Abstract

Purpose of the Review Peanut oral immunotherapy (OIT) is one of the most studied experimental therapies for food allergy. With the recently FDA-approved peanut product, Palforzia, the goal of this article is to review the most recent data from clinical trials, discuss recent trends, and anticipate future developments.

Recent Findings The latest research suggests that peanut OIT could be a promising option for peanut-allergic patients, with the majority of participants in research studies achieving the primary efficacy endpoint of desensitization, as well as sustained unresponsiveness in select populations. Some studies also showed improvements in food allergy-related quality of life. However, peanut OIT is not without risk or side effects, including potentially serious allergic reactions.

Summary Future research will need to evaluate the short- and long-term effectiveness of the therapy in the real-world setting, predictors of important treatment outcomes, and the use of adjunctive therapies that may mitigate some of these allergic reactions.

Keywords Peanut allergy · Oral immunotherapy · Desensitization · Sustained unresponsiveness · Food allergy · Oral food challenge

Introduction

Food allergy affects about 5% of adults and 8% of children, with peanut allergy affecting about 2% of the population [1]. The main treatment approach recommended by U.S. guidelines has been strict allergen avoidance and early treatment with rescue medications if reactions occur [2, 3]. However, peanut allergy has a negative impact on quality of life and healthcare costs. These factors highlight an urgent need for alternative options for this potentially life-threatening condition. Currently, there are ongoing clinical research trials to evaluate alternative therapies for peanut allergy. Peanut oral immunotherapy (OIT) is one of the most investigated alternative options with a recent United States Food and Drug Administration (FDA) approval in early 2020 for a peanut OIT product, Palforzia. In this review, we examine data from peanut OIT clinical trials and discuss the recent trends and future developments in peanut OIT.

Peanut Oral Immunotherapy

General Protocol

Peanut OIT is currently considered an investigational therapy for peanut-allergic patients. The overall goal of OIT is to facilitate a state of desensitization by exposing the participant to increasing doses of peanut protein. While considerable differences exist between clinical trial protocols, the desensitization process is conceptually similar. Participants are initially selected based on specific criteria such as a physician-confirmed history of peanut allergy (though this is not universally the case), along with test results that support that history. Patients have typically been excluded if they had a history of
a life-threatening reaction, poorly controlled asthma, suspicion of eosinophilic gastrointestinal disease, or other factors that would hinder their ability to cooperate with the study [4]. Importantly, high-specific IgE levels do not disqualify participants from these trials. Some but not all studies then uses double-blind, placebo-controlled food challenges (DBPCFC) to confirm eligibility. On a subsequent day, qualifying participants then consume an initial starting dose below the participant’s threshold, with rapid same-day dose escalation until the participant has a reaction or reaches the maximum dose for that day, typically in the range of 5–50 mg of protein. The participant will return at scheduled intervals for the build-up phase with the goal of increasing the daily dose. Ultimately, the participant reaches a maintenance dose (or highest dose tolerated) which will be continued daily for a specified period [4].

**Efficacy vs Effectiveness**

While there is no single definition of efficacy, in clinical trials this may be defined as achieving specific endpoints. The primary efficacy endpoint of most peanut OIT is desensitization, which can be defined as a transient shift upwards in the reactive allergen dose threshold requiring continued consumption of the allergen. It may be a state of clinical remission (also known as sustained unresponsiveness (SU)), based on a successive allergen dose threshold requiring continued consumption of the allergen. It may be a state of clinical remission (also known as sustained unresponsiveness (SU)), based on a successive allergen dose threshold requiring continued consumption of the allergen. It may be a state of clinical remission (also known as sustained unresponsiveness (SU)), based on a successive allergen dose threshold requiring continued consumption of the allergen. 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at-risk population and ideally predict these events and/or identify such patients as candidates for other approaches (e.g., co-treatment with a biologic, very slow up dosing, continued avoidance). Another important goal of future research is a better understanding of the augmentation factors like exercise, viral infection, menses, and others that have been repeatedly shown to play a role in many such events [14, 15].

Regarding the benefits, clinical trials have demonstrated desensitization, sustained unresponsiveness, and an improvement in quality of life (QoL). We will discuss this in further detail.

**Peanut OIT Clinical Trials Summary**

Table 1 summarizes the results of relevant peanut OIT clinical trials published within the last 5 years. The PALISADE group of clinical investigators conducted an international phase 3 randomized placebo-controlled clinical trial evaluating AR101 (a peanut-derived OIT drug) [11]. This study remains the largest peanut allergy immunotherapy trial conducted. In addition, it included patients with a history of severe or life-threatening reactions and did not use medical trial conducted. In addition, it included patients with a history of severe or life-threatening reactions and did not use medical

In comparison, a more recent study by Blumchen et al. evaluated 62 participants ages 3–17 years in a double-blind, randomized, placebo-controlled (DBRPC) trial assessing the efficacy of relatively low-dose OIT [8••]. This trial evaluated whether a lower and slower dosing regimen could achieve similar outcomes to prior studies and improve safety. The dose-escalation occurred over a maximum of 14 months (median of 13 months) followed by 16 months of maintenance. This is compared to the PALISADE group in which the patient was dose escalated from 3 to 300 mg every 2 weeks followed by a 24-week maintenance with a total duration of the study of 12 months [11]. The active group received between 125 and 250 mg/day of peanut protein and the control group received placebo for 16 months. The primary endpoint was to evaluate the proportion of participants who could tolerate at least 300 mg of peanut protein in the final challenge. The authors showed that 74.2% of the OIT group tolerated at least 300 mg of peanut protein vs 16.1% in the placebo group. Treatment-related AEs, which were all mild-moderate in severity, occurred in 90% of the active group vs 77% of the placebo group. There was no epinephrine use for AEs. They found no difference between the groups in dropouts due to AEs, occurrence of SAEs and objective OIT-related AEs, severity of symptoms, treatment of symptoms, or worsening of preexisting atopic diseases. The dropout rate was 6.7% and no patients had development of EOE [8••]. These results suggest that a slower up-dosing schedule and lower maintenance doses than was tested in PALISADE could potentially still yield clinically meaningful desensitization with improvement in the safety profile of OIT, which if validated could help to optimize OIT regimens.

Another study similarly explored ways to optimize peanut OIT by focusing on a younger patient population. Vickery et al. evaluated 37 newly diagnosed preschool children ages 9–36 months with suspected or known peanut allergy confirmed by an entry food challenge. They were randomized to receive early-OIT (E-OIT) at goal maintenance doses of 300 or 3000 mg/day with the primary endpoint evaluating sustained unresponsiveness at 4 weeks (4-SU) after stopping treatment. The results showed that 78% of participants achieved 4-SU with a decline in peanut-specific IgE recognizing the natural history of peanut allergy in which ~20% of peanut allergy resolves in children by age 4 years [16•]. There were no SAEs and 95% of participants had AEs likely related to OIT more frequently during the build-up phase. Of these AEs, 85% were mild and 15% moderate. About 47% of participants required treatment with antihistamines and no one required epinephrine during dose escalation, with one requiring at home after a dose [6]. A cross-Canadian group of clinicians recently published a similarly reassuring adverse event profile in 270 young children ages 9–71 months treated with peanut OIT in their clinics, as is common practice there. Over 16 to 22 weeks, participants underwent escalation dosing with
| Reference, year | Sample size (age range) | Study design | N: peanut protein OIT dose/day | Duration | Results | Adverse events | Conclusions/additional notes |
|----------------|-------------------------|--------------|-------------------------------|----------|---------|---------------|-----------------------------|
| Chinthrajah [9] | 120 (7–55 years)        | DBRPC        | 60: 4000 mg/day; 0 mg/day (peanut-0) 35: 4000 mg/day; 300 mg/day (peanut-300) 25: placebo | 156 weeks | In the peanut-0 group, in which eight (13%) of 60 participants passed DBPCFCs at week 156, higher baseline peanut-specific IgG4 to IgE ratio and lower Arah 2 IgE and basophil activation responses were associated with sustained unresponsiveness. | Mild GI symptoms Peanut-0: 50/60 Peanut-300: 29/35 Placebo: 11/25 Skin symptoms Peanut-0: 26/60 Peanut-300: 15/35 Placebo: 9/25 | Suggests peanut OIT could desensitize individuals with peanut allergy to 4000 mg of peanut protein however discontinuation or reduction in dose could result in regaining clinical reactivity. |
| Blumchen et al. 2019 [8] | 62 (3–17 years)         | DBRPC        | 31: 125 mg–250 mg/day 31: placebo | 16 months | 23/31 (74.2%) or OIT group tolerated at least 300 mg of peanut protein in final OFC vs 5/31 (16.1%) in the placebo group | Peanut OIT (83%) AEs Placebo (45%) AEs 4.3% vs 1.2% AEs in POIT vs placebo occurred within hours of ingestion 1 had severe adverse event related to OIT Peanut OIT: 35 per 1000 doses resulted in AEs Placebo: 31 per 1000 does resulted in AEs | Low-dose OIT is effective in treatment for peanut-allergic children, leading to tolerance and improved quality of life |
| Fauquert et al. 2018 [10] | 30 (12–18 years) | DBRPC | 21: 400 mg/day 9; placebo | 24 weeks | 17/21 in the peanut group achieved unresponsiveness 1/9 achieve unresponsiveness in the placebo group | Peanut OIT: 35 per 1000 doses resulted in AEs Placebo: 31 per 1000 does resulted in AEs | The GIDOIT protocol demonstrated clinical and immunological efficacy |
| Palisade group et al. 2018 [11] | 496 (4–17 years) | DBRPC | 372: 300 mg/day 124: placebo | 24 weeks | 250/372 (67.2%) of OIT group were able to ingest 600 mg or more of peanut protein | Mild: 34.7% in peanut OIT Moderate: 25% peanut OIT Severe: 4.3% in peanut OIT Mild: 50% in placebo Moderate: 59% in placebo Severe: 0.8% in placebo | Treatment with AR101 resulted in higher doses of peanut protein that could be ingested without dose-limiting symptoms and in lower symptom severity during peanut exposure at the exit food challenge than placebo |
| Vickery et al. 2017 [6] | 37 (9–36 months) | Double blind, randomized, controlled | 20: 300 mg/day 17: 3000 mg/day | ≥ 12 months | 30/37 (81%) were desensitized 29/37 (78%) achieved 4-SU | 95% of subjects were affected by AEs 85% were mild, 15% moderate, and 0% severe | E-OIT had an acceptable safety profile and was highly successful in rapidly suppressing allergic immune responses and achieving safe dietary reintroduction. |
| Kukkonen et al. 2017 [25] | 60 (6–18 years old) | DBRPC | 39: 800 mg/day 21: placebo | 8 months | 26/39 (67%) were desensitized with no 30/39 (77%) reported AEs and 16/39 (41%) required antihistamines with 1/39 | Peanut OIT did not cause changes BHR, FEV1 from baseline or FeNO |
| Reference, year | Sample size (age range) | Study design | N: peanut protein OIT dose/day | Duration | Results | Adverse events | Conclusions/additional notes |
|----------------|-------------------------|--------------|------------------------------|----------|---------|----------------|-----------------------------|
| Tang et al. 2015 [18] | 62 (1–10 years old) | DBRPC | 31: 2000 mg/day 31: placebo | 18 months | change from baseline in FEV1 or FeNO: 23/28 (82.1%) of PPOIT achieved SU 28 (3.6%) of placebo achieved SU 26/29 (89.7%) of PPOIT achieved desensitization 2/28 (7.1%) of placebo achieved desensitization | (2.6%) requiring epinephrine 1/31 (3.6%) of children in PPOIT 2/28 (7.1%) of placebo achieved desensitization | Co-administration of probiotic and peanut oral immunotherapy showed efficacy in desensitization and SU in children with peanut allergy 4-year follow-up showed participants from PPOIT group were significantly more likely than those from the placebo group to have continued eating peanut [19] |
| Bird et al. 2015 [30] | 11 (4–16 years old) | Open-label | 11: 2000 mg/day | 41 weeks | 9/11 subjects tolerated 2000 mg in the maintenance phase and passed the 5000 mg exit DBPCFC | AEs occurred in 264/3265 (7.9%) of total doses administered with mostly mild reactions | A lower maintenance dose of 2000 mg induced desensitization |
| Narisetty et al. 2015 [31] | 16 (7–13 years old) | DBRPC | 11: 2000 mg/day | 12 months | 7/11 achieved a 10-fold increase compared to baseline | 33.3% experience adverse effect with majority mild reactions | OIT was effective in treatment of peanut allergy. SU after 4 weeks of avoidance was seen in a small proportion of patients |
| Vickery et al. 2014 [32] | 24 (1–16 years old) | Open-label, non-randomized, non-controlled | 24: 4000 mg/day | ≤ 5 years | 12/24 passed challenge after 1 month of stopping treatment (SU) | | 50% of participants had SU after peanut OIT with smaller skin test and lower allergen specific IgE levels being more predictive of successful outcome |
| Anagnostous et al. 2014 (33) | 104 (7–16 years old) | Open-label, randomized, controlled | 49: 800 mg/day 50: no intervention | 26 weeks | 62% achieved desensitization (tolerated 1400 mg of peanut protein) | The number and nature of adverse events was similar in both groups after treatment. Most events were mild with gastrointestinal symptoms being the most common | Primary endpoint met with most children becoming desensitized with increase in peanut threshold and improved quality of life |
goal maintenance dose of 300 mg of peanut protein. Of those who reached maintenance, 243, 10% dropped out, 67.8% experienced reactions during build-up: 36.3% grade 1, 31.1% grade 2, and 0.4% grade 3. 11/243 (4.1%) required epinephrine. This represented 2.23% of reactions (12 of 538) and 0.029% of doses (12 of 41,020) [17]. This data suggests that the peanut OIT is generally tolerated with few and generally, mild reactions however that life-threatening reactions, although rare, can occur [17].

In an alternative perspective, a few studies have looked to evaluate other approaches to peanut OIT in order to induce desensitization. In 2018, Fauquet et al. performed a DBRPC trial to evaluate a new modality of peanut OIT to induce desensitization in 30 peanut-allergic adolescents. Participants in the active group ingested sealed capsules of peanut bypassing the upper digestive tract for a method the authors termed gastrointestinal delivery oral immunotherapy (GIDOIT). Peanut or placebo capsules were ingested daily over 24 weeks (build-up phase) at 2-week increments from 2 to 400 mg of peanut protein with the goal of tolerance of 400 mg. Of the participants recruited, 81% in the peanut group achieved unresponsiveness to 400 mg of peanut protein compared to 10% in the placebo group [10]. The number of participants experiencing AEs was not different between the two groups; however, the number of AEs per patient was higher in the OIT group than the control group. The number of doses that resulted in AEs was 35 per 1000 in the intervention group vs 31 per 1000 in the placebo group. In the OIT group, 91 per 1000 doses required medication and 36 per 1000 in the placebo group. Five SAEs occurred in 4 participants in the OIT group and 0 in the placebo group [10]. Tang et al. conducted a DBRPC trial combining the probiotic *Lactobacillus rhamnosus* combined with peanut OIT for 18 months in 62 children ages 1–10 years with peanut allergy. The peanut OIT protocol was a 1-day rush induction phase with a build-up phase with up dosing every 2 weeks to a maintenance dose of 2 g of peanut protein for a total of 18 months. The active group received the probiotic with the peanut OIT (PPOIT) daily and the placebo group received placebo with placebo daily. An oral peanut DBPCFC was performed on the last day of study treatment to assess for desensitization to 4 g of peanut protein. Those who passed underwent another challenge at 2 weeks or more of the study treatment to assess for SU. The primary outcome assessed was SU. 82.1% of the participants treated with PPOIT and 3.6% of placebo-treated participants achieved SU. Desensitization was achieved in 89.7% of participants in the PPOIT group and 7.1% in the placebo group. At least 1 SAE was reported in 45.2% of children in the PPOIT group compared with placebo group, however, 1 child in the PPOIT group had 13 SAEs. The number of SAEs per participant during the build-up was similar between groups; however, reactions during maintenance were more common in the PPOIT group than placebo group [18]. Because this study did not control for the effect of the probiotic, it is not possible to determine whether there was an adjunctive effect with combination therapy. In a follow-up study 4 years after treatment was stopped, participants from the PPOIT group were more likely than those from the placebo group to have continued eating peanut (67% vs 4%). Fifty-eight percent of participants from the PPOIT had SU at 8 weeks compared to 17% in the placebo group [19]. These results continue to show the effectiveness in peanut OIT; however, additional studies with these specific therapies (i.e., sealed peanut capsule and adjunctive probiotic use) would need to be replicated in order to assess the role it played in achieving the primary endpoints in comparison to other larger peanut OIT clinical trials. A larger more definitive study of PPOIT, with a probiotic-only control arm in addition to placebo, is underway.

**Quality of Life**

An additional area that is important to address in peanut OIT is quality of life (QoL). A number of community practices have reported QoL data in their patients treated in real-world practice, and these reports often show some benefit but should be interpreted with caution due to potential bias. Some but not all clinical trials report QoL as a secondary endpoint but importantly, the instruments used to measure QoL were not developed and validated for use in a therapeutic context. A true patient-reported outcome measure developed specifically to address clinical benefit after food immunotherapy is an urgent need. This has been pointed out by several authors, with whom we agree [13, 20, 21].

In a prior study by Tang et al. that evaluated PPOIT vs placebo, a longitudinal impact on health-related quality of life (HRQOL) was also evaluated [22••]. Fifty-one participants completed the Food Allergy Quality of Life Questionnaire (FAQLQ-PF) and Food Allergy Independent Measure (FAIM) at pre-treatment, end-of-treatment, and 3 months after end-of-treatment; 42 of the 51 participants completed the questionnaires at 12 months post-treatment. The results showed that PPOIT was associated with a significant improvement in the FAQLQ-PF and FAIM while there was no change in the placebo group. Overall, the PPOIT group showed a benefit in the HRQOL specifically in those that acquired sustained unresponsiveness [22••]. Reier-Neilsen et al. conducted a study in 96 patients ages 5–15 years who had undergone peanut OIT and reviewed the QoL responses taken at the initial screening, during the up-dosing, and maintenance with desensitization. The children completed the validated age-adapted generic Pediatric Quality of Life Inventory questionnaire (PedsQL 4.0). Parents completed both the PedsQL 4.0 proxy-report as well as the Food Allergy Quality of Life-Parental Burden (FAQL-PB) questionnaire. The results showed that the child reported QoL improvement after 2 years of OIT was not significant between the OIT group and the
control group. However, in the child QoL reported by the parents, there was a two-fold significant change in the OIT group compared to the control group. Overall, parental proxy but not child self-reported QoL improved with OIT [23••]. In the DBRPC trial conducted by Blumchen et al., QoL was a secondary endpoint that was evaluated [8••]. Similarly, they evaluated HRQOL using the FAQLQ-PF (for mothers), FAQLQ-CF (for children), and FAQLQ-TF (for teenagers) before the initial OFC and 4 weeks after the final OFC. They also evaluated the burden of treatment (BOT) via a BOT questionnaire. The results showed a significant improvement in the HRQOL for the domains of “risk of accidental exposure” and “emotional impact” after OIT. Mothers of the peanut OIT group but not the placebo group reported an improvement in HRQOL within the domain of “social and dietary limitations.” There was no significant difference in HRQOL for all domains reported by mothers in either group. In children, the peanut OIT group reported a significant improvement in HRQOL within the domains of “risk of accidental exposure” and “emotional impact” when compared with placebo. Eighty-two percent of mothers of the peanut OIT group and 100% of the placebo group reported a positive BOT. 3.7% in the OIT group would not perform OIT again. Eighty-two percent of children of the OIT group and 90% in the placebo group were positive about their treatment [8••]. Overall, there is data to suggest improvement in certain aspects of the quality of life in both the parents and children, though the effect is complex, may be more pronounced in caregivers than the children themselves, and varies over time. The beneficial effects of trial participation, such as access to experts and guided exposures through a DBPCFC (which itself has a beneficial effect on QoL independent of outcome), must be considered. More study, and development of new validated tools, is urgently needed.

Predictors and Adjunctive Therapies

Baseline Predictors of Allergic Side Effects during Peanut OIT

Peanut OIT is a promising therapy for peanut-allergic patients, but AEs may limit patient enrollment and compliance. A retrospective analysis evaluated if there were baseline predictors of allergic side effects during peanut OIT. Of 111 peanut-allergic children, 104 tolerated escalation with home administration of OIT. The final study evaluated 104 participants of mostly Caucasian descent. Comorbid conditions included allergic rhinitis (AR) (46%), asthma (44%), and atopic dermatitis (77%). They found that 80% of participants experienced AEs related to OIT (72% during build-up); 7% of events occurred in the research unit while 93% occurred while at home. Eighty-five percent of the reactions were mild, 15% moderate, and there were no severe events or SAEs. Forty-two percent experienced systemic reactions and 49% experienced GI symptoms. Participants with AR were 2.9-fold higher than those with AR to experience AEs and for every 5 mm increase in peanut skin prick test (SPT) there was a 1.4-fold increase in AEs. The overall presence of asthma increased AEs by 2.3-fold during the maintenance phase. Overall, in a multivariate model, baseline allergic rhinitis, asthma, and peanut SPT were significant predictors of higher rates of AEs [24].

In addition to achieving the primary endpoints or peanut OIT, clinical studies are evaluating the utilization of biomarkers in explaining the heterogeneity of the clinical response to the treatment. Kukkoken et al. evaluated 60 participants ages 6–18 years in a double-blind placebo-controlled peanut challenge to assess the efficacy and safety of peanut OIT. Thirty-nine received OIT and 21 avoided peanut protein. Biomarkers including specific IgE and IgG4 were measured as well as AEs of bronchial hyperresponsiveness (BHR) to methacholine and the fractional concentrations of exhaled nitric oxide (FeNO). The results showed that 85% of the OIT participants passed the build-up phase and 67% tolerated 5 g of peanuts during the post-treatment challenge. There was no harmful effect on BHR to methacholine. FeNO showed no change. Regarding AEs, 77% reported AEs and 41% required antihistamines with 2.6% requiring epinephrine. During the build-up phase, five adverse events led to emergency medical contact at a rate of 4.6 per 10,000 patient days. During the follow-up period, 72% of participants consumed 100 to 2000 mg of peanut protein on 2 to 7 days weekly and 77% of the responders continued the 800 mg dose [25].

A recently published DBRPC clinical trial evaluated the sustained effects of long-term peanut OIT in adults and children. One hundred twenty patients ages 7–55 years old with a confirmed peanut allergy were randomized to 3 different groups: built up to a maintenance dose of 4000 mg through week 104 then discontinued on peanut (peanut-0 group), built up to a maintenance dose of 4000 mg through week 104 then maintained on 300 mg of peanut for 52 weeks (peanut-300 group), or placebo. DBPCFCs to 4000 mg peanut protein were done at baseline and weeks 104, 117, 130, 143, and 156. The primary endpoint was the proportion of participants who reached and passed the DBPCFC to cumulative dose of 4000 mg at weeks 104 and 117. In addition, specific biomarkers were followed including skin testing, basophil activation tests, and assays of peanut-specific IgE and IgG4, and total IgE. Twenty-one (35%) of peanut-0 group participants and one (4%) placebo group participant passed the 4000 mg challenge at both 104 and 117 weeks (odds ratio (OR) 12.7, 95% CI 1.8–554.8; p = 0.0024). There was no significant difference in success between the peanut-0 group and then peanut-300 group at week 117 (35% vs 54%, p = 0.086), however, in all subsequent DBPCFCs, the peanut-0 group was less likely to reach 4000 mg than the individuals in the peanut-300
undergoing OIT is vital. In a parallel, randomized phase II group, which eight (13%) of 60 participants passed DBPCFCs at week 156, higher baseline peanut-specific IgG4 to IgE ratio and lower Ara h 2 IgE and basophil activation responses were associated with sustained unresponsiveness. Neither the cumulative tolerated peanut dose at baseline, age, atopic comorbidity, peanut skin wheal size, were associated with higher risk of treatment failure. Overall, peanut OIT was able to desensitize patients with peanut allergy to 4000 mg of peanut protein, however, with reduction or discontinuation, there was an increased risk of clinical reactivity [9].

Another recently published study evaluated how basophil sensitivity and area under the curve (AUC) to Ara h2 correlated with clinical response to OIT. Twenty-two of 30 participants (ages 7–13 years) successfully underwent treatment with OIT. Of those, nine achieved SU and 13 had transient desensitization (TD). Similar to prior studies, the pre OIT peanut-specific IgE and Ara h2-specific IgE were greater in those with TD than those with SU (p = 0.002); however, the ratio of Ara h2-specific IgE to total IgE was not statistically significant. A significant decrease in Ara h2-specific IgE from pre OIT occurred after OIT in those with TD (p = 0.004) with similar trends that did not reach significance in those with SU. Additionally, Ara h2-specific IgG and IgG4 increased during OIT. The Ara h2-specific IgE levels before OIT were similar in those with TD and SU. After OIT, basophil AUC was significantly suppressed from baseline in patients with SU (p < 0.001) and TD (p < 0.001). Basophil AUC to both Ara h2 and peanut were similar in participants with SU and those with TD at the end of OIT; however, after 1 month of avoidance, the basophil AUC in the participants with TD rebounded as opposed to those with SU (p < 0.001) [26].

**Adjunctive Therapies**

OIT is an investigative therapy that can lead to desensitization. While the hope is to allow for protection from accidental exposures and thus improve the quality of life, the process of OIT involves continued exposure to the allergen. Allergic reactions can be expected, which in some patients may cause additional anxiety and treatment dropout. Therefore, exploring alternative ways of improving patient experience while undergoing OIT is vital. In a parallel, randomized phase II controlled trial, 50 participants from ages 7–17 years consumed doses of peanut OIT at home over 24 weeks. Families attended monthly group clinic visits throughout the 7-month study. Each parent had a monthly call with the head of the patient support team, where parents could express any concerns about the treatment. The symptoms were described as “symptoms as positive signals” (SAPS) or “symptoms as side effects” (SASE). The SAPS group was encouraged to think of symptoms as a positive signal associated with increasing desensitization. By use of questionnaires, the endpoint treatment experiences evaluated were symptom anxiety, dosing experience, staff contact about symptoms, and symptoms occurrence. The endpoint treatment outcomes evaluated were adherence, time to treatment completion, biomarkers, and statistical analysis. Overall, the results found that the SAPS mindset improved treatment experience (anxiety, symptom rates) and outcomes (adherence, change in specific IgG4 levels) [27]. This suggests an important discussion that the clinician should have throughout OIT.

Another adjunctive therapy being evaluated to improve the rates of these side effects as well as improve the compliance of treatment is co-administration of a biologic. In one study, omalizumab showed that the peanut dose tolerated on initial desensitization was 250 mg vs 22.5 mg for the placebo group. Additionally, 79% of subjects in the omalizumab group tolerated 2000 mg of peanut protein 6 weeks after stopping omalizumab versus 12% receiving placebo [28]. Additionally, there are current trials evaluating the role of dupilumab in facilitated desensitization as well.

**Current Perspective**

Currently in practice, many allergists have adopted similar protocols based on ongoing clinical research trials in their outpatient practices. A 2019 study sought to better understand the current use of peanut allergy challenge protocols, which practices choose to offer peanut OIT, compare published and non-published approaches of peanut OIT, and the obstacles that limit peanut OIT in U.S. allergy practices [29]. This study used qualitative in-depth telephonic interviews with 34 allergists and nurse food allergy specialists across the USA. Peanut allergy was confirmed by history and skin testing with about 5–10% utilizing diagnostic food challenges only when testing was inconclusive. They found that 94% of practices interviewed did perform peanut food challenges. Practices cited many reasons for not performing peanut OIT: perceived risk of increased potential to trigger anaphylaxis, lack of access to a validated protocol, and insurance reimbursement. The patients that were offered peanut OIT seemed to be patients ages 4–7 years; exclusion factors include patients with multiple allergies, allergic comorbidities, and/or a history of anaphylaxis. Social factors were also important including motivated and supportive families. The hope is with the recently FDA-approved product, Palforzia and accompanying protocol, allergists will feel more equipped to offer peanut OIT [29].
Conclusions

In summary, the major themes that have emerged from these clinical trials include a consistent demonstration that peanut OIT raises the threshold of reaction and in certain patients can achieve sustained unresponsiveness. Although many of the clinical trials were heterogeneous in their design (i.e., the patient population, the OIT product, the dosing regimen, and duration of therapy), the general suggestion is that children as young as 9 months to 17 years may benefit from this therapy. In regard to the overall safety, lower doses and slower escalation resulted in lower rates of SAEs and lower dropout rates. However, adjunctive therapy may assist in faster escalation with similar or lower rates of SAEs. Higher rates of adverse reactions may be related to specific predictors such as baseline allergic rhinitis, asthma, and peanut SPT which the provider may want to consider prior to starting therapy. Although data are sparse, the quality of life data that are available suggest improvement over time in most studies.

As discussed earlier, peanut OIT is not without risk even in those who have undergone effective desensitization. Optimizing the dosing regimens themselves and/or the selection of patients (e.g., those with low IgE levels, younger patients, milder reaction histories, adherent to dosing guidance about augmentation factors) may help to mitigate risk. Adjunctive therapy with biologics added to OIT may also prove to be helpful in further mitigating risk.

However, there are still many questions that need to be further investigated in clinical studies. These include the clinical effectiveness of peanut OIT in real-world practice including the optimal dose and duration of therapy of peanut OIT to achieve SU. Evaluation of distinct features or biomarkers in patients which may help categorize those at higher risk for reactions and guide treatment and duration of therapy. These trials were clinically significant in the pediatric setting, however, more research in the adult population would potentially allow a wider population to benefit. Testing these therapies in other key populations (i.e., ethnic and racial groups who were not widely represented in trials; those with poor asthma control and/or EoE; others) will also be helpful. Other questions include how this therapy compares in effectiveness with the other treatment modalities and adjunctive therapies. Lastly, evaluation of the real-world impact on the quality of life with the development of more specific and validated tools to better report these measurements.

In conclusion, peanut OIT appears to be a promising treatment option for peanut-allergic patients who would benefit from increasing the threshold of tolerance for protection from accidental ingestion and possibly achieving sustained unresponsiveness. With the recently FDA-approved peanut OIT product, Palforziza, the importance of ongoing research and data analysis will be crucial in assessing the effectiveness in the real-world setting.

Compliance with Ethical Standards

Conflict of Interest  Dr. Vickery reports grants and personal fees from Aimmune Therapeutics, personal fees from AllerGenis, grants and personal fees from Food Allergy Research and Education, grants from Genentech, grants from DBV Technologies, grants from NIH-NIAID, grants from Regeneron, outside the submitted work. The other authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent  This article does not contain any studies with human or animal subjects performed by any of the authors.

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