorporate into the liquid and often stick to the sides of the container, thus failing to deliver a consistent full dose.

Mixing OIT doses with semisolid food also helps to cover the taste and smell of the allergen, which is often very noxious to children who are allergic. Taste aversion has been reported to be a challenge in OIT treatment.[15,16,50,51] Working with patients and families on taste issues increases adherence, and there is a vast online patient-to-patient support providing OIT taste-masking suggestions. Choosing a food vehicle with a strong flavor, such as cinnamon or chocolate, can help mask the taste of the OIT product. An advantage of using a low-maintenance dose, such as 300 mg of peanut protein, is that there is a greater likelihood of acceptability by the patient compared with higher doses, which are harder to mask. In an open-label, single-center peanut OIT study for children 4 years or older (average age of 6 years), adherence at a median follow-up length of 18 months was significantly better on the lower maintenance dose of 1200 mg of peanut protein (73 of 76; 96%) compared with the higher maintenance dose of 3000 mg (24 of 35; 72%) ($P < .001$).[52] Those with food aversion were more likely to discontinue OIT.

Additional precautions should be taken when using non–FDA-approved peanut or other food allergen products as OIT.[14] Unlike a quality-controlled, pharmaceutical grade product such as Palforzia, food products may vary in protein content of specific allergens and manufacturing processes can change at any time.[53,54] Packaging should be examined each time to verify ingredients and amount of protein, and to check for advisory labels.

Dose modifications

Significant or persistent symptoms with home doses may indicate that the dose is not being tolerated and requires evaluation. Actions that could be taken are listed in Box 2. It is prudent to be cautious early in the course of treatment when it may not be known how a patient will tolerate OIT. If it is unclear whether the dose is being tolerated, one option is to bring the patient back into clinic for an observed current dose or decreased dose. There may be patients who report mild, self-resolving subjective symptoms such as itchy mouth with most doses. In these cases, with physician discretion, the patient may be able to continue on schedule. New, nonacute gastrointestinal (GI) symptoms may also require dose modification. See *Adverse Effects* section below for more in-depth discussion.

Temporarily holding or decreasing a dose may be necessary when a patient develops an acute illness, an asthma flare, during menstruation, or in the setting of any augmenting factors discussed above. Mild upper respiratory tract illnesses without fever may not require an adjustment if the patient has been tolerating doses well. Holding or decreasing the dose (ie, from 1-step to 50% reduction) should be considered if the patient develops fever, inability to tolerate food and/or emesis, more than mild cough, and/or significant changes in energy, for example. If the dose is held or decreased for no more than 2 days, the full dose could be resumed at home.

Box 2. Dose modification and responses to OIT-associated symptoms

- Continue the current dose and stay on schedule if symptoms resolve
- Continue the current dose for a longer time period (ie, 3-4 wk)
- Split the dose (ie, half dose taken 8-12 h apart)*
- Decrease the dose (ie, 1- to 2-step reduction)
- Discontinue treatment

*If the dose is split and tolerated well, after 1-2 wk the patient could go back to full dose once a day for another 1-2 wk and if tolerated, continue with updosing.

Desensitization can be affected by even a short discontinuation. If doses are missed for 1 to 2 days, the same dose could be resumed at home. If doses are missed for 3 to 5 days, the same dose could be given in clinic under observation. Alternatively, the dose could be reduced by 50% and taken at home daily for 1 to 2 weeks before coming in to increase to the next dose and gradually returning to the previously tolerated dose that was missed. If doses are missed for 6 to 14 days, a 50% to 75% reduction could be considered in clinic. If more than 2 weeks of doses have been missed, discontinuation of OIT should be discussed. Patients must be monitored closely during treatment, and discontinuation of OIT should be considered in patients who have 1 or more severe reaction to OIT at home or in the office, who need frequent dose modifications due to medical reasons or lack of commitment, or who frequently adjust doses on their own at home.

Maintenance dose

A daily maintenance OIT dose is required to preserve treatment effect. Daily OIT dosing versus every-other-day dosing shows better adherence, effectiveness, and safety during maintenance.[55] The general principle defining an adequate maintenance dose in OIT is a dose that would protect the patient in the case of an accidental ingestion. In 2 recent studies with peanut OFC data, the median threshold dose was reported as 67 mg (interquartile range, 16-244 mg; n = 204 OFCs) and 75 mg (range, 0.1-500 mg; n = 347 OFCs) of peanut protein.[56,57] Limited data have shown that the amount triggering an accidental reaction from products and undeclared ingredients can range from 0.4 to 170 mg of peanut protein (n = 6 samples).[58] Estimates of an average amount of allergen in 1 to 2 bites of a typical food have helped define lower limits for maintenance dosing. A common maintenance daily dose for peanut is 300 mg (equivalent of ~1 peanut). Different maintenance doses may be effective for other allergens. In Blumchen et al,[25] 17% of children treated with low-dose (125-250 mg) peanut OIT experienced accidental allergic reactions possibly or certainly caused by peanut versus 45% on placebo ($P = .026$). Only 1 reaction (12.5%) in the active group versus 10 (42%) in

the placebo group was graded as severe, and the 1 in the active group was when the subject was early in the build-up phase (4.5-mg dose).[59]

Higher levels of desensitization have been achieved in other studies and the 2 community practice reports.[2,15,16] Sustaining these higher doses long-term can be complicated by nonadherence due to adverse effects or issues with taste. It appears that peanut OIT maintenance doses as low as 125 to 300 mg are comparable in clinical outcomes to higher maintenance dose and with better tolerability.[25,41] In Vickery et al,[41] 85% of subjects on 300 mg peanut OIT and 71% on 3000 mg achieved 4-week SU. Andorf et al[8] reported that in a peanut OIT protocol to initial maintenance of 2000 mg of peanut protein, a reduction to 300 mg versus 1000 mg was equally effective at maintaining desensitization.

When patients reach a maintenance dose that is considered protective against reactions to accidental ingestions of the allergen, it is presumed that they are unlikely to react to products with advisory warnings or cross-contact in meal preparation. It is important to emphasize that continued vigilance is needed because factors involved in such potential exposures are neither consistent nor regulated.

ADVERSE EVENTS

Systemic reactions

Systemic reactions have been reported during OIT build-up (8%-23%) and maintenance (8%-19%) phases in the office and at home (Table I).[15-17] Most OIT participants who experience a systemic reaction have just 1 episode during treatment, and just 1 dose of epinephrine is administered in most cases. However, some OIT participants experience multiple episodes of systemic reactions and have been administered 2 to 3 doses of epinephrine. One case of severe systemic reaction during maintenance was reported in the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE), after which the subject discontinued treatment.[17] Most systemic reactions occur within the first year, and most OIT participants continue to reach their target maintenance dose.

Wasserman et al[16] reported that epinephrine-treated reactions tended to occur at higher doses and were associated with a higher baseline peanut sIgE ($P = .003$). In a milk OIT trial, higher baseline α-lactalbumin and casein sIgE levels were associated with a higher risk for anaphylaxis.[60] Additional large-scale studies are needed to better risk stratify OIT candidates.

Nonacute gastrointestinal symptoms

Nonacute GI symptoms may be chronic or recurrent, such as persistent abdominal discomfort or intermittent gastroesophageal reflux disease (GERD), and may vary in severity. These symptoms often emerge early in OIT treatment. Reducing the dose or treating with proton pump inhibitors or H2 blockers has been reported as a strategy in response to such GI symptoms.[15,16] For some patients, these GI symptoms resolve on their own and they are able to continue on to maintenance.[16] If the patient is early in the build-up phase (eg, the first 3 doses) and experiencing nonacute GI symptoms, treatment may be discontinued and restarted from the beginning at a slower pace after a break (eg, 1-2 months).[9] In the PALISADE phase 3 Palforzia study, acute, chronic, or recurrent GI symptoms were reported to resolve an average of 10 days (range, 1-42 days) after OIT discontinuation.[17]

Eosinophilic esophagitis

New, nonacute, and persistent GI symptoms as well as dysphagia should alert the clinician that esophageal inflammation may be developing in response to OIT. A systematic review reported a 2.7% incidence of eosinophilic esophagitis (EoE) in OIT.[47] Up to 30% of participants may experience chronic or recurrent EoE-like symptoms.[61,62] In most cases, esophagogastroduodenoscopy (EGD) is not performed, so EoE cannot be confirmed or refuted. Risk of EoE-like symptoms has been associated with increased baseline peanut sIgE level ($P < .001$).[16]

EoE-like symptoms have occurred primarily during build-up at lower doses (eg, <30 mg peanut protein), and typically increase the time to reach maintenance dose. Although Goldberg et al[9] reported that pediatric patients who developed GI symptoms and peripheral eosinophilia while on OIT were less likely to reach the target maintenance dose ($P < .001$), dose modifications did allow most of these patients to reach partial or full target maintenance dose. Because EGDs were not performed, it is unknown whether chronic inflammation or histologic changes were present. A peanut OIT study in which adult subjects underwent EGDs at baseline (n = 20), after build-up (n = 7), and during maintenance (n = 6) reported that preexisting subclinical GI eosinophilia was common, and that OIT induced or exacerbated esophageal eosinophilia in 6 subjects, but resolved in 4 of these subjects by end of the maintenance phase.[63,64] One subject met EoE criteria and discontinued OIT. At this time, a baseline EGD is not recommended before initiating OIT, but evaluation by a GI specialist may be useful beforehand and even during treatment if chronic GI symptoms develop.

Identifying patients with chronic GI symptoms before starting treatment may be helpful so that symptoms during therapy can be assessed within context. The phase 3 PALISADE trial actively excluded patients with a history of any eosinophilic GI disease, chronic, recurrent, or severe GERD, symptoms of dysphagia, or recurrent GI symptoms of undiagnosed etiology.[17] A smaller proportion of subjects on active treatment in PALISADE withdrew from treatment because of chronic GI symptoms compared with the phase 2 study of the same OIT product in which only patients with eosinophilic gastrointestinal disease were excluded (4.3%, 16 of 372, vs 21%, 6 of 29, respectively).[17,65]

The prescribing information for Palforzia lists eosinophilic GI disease as a contraindication to the use of the product, but some patients with a history of EoE or who develop EoE while on OIT may be willing to use a daily treatment such as oral viscous budesonide or a proton pump inhibitor to control EoE symptoms so that they can potentially derive the benefit of OIT in reducing the risk of a life-threatening allergic reaction to peanut. This is a reasonable discussion for a patient and family to have with the allergist/immunologist and GI specialist. Dose modification may be another possible option. In Goldberg et al,[9] decreasing or suspending doses until GI symptoms and peripheral eosinophilia resolved (without use of proton pump inhibitors or H1- or H2-blockers) and then resuming updosing permitted half the subjects to reach full desensitization and two-third to reach a partial desensitization. More research is needed to help understand the risks and benefits of OIT in patients with preexisting GI symptoms, and to help identify strategies to help patients who develop EoE-like symptoms while on OIT.

Discontinuation

GI symptoms, particularly ones that are eosinophilic esophagitis (EoE)-like, have been some of the main reasons for

TABLE III. Long-term studies of OIT

Characteristic	Dantzer et al[50]	Cook et al[51]	Kim et al[67]	Keet et al[45]	Mota et al[68]	Kauppila et al[69]
Type of study	Single-center survey	Single-center survey	Multicenter survey	Single-center questionnaire and/or clinical follow-up	Single-center prospective	Multicenter questionnaire and/or clinical follow-up
Length of follow-up	Up to 8 y	Median, 2.9 y	5 y	Up to 5 y	5.75 y	6.5 y
Type of immunotherapy	Peanut OIT/SLIT	Peanut OIT or SLIT	Egg OIT	Milk OIT or SLIT/OIT	Milk OIT	Milk OIT
Type of patients	Completed randomized peanut OIT vs SLIT with crossover	Completed either peanut OIT or SLIT and tolerated ≥300 mg peanut protein	Completed randomized OIT trial	Completed DBPC OIT trial or open-label, randomized SLIT followed by OIT trial	Completed at least 3 y of OIT	Completed open-label OIT
No. of participants	21	55 (40 OIT, 15 SLIT)	32	32	39	244
Age	Median, 11 y	Median, 10.8 y	Median, 12.7 y	Median, 9 y	Median, 13 y at last clinical evaluation	Median, 7-8 y at OIT initiation
Allergen consumption	52% regular peanut consumption; 69% (11 of 16) of those given recommendation for regular consumption	89% consumed peanut; 64% daily	72% consumed all forms of egg	50% consumed unlimited milk or ≥1 serving/d	92% consumed ≥200 mL milk daily	56% consumed ≥200 mL milk daily
Reported symptoms/reactions	82%	20%	41%	78%	>40%	68%
Reasons for discontinuation	Reactions, taste, anxiety	EoE (n = 1), taste (n = 2), reactions (n = 3)	NA	Symptoms, anxiety, taste	NA	GI symptoms, other symptoms, taste
Comments	Additional 4 subjects decreased amount of peanut ingestion because of taste ± symptoms/reactions.	Only 55 of 130 eligible subjects responded	36% (4 of 11) of subjects randomized to placebo also tolerated all forms of egg	Anaphylaxis was reported at least once by 19% (6 of 32) of subjects		

DBPC, Double-blind, placebo-controlled; *GI*, gastrointestinal; *SLIT*, sublingual immunotherapy.

withdrawal in OIT clinical trials and comprised 40% to 44% of reasons for discontinuing in community practice OIT.[15-17] Systemic reactions were the next most common discontinuation reason (9%-17%). Taste aversion has also been reported to be a barrier to maintenance of treatment.[15,16,50,51] Other reasons patients reported for discontinuing OIT included inconvenience, time constraints, travel, and expense.[15]

LONG-TERM FOLLOW-UP

A retrospective study on the adherence of patients to SCIT and sublingual immunotherapy for environmental allergies showed poor adherence to immunotherapy protocols, which may affect efficacy and safety of treatment.[66] SCIT adherence was reported at 60.1% to 61.8% and 35.0% to 37.5% at 2 and 3 years, respectively. Sublingual immunotherapy adherence was lower at 29.5% to 36.5% and 9.6% to 18.2% at 2 and 3 years, respectively. It remains to be seen whether patients on OIT will commit to long-term adherence, as currently recommended to maintain desensitization.

Few studies have looked at long-term follow-up for more than a few years after completing a food allergy immunotherapy protocol or reaching maintenance (Table III).[45,50,51,67-69] It is difficult to interpret the results of long-term follow-up studies due to heterogeneity of patient populations, protocols, and maintenance doses, as well as lack of control groups and potential survey nonresponse bias. In addition, patients in studies performed at tertiary centers may represent a more severe phenotype. In one of the community practice peanut OIT studies, only 11% (12 of 105) of patients on OIT for 3 or more years discontinued during maintenance.[16] Long-term follow-up of milk and egg OIT may be more complicated because most children are expected to develop natural tolerance. Overall, reasons for discontinuation long-term, such as taste aversion and reactions, are similar to those during build-up and maintenance phases in short-term follow-up studies. Thus, palatability and safety are vital for patients to successfully reach maintenance and benefit from OIT long-term.

OIT VARIATIONS AND ADJUNCT THERAPIES

In a population-based survey study, 40% of children reported 1 or more food allergy.[1] Because desensitization to one allergen does not confer protection to another, patients with multiple

food allergies must be just as careful to avoid cross-contact (in a restaurant, for example) if they are desensitized to only 1 of their allergens. Simultaneous multiple allergen OIT, or multi-OIT, could address this. Multi-OIT has been reported to be feasible and have a similar safety profile as single-allergen OIT, although in 1 study it took significantly longer to reach maintenance on multi-OIT compared with single-allergen OIT.[70] Additional research is needed to identify appropriate candidates and assess whether safety and efficacy differ from single-allergen OIT.

Research focused on increasing efficacy and improving the safety profile of OIT is ongoing. Modified allergen may be a less allergenic and safer form of OIT. Pilot studies using boiled peanut and hydrolyzed casein as OIT have been published with modest results.[71,72] Efficacy is typically evaluated in studies by SU after discontinuation of OIT treatment for 4 to 13 weeks.[73-75] A longer duration of OIT may increase SU. In 2 multicenter trials following subjects on peanut or egg OIT for 4 to 5 years, 50% demonstrated 4- to 6-week SU.[74,76] SU has been associated with higher serum $sIgG_4$ levels, lower skin prick test wheal size, and lower allergen-induced basophil activation.[74,75,77]

The adjunct use of probiotics to improve efficacy has some promise. In an OIT study with adjunct *Lactobacillus rhamnosus* treatment, 7 (58%) from the active group achieved 8-week SU, compared with 1 (7%) from the placebo/untreated group ($P = .012$).[78] Additional studies are needed to confirm this finding, and the results cannot be extrapolated to include other probiotic strains.

Biologics have been of interest in OIT as adjunct therapies that can suppress the allergic response and potentially enhance long-term benefits.[79] Patients with high sIgE levels and/or reactive to trace amounts of allergen are more likely to struggle with OIT and less likely to achieve SU.[24,76] Omalizumab has been shown to increase food allergen thresholds.[80-82] A multicenter, randomized peanut OIT study reported that omalizumab administered before OIT improved the level of initial peanut desensitization (median, 250 mg peanut protein) compared with placebo (22.5 mg), and facilitated rapid desensitization.[82] In a small single-center peanut OIT study (n = 13; age, 8-16 years), omalizumab used as an adjunct therapy helped subjects with high sIgE (median, 229 kU/L) achieve desensitization in a shorter amount of time; however, 50% discontinued because of adverse effects, mostly during maintenance.[81] In a larger multicenter, double-blind randomized milk OIT study (n = 57; age, 7-32 years), omalizumab adjunct therapy improved safety measures but not rates of desensitization or SU.[83] Additional studies are needed to clarify the role of biologics in OIT. Cost analyses will also be needed because the use of biologics may be prohibitive in practice unless the patient has another condition for which they are already approved.

FOOD ALLERGY THERAPIES IN RESEARCH

Other forms of food allergy immunotherapy continue to be studied.[2,84,85] These include epicutaneous immunotherapy, sublingual immunotherapy with immunomodulatory CpG nanoparticles, SCIT using chemically modified allergen, and allergen peptide or lysosomal-associated membrane protein vaccines. The Viaskin Peanut epicutaneous immunotherapy patch was under FDA review. In August 2020, the FDA expressed concerns regarding the patch site adhesion on efficacy and indicated the need for patch modifications and requested additional data. The FDA did not raise any safety concerns related to Viaskin Peanut. Additional adjunct therapies, such as dupilumab, Chinese herbal formula, short-chain fatty acids, and commensal bacteria, are also currently in trials with immunotherapy.

SUMMARY

For the first time there is a viable alternative to avoidance that allergist/immunologists can offer in peanut allergy management. Food allergy treatment is something that families and advocates have been supporting even if a cure is still elusive. Benefits of treatment may include protection against accidental ingestions, decreased severity of reactions, and increased QOL. Patients should understand that treatment may be indefinite, that a protective effect is not unlimited (thus, the diet should remain allergen-free), and that systemic reactions can occur (therefore, emergency medications must be available at all times). OIT in particular is time- and resource-intensive for allergy practices. When establishing OIT in practice, allergist/immunologists should consider necessary staffing and resources, create standardized policies and procedures, and optimize patient selection and education. Reviewing emergency readiness and availability of experienced staff and space is useful in assessing the ability to offer this and future food allergy therapies. Ongoing studies are investigating ways of making treatments safer and more efficacious. Additional research into predictors of treatment success would assist allergist/immunologists in determining which approach may be beneficial for which patient and promote personalized medicine.

What do we know?

- **OIT has been proven to effectively desensitize patients to known food allergens, increasing the reaction threshold for patients who are accidentally exposed to their allergen.**
- **Thus far, peanut is the only OIT product to receive FDA-approval**
- **OIT can be administered safely in the allergist/immunologist's office, with relevant policies and procedures in place to maximize patient safety and treatment success.**

What is still unknown?

- **Which food-allergic patients are best suited for intervention versus strict avoidance?**
- **What patient factors predict successful desensitization?**
- **Who is most at risk for reactions or failure of treatment in food OIT?**
- **What protocol modifications or adjunct therapies can make OIT safer and more efficacious?**
- **Standardized products and desensitization protocols for foods other than peanut.**

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