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Oral immunotherapy for peanut allergy: The pro argument

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ABSTRACT

Food allergy (FA) is a growing public health problem with personal, social, nutritional, and economic consequences. In the United States, it is estimated that 8% of children and 10.8% of adults have food allergies. Allergies to peanuts are particularly worrisome as unlike allergies to other allergenic foods, such as milk and egg, which are commonly outgrown by 5 or 10 years of age, 80% of peanut allergies persist into adulthood. The first drug for peanut allergy, Palforzia, was approved by the US Food and Drug Administration (FDA) in January 2020. For other food allergies, the current standard of care for the management of FA is suboptimal and is limited to dietary elimination of the offending allergen, vigilance against accidental ingestion, and treatment of allergic reactions with antihistamines and epinephrine. However, dietary avoidance can be challenging, and it is estimated that approximately 40% of patients with food allergies report at least one food allergy-related emergency department in their lifetime. Reactions, even from minimal exposures, can be life-threatening.

Oral immunotherapy (OIT) has been the best researched therapeutic approach for treating FA over the last decade, with clinical trials investigating its efficacy, safety, and ability to improve participants' quality of life (QoL). A number of studies and meta-analyses have shown that OIT treatment is effective in raising the threshold of reactivity to peanuts and other foods in addition to producing a measurable serum immune response to such therapy. Although OIT-related adverse events (AEs) are common during treatment, serious reactions are rare. In fact, while the majority of patients experience AEs related to dosing, most continue daily dosing in hopes of achieving protection against the culprit food. Moreover, the majority of participants report improvement of QoL after OIT and are positive about undergoing OIT. These results show patients' commitment to OIT and their optimism regarding the benefits of treatment. As a first step in therapeutic options to protect from reactions to unintentional ingestion of allergenic foods, and importantly, to address the many psychosocial aspects of living with FA, OIT shows promise. Future research will focus on identifying optimal OIT regimens that maintain protection after therapy and allow for regular food consumption without allergic symptoms. Education and informed shared decision making between patients and providers are essential in optimizing current therapy regimens.

Keywords: Oral immunotherapy, Peanut allergy, Efficacy, Safety, Quality of life

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INTRODUCTION

Food allergy (FA) is a public health problem with personal, social, nutritional, and economic consequences. And it is a growing *global* problem.[1] In the United States, recent studies by Gupta et al indicate that up to 8% of children and 10.8% of adults have food allergies.[2,3] Although allergy to milk and egg are commonly outgrown by the age of 5–10 years, allergies to peanut and tree nuts are often lifelong, persisting into adulthood in 80% of cases.[4,5] In the United States, peanut allergies affect 1.8% of adults[2] and 2.2% of children.[3]

For FAs other than peanut allergy, there are no approved drugs, and current standard of care is limited to dietary elimination of the offending allergen, vigilance against accidental ingestion, and treatment of reactions with antihistamines and epinephrine.

However, dietary avoidance can be challenging and it is estimated that approximately 40% of patients with FAs report at least one food allergy-related emergency department visit in their lifetime.[2] FA is one of the most common causes of anaphylaxis, with most surveys indicating that food-induced reactions account for 30%–70% of cases.[6,7] Accidental ingestion rates range from 14 to 33% for peanut,[8] 19–50% for hen's egg,[9] and 17–36% for cow's milk.[9] Reactions, even from minimal exposures, can be life-threatening, presenting with various clinical symptoms among different individuals. In addition to the physical consequences of an allergic reaction, a multitude of adverse psychosocial aspects of living with FA exist, such as anxiety, social isolation, and related bullying.[10,11]

The approval by the US Food and Drug Administration (FDA) of Palforzia in January 2020, the first drug approved for FA in the form of peanut oral immunotherapy (OIT),[12] is a first step towards safe and effective treatments for FA. Palforzia is a highly characterized and standardized peanut OIT formulation. However, research into further optimization of peanut OIT for efficacy, safety, and ability to improve participants' quality of life (QoL) continues. Numerous publications have shown the potential benefits of OIT in treating FA, however, they have been criticized due to the heterogeneity across studies, and the absence of a standard for study design, OIT doses, primary endpoints, and instruments in assessing QoL. In this review, we searched electronic databases such as Ovid MEDLINE, PubMed, EMBASE, and Web of Science for relevant studies on peanut OIT. Here, we present the latest, up-to-date evidence on efficacy, safety, and QoL with OIT treatment in patients with FA.

Efficacy

The ability to increase the threshold of sensitivity of FA individuals from food crumbs to actual serving sizes of the allergenic food has best been achieved through OIT. There has been debate regarding the feasibility and implementation of peanut OIT in recent years; however, based on safety and efficacy data, the FDA eventually approved Palforzia, a highly characterized and standardized peanut OIT formulation that provides consistent dosing of key peanut allergens. At the current time, however, it is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Palforzia REMS because of the risk of anaphylaxis.[12]

OIT treatment has been shown to be effective in raising the threshold of reactivity to peanuts and other foods in addition to producing a measurable serum immune response to such therapy.[13–15] In the PALISADE study, patients exposed to peanut protein were able to tolerate relatively small doses of peanut protein (300 mg or roughly one peanut) on a daily basis as a maintenance dose.[16] Increasing the reactivity threshold from 100 mg or less of peanut protein to at least 300 mg reduces the reaction risk to 4 common food product categories that may contain trace levels of peanut residue by more than 95%.[17] Further increase in the threshold to 1000 mg peanut protein has additional quantitative benefit in risk reduction. A systemic review and meta-analysis by Nurmatov et al in 2017 across 31 studies showed a substantial benefit in desensitization to peanuts (RR = 0.16, 95% CI 0.10, 0.26).[18] An increasing number of clinical trials have supported the same conclusion. A randomized

Study, Year	Study Design	Adjuvant	Age	N (Active/ Control)	Daily Maintenance Dose	Allergen Withdrawal Phase	Outcomes
Hofmann et al[35] 2009	Open-label	None	Mean 4.8 years	28, 0	300 mg PP	N/A	20/28 (71.4%) completed maintenance phase
Jones et al[36] 2009	Open-label	None	Median 57.5 months	39, 0	300 mg PP for 12 months and if peanut IgE remained > 2 kU/L, dose was increased to 1800 mg PP	N/A	27/39 (69.2%) passed OFC (3900 mg PP)
Blumchen et al[37] 2010	Open-label	None	Median 5.6 years	23, 0	500mg whole peanut	2 weeks	14 reached maintenance dose. Median final DBPCFC threshold values (1000 mg PP) significantly increased from baseline DBPCFC (190 mg PP) (n = 14)
Varshney et al[20] 2011	Randomized, double-blind, placebo-controlled	None	Active median 84 months, placebo median 69 months	19, 9	4000 mg PP	N/A	16/19 (84.2%) of active group passed OFC to 5000 mg PP, median cumulative dose ingested by the placebo group was 280 mg PP
Anagnostou et al[38] 2011	Open label	None	Median 11.0 years	22, 0	800 mg PP	N/A	12/22 (54.5%) passed OFC (2600 mg PP) after 6 weeks on a maintenance

(continued)

Study, Year	Study Design	Adjuvant	Age	N (Active/ Control)	Daily Maintenance Dose	Allergen Withdrawal Phase	Outcomes
							dose, 14/22 (63.6%) passed OFC (6600 mg PP) after 30 weeks on a maintenance dose.
Schneider et al[39] 2013	Open label	Omalizumab	Median 10.0 years	13, 0	4000mg peanut flour	N/A	12/13 (92.3%) passed OFC to 8000mg peanut flour
Vickery et al[40] 2014	Open label	None	1–16 years	24, 0	4000 mg PP	4 weeks	12/24 (50.0%) passed OFC (SU) to 5000 mg PP
Anagnostou et al[41] 2014	Phase 2, randomized Placebo-controlled cross-over trial	None	Median 12·4 years	49, 50	800 mg PP	N/A	24/39 (61.5%) phase 1 and 24/45 (54%) cross over phase 2 passed OFC to 1400 mg PP; 0/50 (0%) passed OFC (phase I)
Tang et al[42] 2015	Randomized, double-blind, placebo-controlled	Lactobacillus rhamnosus	Active: Mean 6.1 years Placebo: Mean 5.8 years	31, 31	2000 mg PP	Median 2.3 weeks, range 2–5.3 weeks	26/31 (83.9%) passed OFC to 4000 mg PP at end of maintenance phase; 23/31 (74.2%) passed a second OFC to 4000 mg PP at end of peanut elimination diet. In the placebo group only 1 achieved SU

MacGinnitie et al[43] 2016	Randomized-placebo-controlled	omalizumab	Active: Median 10 years Placebo: Median) 10 years	29, 8	2000 mg PP	N/A	22/29 (75.9%) of active and 1/8 (12.5%) of placebo passed OFC to 4000 mg PP
Vickery et al[22] 2017	Randomized, double-blind, controlled	None	Median 28.5 months	37 (20 low dose, 17 high dose), 154	300 (low dose) or 3000 mg PP (high dose)	4 weeks	17/20 (85%)low dose and 12/17 (70.6%) high dose passed OFC to 5000 mg PP and achieved SU
Kukkonen et al[44] 2017	Controlled	None	Active: Median 8.3 years Placebo: Median 8.6 years	39, 21	800 mg PP	4 weeks	26/39 (66.7%) active and 0 placebo (0%) passed OFC to 1225 mg PP
Hsiao et al[45] 2017	Randomized, double-blind, placebo-controlled	Lactobacillus rhamnosus	Active: Mean 12.1 years Placebo: Mean 11.7 years	24, 24	N/A	8 weeks	16/24 (66.7%) of active and 1/24 of placebo (4.2%) continued eating peanut (4 year follow-up); 7/12 (58.3%) of active and 1/15 (6.7%) of placebo passed OFC to 4000 mg PP and attained SU.
Bird et al[46] 2018	Randomized, double-blind, placebo-controlled (phase 2)	None	Active: Median 7 years Placebo: Median 8 years	29, 26	300mg characterized PP (AR101)	N/A	23/29 (79.3%) and 18/29 (62.1%) of active group passed OFC (443 and 1043 mg respectively); 5/26 (19.2) and 0/26 (0%) of placebo group passed OFC (443 and

(continued)

Study, Year	Study Design	Adjuvant	Age	N (Active/ Control)	Daily Maintenance Dose	Allergen Withdrawal Phase	Outcomes
							1043 mg respectively)
Nagakura et al[47] 2018	Open label, control group (historical)	None	Active: Median 8.5 years Placebo: Median 7.9 years	22, 11	795 mg PP	2 weeks	15/22 (68.2%) active and 2/11 (18.2%) controls passed OFC to 795 mg PP
Blumchen et al[19] 2019	Randomized, placebo-controlled	None	Active: Median 6.6 years Placebo: Median 7.9 y	31, 31	Median 125 mg PP, range 50–250 mg PP	N/A	23/31 (74.2%) and 13/31 (41.9%) of the active group passed OFC (300 and 4500 PP, respectively); 5/31 (16.1%) and 1/31 (3.2%) of the placebo group passed OFC (300 and 4500 PP, respectively).
Vickery et al[16] 2018	Phase 3, Randomized, double-blind, placebo-controlled	None	4–55 years	416, 139 (372, 124 were 4–17 years of age)	300 mg characterized PP (AR101)	N/A	250/372 (67.2%) active group and 5/124 (4.0%) placebo group passed OFC to 600 mg PP
Chinthrajah[21] 2019	Phase 2, randomized, double-blind, placebo-controlled study	None	Active -peanut-0 group: Median 10 years Active panut-300 group: Median 11 years Placebo: Median 11 years	60 (peanut −0 group), 35 (peanut-300 group), 25 (placebo)	4000 mg PP for 104 weeks followed by either a lower dose of 300 mg PP.	52 weeks for peanut-0 group	51/60 (85%, peanut-0), 29/35 (83%, peanut-300), and 1/25 (4%, placebo) passed OFC to 4000 mg PP at week 104 (desensitization). 8/60 (13.3%, peanut-0), 13/35 (37.1%, peanut-

300), 1/25 (4%, placebo) passed OFC to 4000 mg PP at end of study (week 156; 52 week SU)							

Table 1. Select clinical trials of oral immunotherapy for peanut allergy. *PP = peanut protein*

trial by Blumchen et al in 2019 showed that 74.2% of patients in the active OIT group tolerated at least 300 mg peanut protein (the equivalent of about one peanut), compared to only 16.1% of patients who were receiving placebo ($p < 0.001$).[19] The PALISADE phase 3 study showed that 76.6% of patients in the active treatment group tolerated 300mg or more of Palforzia compared to only 8.1% of patients in the placebo group.[16] Many other randomized controlled trials have shown similar efficacy results (Table 1).

Not only are patients able to tolerate maintenance doses of 300 mg to 4000 mg of peanut protein, but they also have been shown to tolerate doses higher than the maintenance dose, as high as 5000 mg,[20] equivalent to about 16–20 peanuts, or over a tablespoon of peanut butter, after undergoing up-dosing phases of peanut OIT. This has been evidenced by the success rates of patients in what is often the final phase of clinical trials, a double-blind, placebo-controlled, food challenge. In the Blumchen et al study, after maintaining peanut OIT with 125 mg of peanut protein, they found that 41.9% of patients tolerated the highest dose of peanut protein offered (4500 mg) compared to only 3.2% in the placebo group.[19] This ability to tolerate such high doses is particularly noteworthy given that some patients might desire to consume peanut products in larger quantities, particularly if they have not developed the fear associated with food allergies (ie, toddlers who have undergone desensitization), while others may just wish for protection from accidental ingestion. The PALISADE phase 3 study showed that 67.2% of patients in the active treatment group tolerated 600 mg or more of Palforzia compared to only 4% of patients in the placebo group, following maintenance of 300 mg for 6 months; and 50% tolerated 1000 mg of peanut after only 1 year of therapy.[16] The PALISADE group also concluded that patients given Palforzia over a period of time resulted in higher doses of peanut protein that could be consumed with less severe symptoms during peanut exposure at the exit food challenge compared to patients given placebo.

The POISED study also produced evidence of the responsiveness of OIT and addressed questions of durability of treatment effects and

appropriate maintenance doses.[21] For the first time, randomized maintenance doses were investigated and long-term data following OIT were highlighted. Patients who underwent peanut OIT for 2 years were 120.8 times more likely to pass a peanut challenge to 4000 mg protein at 2 years. Optimal dosing regimens for individuals still need to be identified. Blumchen et al[19] used a slower, longer-term updosing period of 13 months with a lower maintenance dose of only 125 mg peanut protein and still produced similar efficacy rates as other studies with shorter updosing periods and higher maintenance doses. Vickery et al[22] showed no differences in efficacy between a high and a low maintenance dose (3000 mg vs 300 mg peanut protein) in toddlers. The POISED study randomized patients to low dose maintenance of 300 mg daily vs avoidance in the third year, after tolerating 4000 mg peanut protein daily for 2 years. However, both a reduction to 300 mg daily and discontinuation of peanut completely increased the likelihood of a patient becoming clinically reactive to peanuts to the 4000 mg protein level over the course of the year. Ultimately, very few people (13% in the avoidance, and 37% in the 300 mg group) were able to retain no clinical reactivity, which they had achieved during the desensitization period, to 4000 mg peanut protein. However, despite failing the 4000 mg peanut protein threshold specified by the study, many were able to tolerate higher thresholds compared to prior to initiation of OIT. The optimal maintenance dose will likely be determined in concert with patient goals: Does the patient want protection against accidental ingestion or do they want to eat ad lib? This, in turn, needs to be balanced with the risks of daily OIT dosing.

Safety

Risks associated with OIT include allergic reactions to the daily dose, which can be mild or, in rare cases, lead to life-threatening anaphylaxis. These risks should be discussed with patients and trial participants and should be emphasized in consent forms for research protocols for OIT. Missed doses should be discouraged and cautionary advice surrounding OIT dosing should be provided to improve safety.

Educating patients that symptoms are expected during the treatment phase and that they can signal desensitization can improve OIT experience and outcomes.[23] A study by Arasi et al found that detailed information including a written plan significantly reduces the risk of adverse reactions during the maintenance phase of OIT while still providing beneficial effects.[24] Adverse events (AEs) during OIT that are related to dosing are common. In the largest pooled safety analysis of 1001 participants who participated in ARC003[16] and ARC007 studies, AEs were found to affect up to 98.9% of participants receiving peanut therapy vs 94.9% in placebo.[25] The pooled dataset from these 2 studies (ARC003 and ARC007) and their follow-up studies (ARC004 and ARC011) showed that the incidence of allergic reactions decreased with longer duration on peanut among Palforzia (AR101) recipients, from 46.7% at 0–13 weeks to 21.9% after 52 weeks.[25] Discontinuation in the pooled dataset due to adverse effects included 1.8% in the Palforzia group versus 1.0% in the placebo group during initial dosing, 9.7%, in the Palforzia group versus 1.3% in the placebo group during up-dosing, and 1.0% in the Palforzia group versus 0% in the placebo group. In the phase 3 AR003 PALISADE study, 83.3% of the active group and 95.2% of the placebo group reached maintenance dose; 11.6% in the active drug group and 2.4% in the placebo group withdrew from the trial because of AEs during the intervention period.[16]

In the POISED study, 14.7% of the active group and 8% in the placebo group withdrew before reaching the maintenance dose. Ninety-four percent in the active peanut vs 64% in placebo group experienced at least 1 dose related reaction in the first year, with a decrease in allergic reactions for those in the peanut arms to 70% in the second year, and 20% in those who maintained 300 mg peanut daily in the third year vs 0% in those who went on to avoidance in the third year. The majority of reactions were mild, predictable in that they occurred within 30 min to 2 h of dosing, and resolved without sequelae.[21]

Clinical studies also report the incidence of anaphylaxis and this is challenging because of the numerous different definitions of anaphylaxis.[26,27] Anaphylaxis is often defined as allergic reactions occurring in 2 different organ systems, and in the

Study design	Study design	Participants (active group)	Food	Intervention	QoL form	Endpoints	Placebo arm	Conclusion
Anagnostou, 2014[41]	Randomized controlled trial (UK)	39 children 7–16 years old	Peanut	OIT	FAQLQ-PF	FAQLQ-PF scores pre- and post-OIT	Yes	Both active and controls groups showed clinical meaningful improvement in FAQLQ-PF overall scores post treatment.
Blumchen, 2019[19]	Randomized controlled trial (Germany)	20 children 3–17 years old	Peanut	OIT	FAQLQ-PF FAQLQ-CF	HRQL scores pre- and post-OIT	Yes	Significant improvement on both FAQLQ-PF and FAQLQ-CF in the active OIT group 10 weeks after final OFC, not in the placebo group.
Dunn Galvin, 2018[31]	Randomized controlled trial (Ireland)	20 children 2–11 years old	Peanut	OIT	FAQLQ-PF FAIM	FAQLQ-PF and FAIM scores pre- and post-OIT	Yes	Significant improvement on FAQLQ-PF and FAIM scores 3 and 12 months after OIT. No change for FAQLQ-PF in the placebo group. Furthermore, significant improvement was reported from 3-month to 12-month post OIT.
Epstein-Rigbi, 2019[33]	Prospective cohort study (Israel)	175 children 4–12 years old	Milk, peanut, egg, sesame, or tree nuts	OIT	FAQLQ-PF	FAQLQ-PF scores pre- and post-OIT	Yes	Significant improvement on FAQLQ-PF overall scores and each domain in the OIT group from the start to the end of treatment. No changes on QoL scores in the control group.
Otani, 2014[48]	Two phase I clinical trials (USA)	40 children 4–16 years old	Peanut, walnut, cashew, pecan, milk, egg, sesame, almond, hazelnut	OIT	FAQLQ-PB	FAQLQ-PB scores pre- and post-OIT	Yes	Significant improvement on FAQLQ-PB scores in the active OIT groups at 6-month and 18-month follow-up. Qol scores in the control group

(continued)

Study design	Study design	Participants (active group)	Food	Intervention	QoL form	Endpoints	Placebo arm	Conclusion
								significantly worsened at 6-month follow-up. No changes on QoL scores in the control group at 18-month follow-up.
Reier-Nilsen, 2019[34]	Randomized controlled trial (Norway	37 children 5–15 years old	Peanut	OIT	PedsQL 4.0 FAQLQ-PB	HRQL scores pre- and post-OIT	Yes	Significant improvement in children and parents after up-dosing and maintenance phases in both OIT and control groups. The change in QoL was significantly different from the controls for the parental proxy-reports only

Table 2. Studies on quality of life.

case of food allergic individuals, often occurring following an ingestion of the culprit food. However, most would agree that the combination of a few hives and abdominal pain is very different from a few hives and hypotension. The Immune studies attempted to distinguish this in the Allergenic Products Advisory Committee (APAC) FDA briefing document by accounting for severity with the definition of anaphylaxis as severe systemic allergic reactions. An additional safety report for clinical studies accounts for serious adverse events (SAE), defined as death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life function, or an important medical event. The category of important medical event is where the FDA and sponsor of the study have more leeway to include relevant concerning events, and where the meta-analysis by Chu et al describe anaphylaxis as an SAE but we would like to point out that all anaphylaxis does not meet the definition of an SAE.[28]

In weighing these risks of OIT related to dosing, one must consider the risk of avoidance and inadvertent exposure. Accidental exposure occurs quite often despite peanut avoidance. The study by Cherkaoui et al 2015[29] reported an annual accidental exposure rate of 12.4% among 2759 patients (567 incidences occurred in 429 children over 4589 patient-years). Only 37% percent of accidental exposures occurred at home. In the studies ARC003 and ARC007, 19–20% reported reactions to accidental exposures in the placebo group over the first year, higher than reported by Cherkaoui et al In those who received peanut, reactions related to accidental exposures decreased with time on therapy (11.5% in first 6 months to 9% in second 6 months). In the POISED study, reactions to accidental exposure within the placebo group ranged from 12 to 16%, and reactions to unintentional exposure within the peanut group decreased with longer duration

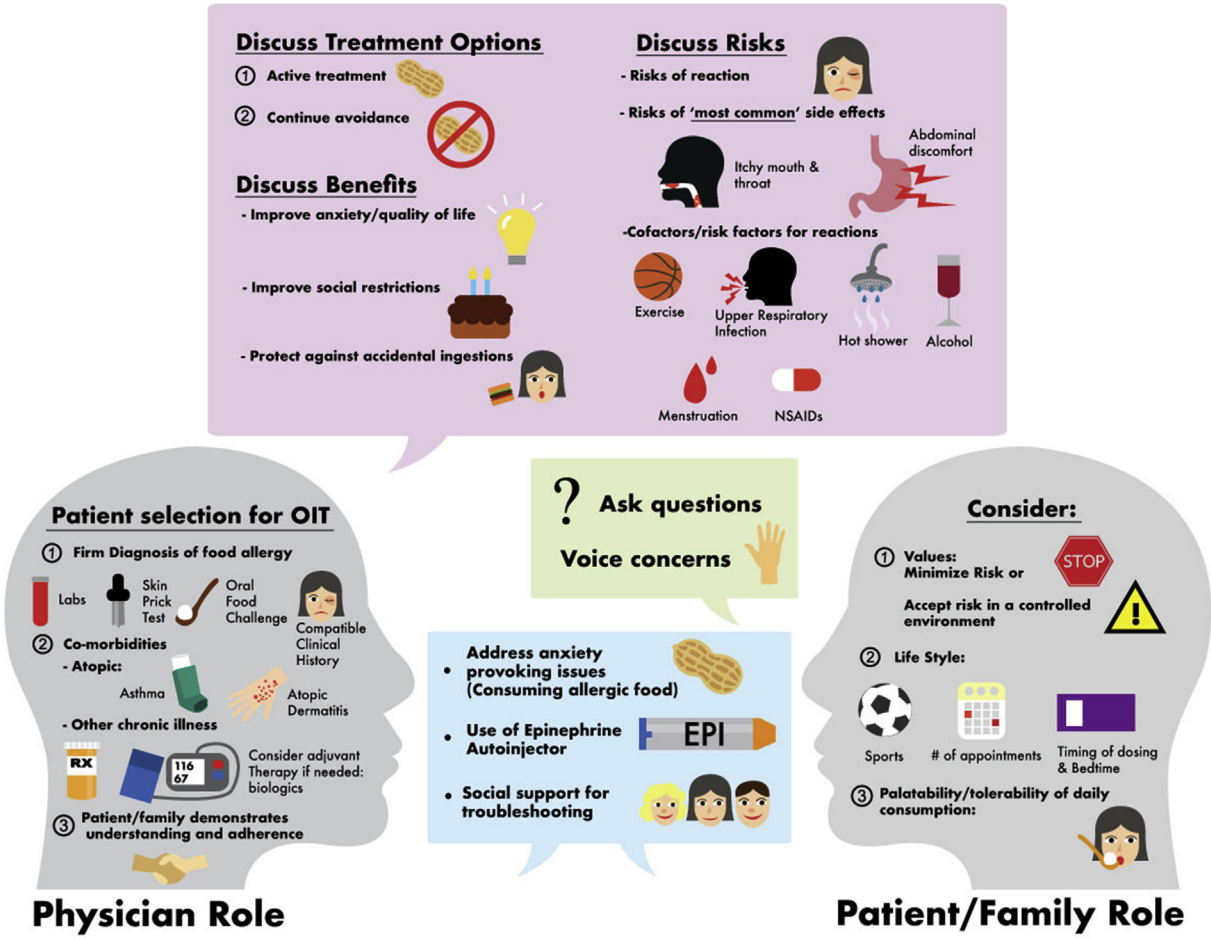

Fig. 1 Legend: Key components of shared-decision making to empower patients and their families to make an informed choice regarding OIT.

of therapy over 3 years (9% in first year, 2% in second year, and 3% in third year).

Recently the early intervention of OIT in preschool children has raised attention. In a clinical trial by Vickery et al[22] peanut OIT was administered to 37 peanut-allergic children aged 9–36 months. Ninety-seven percent reached maintenance dose, and 86.5% completed the study. The safety results showed that early OIT was overall safe and well tolerated with predominantly mild symptoms, only one at-home reaction requiring epinephrine, and only 2 withdrawals due to persistent gastrointestinal tract–predominant AEs. Another study among 270 preschool children conducted by Soller et al[30] reported that 90% of children reached the maintenance dose and that peanut OIT was safe with 36.3% patients reporting grade I (mild) symptoms, and 31.1% patients reporting grade II (moderate) symptoms. AEs requiring administration of epinephrine were only found in 4.10% (11 patients): 6 given in the clinic, 6 given at home, and no accidental exposures. These findings make evident the favorable safety of OIT and high completion rate among preschool-aged children.

In FA OIT intervention studies, patient selection, education, and preparedness are key in controlling the incidence rate of AEs. Patients should be informed about the efficacy and common side effects of OIT treatment, and these conversations should be fully transparent. During the study phases, the OIT-related AEs can be predictable, enabling the patients who undergo the OIT treatment to be more vigilant. However, unpredictable

reactions are present in the "real world", occurring from minimal accidental exposure. For these reasons, higher levels of anxiety and stress are often found in FA patients and their families.

Quality of life

Peanut allergy is usually lifelong and known to affect QoL. A recent study conducted by Dunn-Galvin et al[31] who investigated the psycho-social burden of peanut allergy on individuals' lives and families reported that nearly 40% of participants experience a high level of frustration, stress, and uncertainty in everyday life when managing their peanut allergy by using avoidance. An increasing number of studies have investigated the effects of OIT on QoL of peanut allergy-patients and found substantial improvement of participants' QoL after the treatment. However, the QoL measurements instruments vary widely among studies. In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) provided guidelines regarding the correct questionnaire to assess patient or caregiver QoL based on patient age.[32] They assessed 3 general domains, including general emotional impact, food anxiety, and social and dietary limitations. The most commonly used QoL questionnaires are food allergy quality of life (FAQOL) questionnaires, including parental burden form (PB), parental form (PF), child form (CF), teenage form (TF), and adult form (AF). Other questionnaires include food allergy independent measure (FAIM), pediatric quality of life inventory (PedsQL), QoL by Avery, and burden of treatment (BOT).

Epstein-Rigbi et al[33] reported a significant improvement of FAQLQ-PF scores in "social and dietary limitation," "food anxiety," and total score from study initiation to maintenance phase for children aged 4–12 years old undergoing OIT. Furthermore, the scores had a greater improvement between maintenance phase and 6-month follow-up in all categories.

Similar improvements in QoL were found in the randomized placebo-controlled trial conducted by Blumchen et al[19] in which children in the peanut-OIT group demonstrated a significant improvement in health-related QoL for "risk of accidental exposure" and "emotional impact" compared to the placebo group. Additionally, 22 out of 27 (87%) mothers and 9 out of 11 (82%) children in the peanut OIT group reported low BOT scores between 1 and 3. These results suggest that the majority of mothers and children were positive about undergoing OIT.

In a randomized controlled study performed by Reier-Nilsen et al[34] children and parents were administered the PedsQL 4.0 and FAQL-PB at enrollment, end of up-dosing, and after 2 years. This study reported a significant improvement of the PedsQL scores among children in the OIT group but not in the control group. Parents of children in the OIT group also reported significantly higher parental-proxy PedsQL 4.0 scores than those in the control group. Additionally, results from the FAQL-PB indicated that parental QoL improved significantly for both the OIT and control groups across the two-year timeframe. More studies on FA patients' QoL are summarized in Table 2.

Although many studies have shown the benefit of OIT to improve patients' QoL, the current instruments vary among studies depending on participants' age groups. The number of questions and the scales also vary among instruments. For example, the higher scores indicate the poorer QoL and higher burden in the FAQOL questionnaires including up to 30 items, whereas the PedsQL 4.0 questionnaire which consists of 13 items with a reverse score scale and higher scores represent a better QoL. A more standardized tool to fully understand the balance between the effect of OIT on patients' psychosocial and the burden of treatment is needed.

CONCLUSION

Although the incidence of OIT-related AEs during treatment are common, serious reactions are very rare. In fact, while the majority of patients experience AEs related to dosing, most continue daily dosing in hopes of achieving protection against the culprit food. Moreover, the majority of participants reported improvement of QoL after OIT and were positive about undergoing OIT. These results show patients' commitment to the therapy and their optimism regarding the benefits of treatment. Palforzia offers a first step in therapeutic OIT options to protect from unintentional ingestions for peanut-allergic patients, and

importantly, to address the many psychosocial aspects of living with a FA. Future research will focus on identifying optimal OIT regimens that maintain protection after therapy and will allow for food consumption at normal dietary levels without allergic symptoms. Education and informed, shared decision-making between patients and providers are essential in optimizing current therapy regimens (Fig. 1).

Abbreviations

AEs: adverse events; AF: Adult form; BOT: Burden of treatment; CF: Child form; FA: Food allergy; FAIM: Food allergy independent measure; FAQOL: Food allergy quality of life; OIT: Oral immunotherapy; PB: Parental burden form; PF: Parental form; PedsQL: Pediatric quality of life inventory; QoL: Quality of life; SAE: Serious adverse events; TF: Teenage form

Ethics statement

Not applicable.

Authors' contributions

RSC, Shu Cao, VS, and KN contributed to conception and design of manuscript; all authors drafted, revised, and approved the final version to be submitted.

Availability of data and materials

Not applicable.

Submission declaration

All authors have agreed to the publication of this manuscript.

Declaration of competing interest

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