Oral immunotherapy for treatment of peanut allergy

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ABSTRACT

The US Food and Drug Administration's approval of a peanut oral immunotherapy product in January 2020 is a landmark development in the field of food allergy therapy. While food allergy prevalence has been increasing, this product is the first approved therapy for food allergy. Oral immunotherapy has many similarities to subcutaneous immunotherapy and drug desensitization protocols, but does not lead to sustained unresponsiveness. The studies leading to approval of the Palforzia product demonstrated increase in the amount of peanut protein able to be consumed, with 67% of subjects randomized to the treatment arm able to consume 600 mg of peanut protein in double-blind placebo-controlled food challenge at study exit. However, side effects are an important consideration, and dropout rates in studies of Palforzia ranged from 11% to 21%. Postmarketing surveillance of this product will be critical in assessing its long-term risks and benefits.

INTRODUCTION

Food allergy is a growing problem in the USA and worldwide, currently affecting 5%–10% of the population of the developed world.[1] In the USA, peanut allergy is the most prevalent food allergy, affecting 1 in 70 children, the majority of whom do not outgrow this allergy.[2] Patients with any food allergy can develop life-threatening anaphylaxis on ingestion of even small amounts of the offending allergen, and allergic reactions account for 300,000 emergency visits in the USA annually.[3] To prevent and treat these reactions, patients and their families must adhere to a careful regimen of allergen avoidance and carry injectable epinephrine for treatment of anaphylaxis at all times. Despite these precautions, accidental exposures and subsequent reactions can and do occur, with estimates of annual incidence ranging from 10% to 15% among peanut allergic children.[4] This need for constant vigilance poses a significant burden, and studies have demonstrated that quality of life among those with food allergy is significantly impaired. Because food allergy is currently a lifelong disease without a cure, this creates a long-standing societal disease burden.[5] Peanut allergy in particular has a low rate of being outgrown, making it a good candidate for initial therapeutic trials.[6]

The first Food and Drug Administration (FDA)-approved therapy to treat food allergy, Palforzia, was approved by the US FDA in January 2020 to treat peanut allergic children 4–17 years of age.[7] In this review, we will discuss the history of oral immunotherapy (OIT) as a therapeutic modality for food allergy, understand the current limitations of food allergy research and therapies, and summarize the major studies of peanut OIT leading to the approval of Palforzia. As a review of existing literature, ethics approval was not required for this manuscript.

OIT has its roots in subcutaneous immunotherapy (SCIT), known colloquially as 'allergy shots', a cornerstone of the practice of allergists. SCIT is typically used for the treatment of allergic rhinitis and allergic conjunctivitis among those sensitized to environmental allergens, both perennial and seasonal. SCIT involves the subcutaneous injection of gradually increasing quantities of the allergenic substance to which the patient is sensitized until a maintenance dose is reached, then continuing to administer the maintenance dose over the course of several years, allowing the patient to eventually develop long-lasting tolerance to the allergen, and amelioration of allergic rhinitis, conjunctivitis and asthma symptoms in the majority of patients.[8]

In a similar vein, temporary desensitization to medications is used by allergists for the treatment of drug allergy when no adequate alternative exists for the allergenic drug, most prototypically penicillin. While there exist many similarities between drug desensitization and SCIT, they differ in that drug desensitization offers temporary ability to tolerate the offending drug. Once the drug is discontinued, the patient is again allergic to the drug, and will demonstrate anaphylaxis if the drug is reintroduced.[9]

TERMINOLOGY

To differentiate between these 2 endpoints, temporary and long-term desensitization, the long-term non-reactiveness to allergic stimuli has been deemed 'sustained unresponsiveness' whereas the temporary increase in the threshold for reactivity to an allergenic substance is termed 'desensitization'.[10] Maintenance of the desensitized state requires continued exposure to the allergen in question.[11]

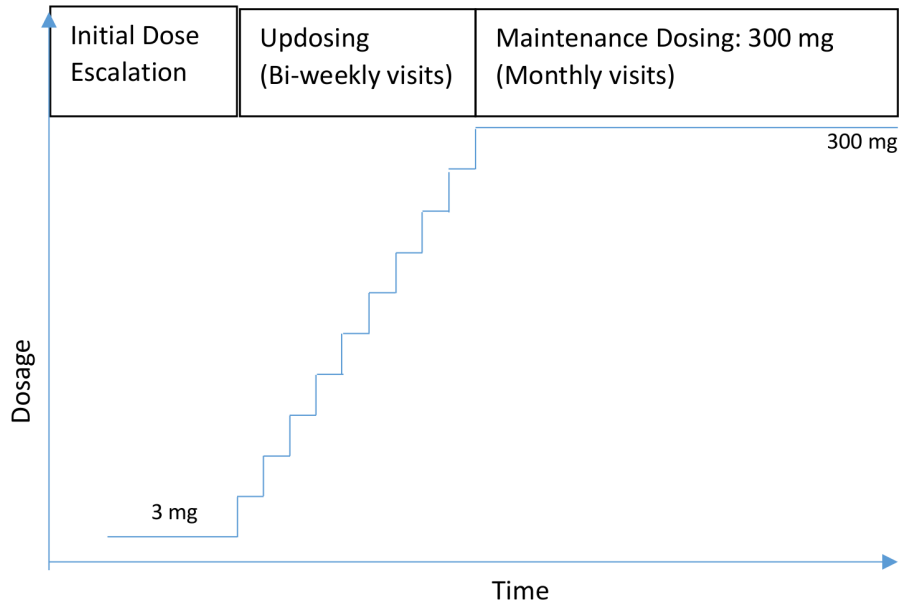

Figure 1 Dosing strategy for oral immunotherapy (OIT).

Both desensitization and immunotherapy protocols typically begin with small amounts of the allergenic substance, with slow increase in the dose, called an 'up-dosing period', until a 'maintenance' dose is reached. There are varying intervals of time used for the up-dosing period, with rush or compressed dosing protocols allowing for rapid increase of the dose in the office or hospital setting (figure 1).

HISTORY

Naturally, when faced with the burgeoning problem of food allergy, allergists attempted to use a long-known therapeutic modality, SCIT, for its treatment. The first studies used subcutaneous peanut extract, and were able to demonstrate desensitization. However, all subjects experienced systemic reactions during the up-dosing and with maintenance dosing. Thus, this modality was deemed infeasible.[2 8]

While reports of OIT date back to the beginning of the 20th century, Patriarca *et al* first demonstrated the successful treatment of allergies to cow's milk, egg, fish, and fruits with standardized OIT protocols in the 1980s and 1990s, setting the stage for clinical trials of OIT.[12] The first proof of concept OIT study for the treatment of food allergy was conducted in 2007 with egg allergy as its therapeutic target. A proof of concept OIT study targeting peanut allergy was published in 2009, using defatted peanut flour, a form of the allergen still used today in peanut OIT.[13] The defatted powder is more stable when stored, and the defatting is also reported to make the product more palatable to patients.[14]

SIDE EFFECTS OF OIT

The greatest risk of OIT, as for SCIT, is acute allergic events related to dosing. The symptoms of an allergic reaction can range from mild nasal congestion or gastrointestinal (GI) discomfort to systemic anaphylaxis (table 1). A meta-analysis of adverse events in peanut OIT studies was published in 2019. The analysis included 12 peanut OIT studies. Overall, the authors concluded that peanut OIT could successfully desensitize subjects to peanut (risk ratio (RR) 12.42, 95% CI 6.82 to 22.61), but subjects using peanut OIT were significantly more likely to experience more episodes of anaphylaxis when compared with those subjects practicing strict avoidance (RR 3.12), regardless of phase of treatment (ie, build-up vs maintenance).[15] A broader analysis of peanut OIT side effects, which included non-blinded studies, concluded that the overall risk of dropping out of the study due to side effects was 6.6%, and the risk of an adverse event requiring epinephrine use was 7.6%.[16]

Table 1 Adverse events affecting more than 5% of subjects in phase 3 clinical trial

Adverse event	Treatment group (%)	Placebo group (%)
Abdominal pain	52.2	24.2
Vomiting	41.4	24.2
Pruritus	41.1	27.4
Upper abdominal pain	40.9	21.0
Cough	40.9	33.9
Throat irritation	40.9	27.4
Oral pruritus	40.6	16.1
Nausea	39.2	23.4
Urticaria	38.4	24.2
Rhinorrhea	30.4	22.5
Sneezing	26.3	14.5
Throat tightness	23.1	6.5
Rash	21.8	14.5
Oral paresthesia	17.5	6.5
Systemic allergic reaction	14.2	3.2
Lip swelling	10.2	4.0
Dyspnea	11.8	4.0
Dysphonia	6.7	1.6
Ear pruritus	6.7	0
Chest discomfort	6.5	0.8

Adapted from Vickery *et al* [14].

A concerning adverse effect of OIT is eosinophilic esophagitis (EOE), which is a non-IgE-mediated disease characterized by eosinophilic infiltration of the esophagus. Symptoms include nausea, odynophagia, and food impaction. Diagnosis is dependent on endoscopically obtained biopsy specimens and long-term complications of EOE include esophageal strictures requiring dilation. In previous OIT studies, EOE has occurred in 2%–5% of subjects and is thought to resolve with cessation of OIT administration. Food allergy is a risk factor for EOE, and some researchers speculate that a large portion of patients undergoing OIT may have pre-existing esophageal eosinophilia.[2 17 18] A major challenge of monitoring the development of EOE in patients undergoing OIT is the invasive means necessary for diagnosis, and thus this may potentially be an underdiagnosed side effect of OIT.

UNIQUE CHALLENGES OF FOOD ALLERGY RESEARCH

One significant hurdle to food allergy research is the relative lack of specificity of food allergy testing. While serum allergen-specific IgE and skin prick test are sensitive for the detection of food allergy, food challenge remains the gold standard for diagnosis, with serum-specific IgE and skin prick test demonstrating specificities of approximately 80%. However, food challenges are time and staff intensive, and carry with them the risk of serious allergic reaction.[1]

Furthermore, food allergy patients may have significant, unpredictable, intrasubject variability in the threshold dose to which they react. Therefore, the most rigorous clinical trials of OIT require double-blind placebo-controlled food challenge (DBPCFC) at study entry and conclusion, a costly and time-consuming effort that carries risk of serious allergic reaction for study subjects.[11]

PEANUT OIT TRIALS

Initial trials of peanut OIT used a range of starting and maintenance doses. At this point, typical peanut OIT protocols begin with 0.5 mg of peanut protein, and reach maintenance doses ranging from 300 to 4000 mg. For reference, a typical peanut pod contains 2 peanut kernels, and each peanut kernel typically contains 250–300 mg of peanut protein. The Palforzia product uses a maintenance dose of 300 mg of peanut protein (figure 1).

Bird *et al* published the phase 2 clinical trial of peanut OIT in 2018.[19] This randomized, double-blind, placebo-controlled trial included 55 patients between the ages of 4 and 26 years. This study used DBPCFCs to determine allergic status for study entry and determination of the primary endpoint, which was consumption of a cumulative dose of 443 mg of peanut protein (300 mg maximum dose). An important consideration is the 21% dropout rate among those in the treatment arm, with 4 subjects leaving due to dosing-related GI symptoms, and 2 additional subjects developing GI symptoms in combination with other symptoms leading to study dropout. Endoscopy was pursued in 1 subject, leading to a diagnosis of EOE. While no subjects received repeat endoscopy prior to study completion, all 6 subjects had demonstrated resolution of GI symptoms within 3 weeks of stopping OIT.

The phase 3 clinical trial of peanut OIT was published by Vickery *et al* in 2019.[14] In the primary phase 3 study, the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE), DBPCFCs were used for entry and exit, in a fashion similar to the phase 2 study. However, the primary endpoint was the ability to tolerate at least the 600 mg dose at the exit challenge, compared with 300 mg in the phase 2 trial. The study enrolled 551 patients between the ages of 4 and 55 years, but the bulk of the patients were in the 4–17 years old age group, and the primary outcome was an analysis of only the subjects aged 4–17 years old. In this phase 3 study, 11.6% of subjects in the treatment arm withdrew secondary to adverse events, compared with 2.4% in the placebo arm.

In this trial, 67.2% of subjects randomized to the treatment arm tolerated a minimum of 600 mg in exit challenge with no more than mild symptoms compared with 4% of subjects in the placebo arm. There were only 56 subjects >18 years of age, and the proportion meeting the 600 mg endpoint did not statistically significantly differ between treatment and placebo groups.

PALFORZIA

The approved Palforzia drug is administered in the office in a fashion similar to that used in the phase 2 and 3 trials. Once again, the drug is a defatted peanut powder which is contained in capsules and sachets. The contents of these packages are sprinkled into a vehicle acceptable to the patient (such as applesauce or ice cream), and consumed daily. Patients are instructed to abstain from vigorous exercise for 2 hours after dosing, and to skip their daily dose if they develop significant illness.

There is no required entry or exit challenge for typical use, and all up-dosing should occur in the office under medical supervision. Patients will continue daily dosing at home between up-dosing visits, and on reaching the maintenance dose, should continue daily dosing at home indefinitely. Currently, patients and providers interested in receiving or providing Palforzia must register with a Risk Evaluation and Mitigation Strategy program as mandated by the US FDA as a condition of this approval.[20]

EXPECTED OUTCOMES OF OIT

It is expected that successful completion of the up-dosing phase and the continuation of maintenance dosing will provide significant protection, preventing reactions to small accidental exposures to peanut, and attenuate reactions to larger exposures, decreasing their severity.

However, the use of this medication will not do away with the need to continue avoidance of peanut products as it does not allow users to achieve sufficient desensitization to consume regular quantities of peanut products in their diet.[21] It will be important to measure patient and caregiver quality of life, to see if expected improvements in quality of life are achieved. Furthermore, patients should continue to carry their epinephrine autoinjectors, perhaps even more diligently, as a meta-analysis has demonstrated that subjects participating in OIT have more episodes of anaphylaxis than those practicing strict avoidance, with no differences seen in anaphylaxis frequency when comparing the maintenance and up-dosing periods.[15]

Patients receiving peanut OIT will continue to be monitored, and postmarketing surveillance will provide

much-needed information regarding long-term OIT outcomes regarding patient practices and anaphylaxis frequency in the real-world setting.

CONCLUSIONS AND FUTURE DIRECTIONS

The approval of an inaugural product for treatment of food allergy is certainly a major step in food allergy research and treatment. As discussed above, while Palforzia will provide protection against accidental ingestions of peanut protein, it will require indefinite daily dosing and is known to cause allergic reactions, even after prolonged periods on maintenance dosing, leaving significant room for improved food allergy therapies.

Other approaches in clinical trials for peanut allergy include epicutaneous immunotherapy, which appears to have decreased risk of adverse events, vaccines, and antigen-specific monoclonal antibodies.[22] The use of the OIT approach for other food allergens is also under clinical investigation, and clinicians and investigators should expect ongoing developments in the field of food allergy therapies over the coming years.

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