



Emerging developments in the forefront of peanut oral immunotherapy

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Purpose of review

Despite the COVID-19 pandemic, progress continued in the field of peanut oral immunotherapy over the past 12 to 18 months. Of importance, the first oral immunotherapy product for the treatment of peanut allergy was approved by the US Food and Drug Administration in January 2020.

Recent findings

Suggested modifications to the practice of oral immunotherapy, some of which may have lasting impacts, were circulated as a result of the pandemic. New advances in pathophysiology, sustained unresponsiveness, quality of life, safety, and cost effectiveness were also published.

Summary

During 2020, COVID-19 influenced the daily practice of allergy and immunology, with peanut oral immunotherapy being no exception. However, clinicians now have a FDA-approved treatment option for peanut allergy in children, a welcome development for a difficult disease. Future research is needed to clarify several knowledge deficits surrounding the best use of peanut OIT.

Keywords

coronavirus disease 2019, food allergy, oral immunotherapy, peanut

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic generated new and unprecedented challenges to the management of the 32 million Americans living with food allergy in 2020 [1]. The clinical practice of peanut oral immunotherapy (OIT) was deferred or paused by many allergists to ensure the safety of patients and staff. Additionally, given the public health crisis, journals prioritized COVID-19 publications with potentially less resources devoted to food allergy manuscript review than in recent years. Despite these challenges, OIT clinical research visits continued with caution in many areas of the country. Several articles referenced in this review discuss modifications to OIT in the setting of a global pandemic. However, 2020 also brought the first US Food and Drug Administration (FDA)-approved peanut allergy treatment, Palforzia (Aimmune Therapeutics, Brisbane, California, USA). Progress in the areas of pathophysiology, sustained unresponsiveness, quality of life, safety, and cost effectiveness achieved during the past 12 to 18 months and future research needs are also summarized.

PEANUT ORAL IMMUNOTHERAPY PATHOPHYSIOLOGY

The mechanisms underlying OIT and changes in immune responses leading to an 'induced' state of

tolerance remain poorly understood but appear to be distinct from natural oral immune tolerance. Successful desensitization requires concerted coordination of the immune system involving T and B cells, mast cells, basophils, and other local immune cells in the gut through various parallel or overlapping mechanisms. Mechanistic studies evaluating the effect of OIT in human participants have been conducted primarily using peripheral blood because of the difficulty in routinely sampling gastrointestinal mucosa or its associated lymphoid structures [2^{••}].

There is a growing evidence that suppression of basophil activation occurs during OIT, as in various forms of allergen immunotherapy, and may reflect clinical outcomes. Yet, the mechanisms by which OIT modulates basophil activation remain elusive. A

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KEY POINTS

- The COVID-19 pandemic impacted all areas of food allergy treatment in 2020, including peanut OIT.
- The FDA approval of Palforzia was an important first step in developing OIT regimens for food allergic patients.
- There are significant research needs to better understand the role of OIT in the management of food allergy.
- New and better therapeutic options are desperately needed for food allergy.

decrease in basophil activation and pro-allergic cytokines including IL-5, IL-13, and IL-9 was observed in preschool aged children receiving daily maintenance peanut OIT, and the findings were similar in both high-dose (3000 mg) or low-dose (300 mg) groups [3]. Patil *et al.* [4] demonstrated a correlation between the decline in basophil sensitivity to Ara h 2 within the first 3 months of peanut OIT and sustained unresponsiveness after cessation of treatment. Moreover, a significant rebound in basophil reactivity to Ara h 2 was found to mirror the return of clinical reaction after discontinuation of peanut OIT. A study by Tsai *et al.* [5] explored the association between basophil activation, along with peanut-specific immunoglobulins, and OIT treatment outcomes of participants enrolled in the POISED study.[6"] The study also found that low basophil responsiveness and peanut sIgE correlated with higher treatment success to peanut OIT. The authors concluded that persistent suppression of peanut-induced basophil activation is required to maintain clinical tolerance after discontinuation of OIT.

PALFORZIA FOOD AND DRUG ADMINISTRATION APPROVAL

On 31 January 2020, Palforzia became the first treatment for children ages 4–17 years with peanut allergy approved by the FDA [7,8"]. The pivotal phase 3 clinical trial was published in 2018 and previously reviewed [9,10]. The incorporation of this therapeutic option into clinical practice was somewhat stifled by the COVID-19 pandemic, as this therapy requires multiple, supervised, in-office visits. In many areas of the country, as discussed in more detail in the next section, nonessential health-care was temporarily prohibited or discouraged in the setting of the public health emergency making it difficult for allergists to prescribe and administer Palforzia. In October 2020, Nestle purchased Aim-mune Therapeutics and will continue the corporation's food allergy developmental program [11]. It remains to be seen if Palforzia will become a widely utilized treatment option for peanut allergy once the pandemic is resolved or better contained.

CORONAVIRUS DISEASE 2019 IMPACTS ON ORAL IMMUNOTHERAPY

During the early stages of the COVID-19 pandemic in the United States, guidance from regulatory authorities and professional organizations deprioritized nonemergent care with various consequences to the clinical practice of peanut OIT (Table 1). In March 2020, a consensus-based prioritization schematic to temporarily triage allergy/immunology services was published from an expert panel of American and Canadian allergy/immunology specialists [12"]. This document recommended deferral of the initiation and updosing of OIT but left the ultimate decision up to the individual treating physician in the context of local community

Table 1. Coronavirus disease 2019 impacts on peanut oral immunotherapy clinical practice

Suggested actions	
Minimizing in-office visits	Deferring oral food challenges frequently completed before OIT initiation Halting updose appointments and deferring reaching maintenance Offering telehealth for preinitiation counseling and maintenance visits
Conserving PPE supplies	Evaluating the needs for OIT office visits and procedures to minimize PPE use, especially when supplies are not readily available
Limiting aerosol-generating procedures during visits	Determining benefit:risk of performing lung function assessments of asthma severity prior to and during OIT
Managing milder OIT systemic reactions at home	Treating milder systemic allergic reactions with a favorable response to epinephrine without activating emergency services

OIT, oral immunotherapy; PPE, personal protective equipment.

transmission, availability of personal protective equipment (PPE), and local regulations [12[¶]]. Many OIT clinical office visits were deferred temporarily while research visits largely continued with caution [13]. In July 2020, additional recommendations specific to the treatment of food allergy during the pandemic were published [14[¶]]. OIT counseling and preinitiation visits, adherence monitoring visits, and peanut OIT for lower risk preschoolers could be done virtually but most up dosing visits should be postponed until viral transmission wanes and non-essential medical care resumes [14[¶]]. Further complicating OIT treatment, lung function assessments that were frequently performed prior to the initiation of OIT or screening food challenges, especially for patients with asthma, became difficult to safely perform. Spirometry is considered by some institutions and clinical practices to be an aerosol-generating procedure, requiring additional safety precautions and PPE. Given the prolonged nature of this pandemic, even with vaccines becoming available, clinicians must decide when it is safe to resume OIT in their individual practices [14[¶]]. OIT up dosing should not be done in symptomatic patients or those with ongoing COVID-19 infection, as acutely ill patients are more likely to experience adverse events. Furthermore, the lengthy visits could put healthcare personnel and other patients at risk for contracting COVID-19.

Another recommendation arising from the COVID-19 pandemic is the home management of milder systemic allergic reactions, including those related to peanut OIT, without immediately activating emergency services. An algorithm published in April 2020 suggests patients without a history of intubation or requiring more than two doses of epinephrine during a reaction could be given the option of home management [15[¶]]. If severe symptoms do not resolve or improve after two doses of epinephrine, emergency activation is needed [15[¶]]. Other articles suggest activating emergency services if more than one dose of epinephrine is needed [14[¶]]. The purpose of these suggestions is to limit patient exposure to COVID-19 in the emergency department and reserve emergency resources for treating the sickest patients [14[¶],15[¶]].

All COVID-19 consensus reports, suggested algorithms, and alterations to standard food allergy care are not official requirements or guidelines [12[¶],14[¶],15[¶]]. Each physician and patient must decide what is the best course of action via a shared decision-making process. As the pandemic progresses and PPE becomes more widely available, the benefit of continuing routine and preventive peanut allergy care may outweigh the potential risks of COVID-19 exposure in clinical and emergency settings.

SUSTAINED UNRESPONSIVENESS

The POISED study evaluated and quantified sustained unresponsiveness after peanut OIT [6[¶]]. Participants who reacted to 500 mg or less of peanut protein (approximately two peanut kernels) on a screening double-blind placebo-controlled food challenge (DBPCFC) were placed on placebo or built-up to 4000 mg per day of peanut protein OIT through 2 years (week 104). Those participants on OIT were then split into two groups: one ceasing OIT and one continuing a reduced dose of 300 mg daily. Participants subsequently underwent serial peanut DBPCFCs over the next year. Thirteen weeks after the OIT group was split (week 117), 54% of participants in the 300 mg group, 35% in the post-OIT group, and 4% in the placebo group passed a 4000 mg peanut challenge. At the end of the study, 3 years after beginning OIT and 1 year after the OIT groups were split, 13% in the post-OIT groups and 37% in the 300 mg group passed the 4000 mg food challenge compared to 4% in the placebo group. In those participants, who maintained sustained unresponsiveness, baseline peanut-specific IgG4 to IgE ratios were higher and Ara h 2 IgE and basophil activation responses were lower. This study illustrates that sustained unresponsiveness is possible for a small number of peanut OIT patients and suggests biomarkers that should be further evaluated. However, most patients had a decrease in tolerance after stopping or reducing the daily dose of peanut OIT [6[¶]].

QUALITY-OF-LIFE IMPACTS

In 2019, the Institute for Clinical and Economic Research (ICER) concluded there was insufficient evidence to demonstrate a superior net health benefit of peanut OIT using Palforzia as compared with avoidance. This was largely because of a lack of demonstration of clear improvements in QoL, one of the main proposed benefits of OIT [16[¶]]. Also, in 2019, the Peanut Allergen immunotherapy, Clarifying the Evidence (PACE) systematic review found no impact of peanut OIT on QoL [17[¶]]. However, as previously discussed in this journal, these analyses mainly considered QoL in the first year of OIT, which is the most fraught with adverse reactions, failed to include other studies demonstrating QoL benefit, and used tools not optimally suited for OIT QoL assessment [10,18]. Despite ICER's conclusions, the FDA Allergenic Products Advisory Committee gave Palforzia a strong approval based on efficacy and the high unmet need for a treatment of peanut allergy.

A small study of 21 pediatric peanut OIT patients demonstrated a statistically significant drop (reflecting improvement in QoL) in the Food Allergy QoL score after successful desensitization to 300 mg

peanut protein. Social and Dietary Limitations subscale scores and the Food Allergy Independent Measure scores also significantly improved after successful maintenance OIT [19[¶]]. A survey of 55 families who had completed peanut OIT in a clinical trial setting demonstrated improved perceptions of safety and life satisfaction in both pediatric participants and their parents [20]. This benefit was also seen in participants with other food allergies and those who were no longer ingesting peanut. However, this study may have been subject to bias, as only 55 families out of 130 originally invited completed the survey [20]. Another survey of trial participants and families who had received oral or sublingual peanut OIT demonstrated improvement in parent-reported Food Allergy QoL scores, but inconsistent results for pediatric participants [21]. Additionally, a meta-analysis of seven peanut and other food OIT studies showed a significant improvement in health-related QoL after treatment compared with baseline [22[¶]]. More robust evaluations of the long-term QoL impacts of peanut OIT, especially after reaching maintenance dosing, are needed.

SAFETY AND PALFORZIA RISK EVALUATION AND MITIGATION STRATEGY

Palforzia carries a black box warning for anaphylaxis and precautions for gastrointestinal side effects and eosinophilic esophagitis. Its use is also prohibited in uncontrolled asthma [8^{¶¶}]. Due to the risk of anaphylaxis and as a condition of the approval of Palforzia, the FDA requires that all prescribers, healthcare settings, pharmacies, and patients enroll in a Risk Evaluation and Mitigation Strategy (REMS) [8^{¶¶},23]. Additionally, physicians and other healthcare professionals, healthcare settings, and pharmacies must be certified in order to prescribe, dispense, and administer Palforzia. The goals of the REMS program are to mitigate the risk of anaphylaxis by ensuring all parties are well educated and prepared. The program confirms that patients are prescribed an up-to-date epinephrine autoinjector and reinforces that the initial dose escalation and subsequent updose visits must be completed in a monitored healthcare setting with the ability to manage anaphylaxis [23]. Other medications with variations of REMS include oral isotretinoin, oral thalidomide, and some opioids [24].

The POISED study also explored the safety of more than 1 year of peanut OIT. Adverse events decreased over time for all study groups. During the second year of treatment, adverse events because of accidental ingestions also decreased in the OIT groups compared with placebo [6^{¶¶}]. Similar to QoL

assessments, additional high-quality studies examining the safety of peanut OIT after the first year of treatment are needed to fully understand the long-term impacts of this therapy.

A large study of 783 patients undergoing peanut OIT in a community allergy/immunology practice reported systemic reactions and epinephrine use in 10 and 4%, respectively, of patients on build-up OIT [25]. Systemic reactions and epinephrine use occurred in 19 and 11%, respectively, of patients on maintenance OIT. Eosinophilic esophagitis was reported in 1% of patients overall. Peanut OIT regimens consisted of peanut flour followed by peanuts, peanut butter, or peanut candies. This study adds to our understanding of the safety of peanut OIT using shelf-bought peanut products in the community practice setting [25].

PEANUT ORAL IMMUNOTHERAPY COST EFFECTIVENESS

Cost-effectiveness of OIT is largely determined by its probability of sustained unresponsiveness, improvement in QoL, risk reduction of anaphylaxis, and cost to the patient [26]. OIT may be associated with greater front-end costs, and frequent reactions from the treatment itself also raise questions about risks and benefits of OIT. There is little evidence describing the cost-effectiveness of peanut OIT using Palforzia or shelf-bought peanut products. The July 2019 ICER report estimated the incremental cost-effectiveness ratio of Palforzia at \$88 000 per quality-adjusted life-year, meaning the treatment did not meet its criteria of cost-effectiveness related to cost for each quality-adjusted life-year gained [16[¶]]. ICER was unable to fully evaluate cost-effectiveness as the market price of Palforzia was unknown at the time of publication. Prior to the FDA approval of Palforzia, a simulated analysis demonstrated that peanut OIT may be cost-effective [26]. Palforzia was initially set a monthly price at \$890 and an annual price of approximately \$11 000 per year, although the cost is not stated on the official website. As of July 2020, there were 39 plans in the United States that have either interim or permanent policies written regarding Palforzia [27]. By the end of 2020, Palforzia was covered by most insurance payors, including Medicaid, although a prior authorization was universally required. Due to the high cost of Palforzia, several copay assistance programs have been made available to eligible patients, including those without insurance or insurance-denied coverage.

The cost of peanut OIT is further complicated by the potential use of biologics as adjunctive treatment to improve the safety and tolerability of OIT, especially during the build-up phase [28]. At an additional annual cost of \$25 000 to \$40 000 per year, the

healthcare system will be stressed to afford this option, especially for a disease that is often lifelong [29].

AREAS FOR FUTURE RESEARCH

In 2019, Food Allergy Research and Education convened a meeting of investigators, leadership of professional allergy medical associations, clinicians, patients, and employees of the FDA and National Institutes of Health to discuss practical issues surrounding OIT. A consensus statement was generated and published in 2020 [30[■]]. This document identified information gaps and unmet needs in OIT research. One clear need identified was standardization of terms used in OIT including desensitization and sustained unresponsiveness, as well as harmonization of terms for tolerated and reactive dose. Until this is done, comparison of different study results will be difficult. As indicated above, another major gap is the development of improved methods to accurately assess the impact of OIT on QoL. The pivotal Palforzia study also demonstrated another gap in OIT knowledge [9]. The patient population included was not representative of the United States demographic and there was clearly a lack of underrepresented minorities. As a result, future studies need to affirm the effects of Palforzia and other OIT products in patients of differing socioeconomic status, race, and ethnicities. Future research is needed to clarify appropriate dosing regimens for both the initiation and maintenance of peanut OIT as dosing varies between studies and the peanut product used. This also includes generation of comparative data from shelf-bought OIT products and pharmaceutical grade products, such as peanut powder or flour and Palforzia. Prospective, well designed studies on the efficacy and safety of multiple food OIT are also needed. Indeed, 40–60% of patients with peanut allergy are allergic to other foods [9]. Thus, information on multiple food OIT is critical. The pretreatment with a biologic or combination of OIT and a biologic, monoclonal antibodies directed against key pathways and mediators involved in the pathogenesis of food allergy, is a nascent area. The ability of anti-IgE, specifically omalizumab, to render peanut OIT safer during updosing has been demonstrated [28]. However, it is not known whether OIT with omalizumab (or other biologics) is as, or more effective than OIT alone, especially for long-term use.

CONCLUSION

Despite the unprecedented challenges to food allergy treatment and research during the COVID-19 pandemic, new developments in peanut OIT pathophysiology, sustained unresponsiveness, quality of life,

safety, and cost effectiveness were achieved in 2020. The approval of Palforzia is an important step in offering treatment options to the 32 million Americans living with food allergy [1]. However, this product is specific for peanut allergy and only approved for children older than 4 years of age [8[■]]. Peanut OIT is a promising therapeutic option but there is a dearth of information on its utility when combined with OIT for other food allergies, effectiveness in minority patients, and appropriate dosing regimens. Biologics might improve the safety and effectiveness of OIT but the additional costs of this will stress the healthcare system. Clearly, better therapeutic options and preventive therapies are needed. In the interim, exploration of how best to use OIT to alleviate the morbidity and potential mortality of peanut allergy is needed. Nonetheless, the availability of one FDA-approved product and the renewed interest in developing new therapies for food allergy bodes well for patients affected by this disease.

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Conflicts of interest

A.P., P.S., and T.C. are investigators for Aimmune Therapeutics-sponsored studies. T.C. is the chief medical advisor for operation at the Food Allergy Research and Education.

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