Alergologia Polska – Polish Journal of Allergology 2024; 11, 2: 1–9
DOI: https://doi.org/10.5114/pja.2024.138919
Received: 19.12.2023, **accepted:** 1.03.2024, **online publication:** 17.04.2024.

Alergologia POLSKA
Polish Journal of Allergology

REVIEW PAPER

Current trends in peanut allergy immunotherapy: a review

Klementyna Łyżwa, Anna Krupa-Łaska, Joanna Zielińska, Marek Kulus, Katarzyna Grzela

Department of Paediatrics, Pneumonology and Allergology, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Peanut allergy (PA) poses significant clinical challenges due to its potentially life-threatening nature and increasing prevalence, particularly in children. Strict avoidance is difficult due to the widespread presence of peanuts in various foods, leading to high rates of accidental exposure. Traditional management includes education, avoidance, and rescue medication. Recent advances in immunotherapy offer promising avenues for the management of PA. Various methods of immunotherapy have been investigated, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Immunotherapy is associated with challenges such as adverse effects, the risk of anaphylaxis, and the long-term persistence of tolerance. Combining immunotherapy with adjuvants such as omalizumab and dupilumab or probiotics is promising, but it raises questions about sustained efficacy and patient response after treatment discontinuation. In addition, the translation of clinical trial results into real-world settings remains a critical issue, as shown by low participation rates in immunotherapy programs. Immunotherapy for peanut allergy has the potential to be a game-changer in the treatment of peanut allergies. However, it is important to note that this treatment is not without its challenges. Further research, collaboration between clinicians and researchers, and addressing patient concerns are needed to establish immunotherapy as a safe and effective treatment option for individuals with peanut allergy.

KEY WORDS

food allergy, peanut allergy, food immunotherapy, oral immunotherapy, children.

ADDRESS FOR CORRESPONDENCE

Dr. Katarzyna Grzela, Department of Paediatrics, Pneumonology and Allergology, Medical University of Warsaw, Warsaw, Poland, e-mail: katarzyna.grzela@wum.edu.pl

INTRODUCTION

Peanut allergy (PA) is a potentially life-threatening condition for which no effective treatment exists. In developed countries, its prevalence in children is estimated to be around 2% [1], and its incidence is increasing [2].

PA poses significant clinical challenges for several reasons. The main peanut allergens are storage proteins – albumin and globulins. Their high resistance to heat and digestion increases their potential to cause allergic reactions. Research has shown that the commonly used roasting process does not reduce the allergenic properties

of proteins from the 2S albumin group [3]. It may even increase the allergenic properties of these proteins [4]. In addition, strict elimination of peanuts from one's diet may be difficult given their widespread presence in various foods, contamination during the food manufacturing process, and misreading labels or ingredient information in restaurants. This results in an accidental exposure rate of about 14% annually [5]. Peanuts are also responsible for the majority of deaths associated with food-induced anaphylaxis [6]. In addition, while most children allergic to milk or eggs develop a tolerance to these allergens with age, only 15–20% of peanut-allergic patients outgrow the allergy [7].

Until recently, there were no approved curative treatments for PA. Standard procedures include education, strict avoidance of peanut proteins, and access to emergency medications such as self-injectable epinephrine.

New approaches to managing PA are being researched. Long-term treatment to induce desensitisation has become a hope for improving patients' safety and quality of life. In this review, we would like to present current options for managing PA and different approaches to food allergen immunotherapy.

FOOD ALLERGY ALLERGEN IMMUNOTHERAPY (FA-AIT)

FA-AIT consists of repeated exposure to an allergen at specific time intervals to modify the immune response and raise the threshold of reactivity to foods [8].

It has been proven that achieving an elicitation dose greater than 300 mg or 1000 mg (depending on the initial elicitation dose) of peanut protein reduces the risk of anaphylaxis due to accidental exposure to an allergen in food products and is clinically relevant for the European peanut-allergic population [9].

To assess the efficacy of FA-AIT, we must distinguish between desensitisation and sustained unresponsiveness. Desensitisation is defined as a temporary state of tolerance to a higher dose of an allergen than the initial dose, depending on the continuation of immunotherapy [10]. Sustained unresponsiveness is a permanent response to treatment characterised by food tolerance despite the discontinuation of immunotherapy. In clinical trials, it is usually assessed 2–8 weeks after the end of the maintenance of the immunotherapy phase.

Patients with IgE-mediated food allergy, for whom avoidance of the allergen is difficult to implement, ineffective, or significantly reduces their quality of life, may be eligible for FA-AIT [8]. Eligibility should be confirmed through allergen skin prick tests (SPT) and/or elevated serum-specific IgE levels. In cases of uncertainty, a food challenge should be performed before considering the therapy. It is important to note that spontaneous tolerance to the allergen may occur with age.

Food oral immunotherapy is the recommended treatment for peanut, milk, and egg allergy according to the European Academy of Allergy and Clinical Immunology (EAACI) [8].

However, due to the long-term nature of the therapeutic process and the high risk of side effects, only patients who demonstrate a strong motivation to undergo treatment and have a thorough understanding of the purpose and potential risks of the intervention should be considered.

The therapy personnel should be experienced in managing anaphylactic reactions and have access to all the necessary equipment [8]. FA-AIT is usually a prolonged therapy that requires good compliance and is associated with numerous side effects. For this reason, full cooperation is necessary, and lack thereof is one of the main criteria for exclusion from the FA-AIT qualification. It should be emphasised that the patient's parents/guardians should be trained to assist in the event of anaphylaxis.

Patients with poorly controlled asthma are at particular risk of severe, life-threatening anaphylactic reactions [11]. For this reason, severe or poorly controlled asthma is an absolute contraindication for FA-AIT. Other uncontrolled allergic diseases are relative contraindications. Food allergy may be one of the causes of eosinophilic esophagitis (EoE). Therefore, a diagnosis of EoE or other gastrointestinal diseases associated with eosinophilic mucositis is an absolute contraindication to immunotherapy.

There are no clear data on the use of FA-AIT in patients with severe chronic diseases, mastocytosis, or during β-blocker or ACE-I therapy. As they are a contraindication to specific immunotherapy, e.g. inhalation allergy, they are currently considered relative contraindications to food desensitisation [8].

ROUTES FOR IMMUNOTHERAPY

ORAL IMMUNOTHERAPY

Peanut oral immunotherapy (OIT) has been extensively studied and evaluated. This therapeutic approach involves the progressive ingestion of increasing doses of peanut protein by oral administration [7]. Peanuts can be taken in their natural form, such as peanut flour, which is often defatted to reduce its volume. Alternatively, they can be mixed with a carrier substance such as fruit mousse or yogurt.

Now, a pharmaceutical product called Palforzia contains defatted peanut powder encapsulated within capsules and sachets [12]. It has received approval from the Food and Drug Administration and the European Medicines Agency.

In principle, OIT protocols include 3 parts: an initial dose, a built-up phase, and a maintenance phase. The initial (starting) dose is the highest dose of allergen tolerated by the patient and is determined during a food challenge test. In some cases, immunotherapy begins with a phase of rapid dose escalation.

In the dose escalation stage, the patient is given daily peanut portions. Dose escalation is usually done at 2-week intervals at the provider site. After this, the food portions are served daily at home. This phase lasts several weeks to months [7, 13, 14].

During the maintenance phase, patients receive a constant dose of peanut protein. To date, the duration of this phase has been the most controversial. Currently, regimens ranging from several months to several years are used.

The advantages of OIT are its high efficacy and cost-effectiveness. The limitations are the large number of side effects, including the risk of developing EoE and the need for frequent visits to the treatment centre.

Efficiency of OIT

Research shows that oral administration of increasing doses of food induces desensitisation in most people [15]. Some of them also achieve tolerance that lasts from 2 to 12 weeks [16, 17]. The problem may be a lack of cooperation or resignation due to side effects [18]. Despite the differences in the dosing regimens, a meta-analysis of 22 clinical trials involving 982 people (children or mixed populations) showed significant efficacy in OIT patients with egg, milk, and peanut allergy [8].

In studies comparing OIT with other immunotherapy routes, OIT efficiency seems to be the most promising. In the placebo-controlled trial of SLIT versus OIT, the median change between tolerated doses at the baseline and final oral food challenge was significantly higher for OIT patients, increasing 141-fold. For SLIT patients, a median 22-fold increase was noted [19].

Considering the potential resolution of peanut allergy (PA) with age, most available studies have primarily focused on children above 4 years old. However, the IMPACT study took a different approach, including 146 children aged 12 to 48 months with PA. Allergy was confirmed during double-blind, placebo-controlled food challenges (DBPCFC), and the symptom-inducing dose was lower than 500 mg of peanut protein. These participants received either oral immunotherapy or a placebo over a 134-week period. The first primary outcome of the study evaluated the number of children who could tolerate more than 5000 mg of peanut protein after 134 weeks of OIT. The results showed that 68 out of 96 participants receiving OIT (84%) achieved this outcome, compared to only one out of 35 participants receiving the placebo. The secondary outcome of the study assessed the remission of PA after 26 weeks of immunotherapy avoidance. The remission was observed in 20 out of 96 participants receiving OIT (21%), compared to only 1 out of 50 participants receiving the placebo (2%). Younger age and lower baseline peanut-specific IgE levels were found to be predictive of remission. The study results suggest that initiating OIT at a younger age may lead to a higher degree of desensitisation and sustained tolerance rate [20].

SAFETY OF OIT

While the efficacy of OIT has been demonstrated in numerous studies, safety concerns remain. Patients receiving active treatment have a higher incidence of allergic reactions, including both localised and systemic manifestations, than those in placebo or avoidance groups [8].

The vast majority of side effects of OIT can be described as local, mild reactions. Patients' most common adverse reactions were oropharyngeal itching, perioral rash, and mild abdominal pain [8].

However, the limiting factor for the widespread use of OIT as a therapeutic method is the prevalence of serious side effects, including anaphylactic reactions. In a meta-analysis of 27 trials involving 1488 patients, the incidence of OIT-related adverse events leading to discontinuation of immunotherapy was 6.6%. The incidence of adverse events requiring treatment was estimated to be 38.3%, while the use of epinephrine was required in 7.6% of patients [21].

The PACE metanalysis of over 1000 patients in 12 randomised trials with PA showed that OIT increases the likelihood of allergic reactions compared with allergen avoidance [15]. The likelihood of anaphylaxis, use of epinephrine, and serious adverse events are more frequent in the active cohort in each phase of immunotherapy. Important cofactors that need to be considered with regard to immunotherapy side effects include infections, menstruation, exercise, hot baths, non-compliance, inadequate management of asthma or allergic rhinitis, irregular medication intake, and the administration of OIT on an empty stomach [8, 15]. Morris *et al.* published a very interesting clinical observation regarding the new potential factor affecting the safety of OIT. They observed an association between evening peanut administration and the incidence of anaphylaxis requiring epinephrine. They analysed 307 patients undergoing immunotherapy, of whom 31 (10%) required epinephrine administration. Almost half (45.8%) of the reactions requiring epinephrine occurred in the evening, leading the authors to postulate evening dosing as a novel cofactor for anaphylaxis in children undergoing oral peanut immunotherapy [22].

However, the PACE study does not directly compare adverse events between the initial phase of immunotherapy and the long-term treatment, which may affect the analysis and require further investigation.

The risk of developing EoE is also worth highlighting. This is a specific side effect of OIT triggered by allergen exposure. According to a meta-analysis by Lucendo, EoE may resolve in up to 2.7% of patients undergoing oral immunotherapy for food allergy [23]. The data were less pessimistic in another meta-analysis involving 630 patients undergoing OIT. Although gastrointestinal symptoms were common during OIT, only 3.9 % of patients discontinued OIT for this reason. Of these, 0.3% of the total 620 patients had biopsy-confirmed EoE [24]. The results of the studies suggest that although EoE is a rare complication of OIT, this diagnosis should be considered in patients with gastrointestinal symptoms.

Despite the fact that OIT is associated with a serious number of adverse reactions, low-dose peanut OIT, especially after reaching the maintenance dose, appears to protect patients from allergic reactions, including severe ones, after accidental peanut exposure compared with placebo in everyday life [25].

Careful patient assessment, SPT results, serum IgE levels, and control of concomitant atopic diseases, especially asthma and allergic rhinitis, have been described as potential ways to minimise side effects during immunotherapy [8, 26]. Potential predictors of higher numbers of adverse events are a rush phase in the immunotherapy protocol and a higher maintenance dose [21].

Long-term prospects

In the 2 meta-analyses cited above (PACE and by Grzeskowiak *et al.*), the majority of studies lasted less than one year [15, 21]. Fewer data are available on the long-term efficacy and safety of OIT. The follow-up study looked at longer-term dosing of Parforzia in patients previously allocated to the PALISADE study (where patients received 300 mg of peanut protein as a maintenance dose for 24 weeks). The results of the study showed that daily administration of peanut OIT for approximately 2 years improved safety and efficacy. Further immunomodulation was observed during the second year of treatment. Desensitisation rates were higher in the daily dosing cohort than in the active treatment arm of PALISADE. The study also evaluated dosing frequency. Daily dosing appeared to have a better safety profile and efficacy compared to a non-daily dosing regimen [27]. Another study suggests that long-term therapy (about 5 years) and increasing the maintenance dose improves treatment efficacy [17, 27].

The question of how long to continue immunotherapy to achieve persistent tolerance remains an important issue. Discontinuing peanuts or even reducing daily maintenance doses after 2 years of OIT and achieving desensitisation reduces the likelihood of tolerating the dose previously achieved [28]. Lower IgE to Ara h 1-3, peanut sIgE, or peanut IgE/IgG4 ratio, and a lower basophil activation test response to peanut have been identified as potential markers of achieving sustained unresponsiveness [28, 29].

OIT with boiled peanuts

Tao *et al.* published a study demonstrating that prolonged boiling can reduce the allergenic properties of peanut proteins. Their research showed that boiling peanuts for 12 h resulted in a 19-fold reduction in peanut allergenicity [30]. This finding was applied in an immunotherapy trial conducted by Grzeskowiak *et al*. Seventy children were enrolled in the trial. The study protocol consisted of 12 weeks of consumption of 12-hour boiled peanuts in gradually increasing doses, followed by 20 weeks of administration of 2-hour boiled peanuts in increasing doses. Finally, in the third phase of the study, the children were given roasted peanuts for a further 20 weeks. The study results were very promising, with 56 out of 70 participants (80%) successfully achieving desensitisation to 3000 mg of peanut protein. Treatment-related adverse events led to withdrawal in only 3 cases. Only 3 participants reported the need to use epinephrine. However, it is important to note that the lack of a control cohort is a limitation of this study [31].

SLIT

Peanut-SLIT uses a glycerinated peanut solution, similar to the extracts used in environmental SCIT, which is administered under the tongue. The substance must remain in the mouth for at least 2–3 min before being swallowed. Because the doses for SCIT are many times smaller than for OIT, this form of therapy has little effect on the gastrointestinal tract [19]. Similarly to OIT, SLIT consists of 3 phases: initial dose, dose escalation, and maintenance. The maintenance phase involves the daily administration of a certain amount of peanut protein. Unlike OIT, SLIT demonstrates superior safety but lower efficacy [19].

Efficiency of SLIT

In the placebo-controlled clinical trial involving 44 patients aged 12–37 years, who received peanut SLIT for 44 weeks at a dose of up to 1386 µg of peanut protein, 70% of patients in the active-treatment cohort met the criteria to

be described as responders. In the placebo group, the rate was 15%. The study identified responders as patients who successfully consumed 5 g of peanuts at the final OFC after the entire course of treatment or 10 times more peanuts than at the baseline OFC. The median successfully consumed dose for peanut SLIT subjects after 44 weeks of immunotherapy was significantly higher than at baseline, at 371 mg and 21 mg, respectively. After unblinding, peanut SLIT participants continued on the maintenance dose for an additional 24 weeks and underwent OFC. The median successfully consumed dose increased scientifically compared to the week 44 dose, amounting to 996 mg [32]. The second phase of this trial assessed the long-term effects of SLIT. After the previous 44 weeks of treatment, original placebo subjects were escalated to a higher dose of peanut protein, amounting to 3696 µg daily, and original peanut subjects continued a maintenance dose of 1386 µg. All participants were treated for 3 years. This study had a drop-out rate of over 50%, notwithstanding the low rate of adverse events. 4/47 participants (10.8%) were fully desensitised to 10 g of peanut powder, and all achieved sustained unresponsiveness [33]. Another long-term trial did not observe such a high discontinuation rate while achieving good efficacy. Better compliance may be a result of starting therapy at an earlier age as opposed to desensitisation in adolescents and adults. Discontinuation was most commonly explained by dosing symptoms, non-compliance, or difficulties in maintaining daily dosing [34]. Patients aged 1 to 11 years old underwent SLIT therapy with a maintenance dose of 2 mg of peanut protein for up to 3 to 5 years. At the final OFC, 67% of participants successfully consumed at least 750 mg of peanut protein, and 25% tolerated 5000 mg of peanut protein. This study also assessed sustained unresponsiveness after 2–4 weeks of break in immunotherapy, which was seen in 10 of 12 patients who passed a 5000 mg OFC. 77% of participants completed the study.

The clinical study published by Kim *et al.* analysed the efficacy of inducing tolerance and remission of SLIT in a group of young children (1–4 years). The DBPC study included 50 children (1 : 1, 25 active, 25 placebo). In the active group, 4 mg of maintenance dose (4443 mg of peanut protein of cumulative dose) was administered sublingually over 36 months, achieving 76% desensitisation versus 0% in the control group. Sustained tolerability (remission) was assessed 3 months after the end of treatment. None of the patients in the placebo group achieved tolerability, compared to 63% in the active group [35].

Safety of SLIT

The safety data for SLIT is promising. Data show a rate of symptomatic doses between 4.78 and 40.1%, and the majority of adverse events are mild oropharyngeal symptoms [32, 34]. In a study including 48 subjects, who received SLIT for 3 to 5 years, no epinephrine was used, and only 0.21% of symptoms required antihistamines [34]. This study also demonstrated excellent compliance, with 95.5% of doses successfully administered. Some symptoms, such as oropharyngeal itching, are most commonly reported in the early phases of immunotherapy. In another long-term study, no patients required epinephrine treatment, and 98% of doses were well tolerated [33].

SLIT also has a good safety profile compared to OIT. A randomised, placebo-controlled trial of sublingual versus oral immunotherapy showed a higher rate of adverse events, amounting to 43% for OIT and 9% for SLIT. All types of adverse events were more common for OIT patients. The use of antihistamines, epinephrine, and β2-agonists was also higher in this group [19].

EPIT

EPIT uses an allergen patch applied on undamaged skin, usually on the upper arm or interscapular space. The allergen is transported by Langerhans cells (antigen-presenting cells) to the regional lymph nodes [36].

The first application is made under medical supervision. The allergen usually remains on the skin for a few hours. Subsequent patches are applied every 24 h, extending the duration of the allergen's effect. During the maintenance phase, new patches are changed every 24 h. This phase is usually continued for more than a year [18]. EPIT is associated with a small number of side effects – irritation at the patch application site being the most common [37, 38]. It is more effective in younger age groups (< 12 years) [39].

It is less effective than OIT and SLIT. Another disadvantage is also the very long duration of this type of therapy. Advantages include less frequent visits to the medical centre, providing therapy, and ease of use. This results in excellent compliance and a low drop-out rate [40–42].

Efficiency of EPIT

EPIT in PA causes clinical desensitisation, but the assessed immune changes are small. This method is still the subject of many ongoing studies. It shows some efficacy of desensitisation, although less than that of OIT and SLIT [37].

In a placebo-controlled clinical trial involving 238 children in the active cohort who received a 250-µg peanut protein patch applied daily for 12 months, there was a statistically significant difference in the proportion of responders in the peanut protein cohort compared with placebo, as demonstrated by an increase in

the eliciting dose on OFC. Good compliance was also noted. However, the study did not meet the prespecified lower bound of the confidence interval criterion for a positive study outcome [43]. The follow-up study, which extended EPIT to 36 months, showed a further increase in the number of responders to 40.4% (57 of 141) at month 12 and 51.8% at month 36. The median cumulative response dose increased from 144 to 944 mg [44]. The VITESSE study currently evaluates the efficacy and safety of a 250-µg patch in children aged 4–7 years. According to the drugmaker, the results of this trial will be crucial in the process of registering the therapy with the FDA.

Safety of EPIT

The majority of reactions during EPIT can be classified as mild and are usually confined to the patch site [40]. They include erythema, pruritus, and local oedema. Most local adverse events occur in the first month of therapy [43, 44].

Non-patch site reactions are rare, reported in 0.1–0.2% of doses in the active-treatment group. The use of epinephrine has been reported occasionally, and topical corticosteroids and antihistamines are, in most cases, sufficient to treat EPIT side effects [40].

The advantages and disadvantages of the described immunotherapies are shown in Table 1.

IMMUNOTHERAPY WITH ADJUVANTS

As mentioned above, immunotherapy is often associated with a significant number of side effects. Efforts have been made to limit these side effects. One approach that has been explored is the addition of antihistamines to OIT. Chu *et al.* conducted a study to assess the effect of pretreatment with H1 and H2 antihistamines compared to OIT with a placebo. Although a difference in the incidence of moderate to severe adverse effects was observed, the use of antihistamines as adjuvants did not lead to improvement in the patient's quality of life or in post-treatment eliciting doses [45].

The combination of FA-AIT with biological treatment has the potential to increase the efficacy and safety of the therapy. The IgE-binding monoclonal antibody omalizumab has been used in combination with FA-AIT in peanut allergy, demonstrating the efficacy of this therapy [46]. The drug is used before desensitisation and then continued with FA-AIT. Several-food immunotherapy in combination with omalizumab treatment is also being investigated. The results of the second phase of the clinical trials are promising and show that FA-AIT in combination with omalizumab is more effective than placebo [47]. However, a patient's response to immunotherapy after stopping omalizumab can be problematic [46].

Another biological agent, dupilumab – an interleukin-4 receptor antagonist – is also under investigation

TABLE 1. Summary of the advantages and disadvantages of particular types of immunotherapy

Immunotherapy method	Advantages	Disadvantages
OIT	• High efficacy: OIT has shown high efficacy in inducing desensitisation and even tolerance in many patients, particularly children • Cost-effectiveness compared to other immunotherapy methods	• Adverse effects: OIT is associated with a significant number of adverse effects, including local reactions like oropharyngeal itching and systemic reactions like anaphylaxis • Need for frequent visits: Patients undergoing OIT require frequent visits to treatment centres for dose adjustments and monitoring • Risk of EoE triggered by allergen exposure during OIT
SLIT	• Superior safety profile: SLIT demonstrates superior safety compared to OIT, with fewer systemic adverse events • Good compliance: SLIT is associated with good compliance due to its ease of administration and minimal side effects	• Lower efficacy: SLIT shows lower efficacy compared to OIT, with a lower rate of desensitisation and tolerance induction • Longer duration: SLIT may require a longer duration of treatment to achieve desired outcomes compared to OIT
EPIT	• Ease of use: EPIT involves the application of allergen patches on the skin, which is easy and convenient for patients • Good compliance: EPIT has excellent compliance rates due to its simplicity • Low rate of adverse effects	• Lower efficacy: EPIT is less effective than OIT and SLIT in inducing desensitisation and tolerance • Long duration: EPIT may require a longer duration of therapy to achieve desired outcomes • Skin irritation: EPIT may cause skin irritation at the application site as a common adverse effect

in FA-AIT. A trial of OIT with Palforzia and dupilumab versus OIT with placebo is underway to assess whether dupilumab added to OIT improves desensitisation at the end of a 40-week immunotherapy course (clinical trial number NCT03682770).

Another study will evaluate OIT for multiple food allergies in combination with biologic treatments, specifically omalizumab, dupilumab, or a combination of both drugs. In this study, identified by its clinical trial registration number NCT03679676, OIT will be administered for 2 or 3 different foods, with peanut allergy being one of the target allergens under investigation.

Another anti-IgE monoclonal antibody currently in clinical trials for peanut allergy is ligelizumab (clinical trial registration numbers: NCT04984876, NCT05678959).

Another approach is to combine FA-AIT with probiotics. An Australian study evaluated the effectiveness of FA-AIT combined with a probiotic containing *Lactobacillus rhamnosus* CGMCC 1.3724. The efficacy of this therapy was demonstrated, as well as promising data on sustained tolerance. Peanut protein tolerance, assessed 2–5 weeks after the end of immunotherapy, was achieved by 82% of patients in the active group and 1 (3.6%) patient in the placebo group [48]. However, the second phase of the study showed that both OIT and OIT with probiotics were effective in inducing sustained unresponsiveness, with no significant differences resulting from the addition of probiotics to the therapy. Probiotics may help reduce side effects, especially in younger age groups [49].

COST-EFFECTIVENESS

The cost-effectiveness of OIT and EPIT was assessed in a cohort of children aged 4–17 years. The analysis shows that both therapies can be cost-effective in certain circumstances. In addition, a separate calculation focused on OIT in preschool children demonstrated the cost-effectiveness of this approach within the healthcare systems of the United States and Canada [50, 51].

CONCERNS AND FUTURE PROSPECTIVE

According to FA-AIT, there are some doubts that need to be answered if immunotherapy is to become the standard of care. Significant differences in published studies regarding dosage, duration, population, and products used do not make standardising the FA-AIT approach easier.

The second major problem is determining how long after desensitisation there is persistent tolerance. This is currently a major challenge for researchers.

Equally important is the assessment of how to translate the results of clinical trials into real-life experience. An observational study conducted by Patrawala *et al.* found that of 237 individuals with peanut allergy who were offered OIT, only 9.3% chose to participate in immunotherapy with the drug Palforzia. Most people continued to follow their standard avoidance routines. Concerns about potential adverse effects and the level of commitment required for the therapy were cited as the main factors influencing their decision [52].

Further research is needed to identify other possible risk factors for poorer prognosis in FA-AIT to ensure the best possible balance of benefits, risks, and potential to improve patients' quality of life with PA. In the coming years, we can expect further intensive development of clinical trials in this area.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Savage J, Johns CB. Food allergy: epidemiology and natural history. Immunol Allergy Clin N Am 2015; 35: 45-59.
2. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol 2018; 141: 41-58.
3. Vissers YM, Blanc F, Skov PS, et al. Effect of heating and glycation on the allergenicity of 2S albumins (Ara h 2/6) from peanut. PLoS One 2011; 6: e23998.
4. Maleki SJ, Viquez O, Jacks T, et al. The major peanut allergen, Ara h 2, functions as a trypsin inhibitor, and roasting enhances this function. J Allergy Clin Immunol 2003; 112: 190-5.
5. Yu JW, Kagan R, Verreault N, et al. Accidental ingestions in children with peanut allergy. J Allergy Clin Immunol 2006; 118: 466-72.
6. Bock SA, Muñoz-Furlong A, Sampson H. A. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001; 107: 191-3.
7. Wood RA. Oral Immunotherapy for Food Allergy. J Investig Allergol Clin Immunol 2017; 27: 151-9.
8. Pajno GB, Fernandez-Rivas M, Arasi S, et al.; EAACI Allergen Immunotherapy Guidelines Group. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy 2018; 73: 799-815.
9. Remington BC, Krone T, Koppelman SJ. Quantitative risk reduction through peanut immunotherapy: Safety benefits of an increased threshold in Europe. Pediatr Allergy Immunol 2018; 29: 762-72.
10. Nowak-Wegrzyn A, Sato S, Fiocchi A, et al. Oral and sublingual immunotherapy for food allergy. Curr Opin Allergy Clin Immunol 2019; 19: 606-13.
11. Burbank AJ, Burks W. Food specific oral immunotherapy: a potential treatment for food allergy. Exp Rev Gastroenterol Hepatol 2015; 9: 1147-59.
12. https://www.ema.europa.eu/en/documents/overview/palforzia-epar-medicine-overview_en.pdf
13. Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract 2019; 7: 479-91.

14. PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, et al. AR101 Oral immunotherapy for peanut allergy. N Engl J Med 2018; 379: 1991-2001.
15. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet 2019; 393: 2222-32.
16. Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014; 133: 468-75.
17. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol 2014; 133: 500-10.
18. Feuille E, Nowak-Wegrzyn A. Allergen-specific immunotherapies for food allergy. Allergy Asthma Immunol Res 2018; 10: 189-206.
19. Narisety SD, Keet CA. Sublingual vs oral immunotherapy for food allergy: identifying the right approach. Drugs 2012; 72: 1977-89.
20. Jones SM, Kim EH, Nadeau KC, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet 2022; 399: 359-71.
21. Grzeskowiak LE, Tao B, Knight E, et al. Adverse events associated with peanut oral immunotherapy in children – a systematic review and meta-analysis. Sci Rep 2020; 10: 659.
22. Morris E, Protudjer JLP, Jeimy S, et al. Evening ingestion as a potential reaction cofactor during peanut oral immunotherapy in children. J Allergy and clinical immunology. In Practice 2023; 11: 1964-6.
23. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014; 113: 624-9.
24. Jin H, Trogen B, Nowak-Wegrzyn A. Eosinophilic esophagitis as a complication of food oral immunotherapy. Curr Opin Allergy Clin Immunol 2020; 20: 616-23.
25. Trendelenburg V, Blumchen K, Bellach J, et al. Peanut oral immunotherapy protects patients from accidental allergic reactions to peanut. J Allergy Clin Immunol Pract 2020; 8: 2437-41.e3.
26. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol 2017; 139: 882-8.
27. Vickery BP, Vereda A, Nilsson C, et al. Continuous and daily oral immunotherapy for peanut allergy: results from a 2-year open-label follow-on study. J Allergy Clin Immunol Pract 2021; 9: 1879-89.
28. Chinthrajah RS, Purington N, Andorf S, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2019; 394: 1437-49.
29. Patil SU, Steinbrecher J, Calatroni A, et al. Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. J Allergy Clin Immunol 2019; 144: 1310-9.e4.
30. Tao B, Bernardo K, Eldi P, et al. Extended boiling of peanut progressively reduces IgE allergenicity while retaining T cell reactivity. Clin Exp Allergy 2016; 46: 1004-14.
31. Grzeskowiak LE, Tao B, Aliakbari K, et al. Oral immunotherapy using boiled peanuts for treating peanut allergy: an open-label, single-arm trial. Clin Exp Allergy 2023; 53: 327-36.
32. Fleischer DM, Burks AW, Vickery BP, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013; 131: 119-27.e277
33. Burks AW, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 2015; 135: 1240-8.e83.
34. Kim EH, Yang L, Ye P, et al. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2019; 144: 1320-6.e1.
35. Kim EH, Bird JA, Keet CA, et al. Desensitization and remission after peanut sublingual immunotherapy in 1- to 4-year-old peanut-allergic children: a randomized, placebo-controlled trial. J Allergy Clin Immunol 2023; 153: 173-81.
36. Bird JA, Sánchez-Borges M, Ansotegui IJ. Skin as an immune organ and clinical applications of skin-based immunotherapy. World Allergy Organ J 2018; 11: 38.
37. Burks AW, Sampson HA, Plaut M, Treatment for food allergy. J Allergy Clin Immunol 2018; 141: 1-9.
38. Sampson HA, Shreffler WG, Yang WH. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA 2017; 318: 1798-809.
39. Xiong L, Lin J, Luo Y, et al. The efficacy and safety of epicutaneous immunotherapy for allergic diseases: a systematic review and meta-analysis. Int Arch Allergy Immunol 2020; 181: 170-82.
40. Jones SM, Sicherer SH, Burks AW, et al. Consortium of Food Allergy Research Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017; 139: 1242-52.
41. Waldron J, Kim EH. Sublingual and patch immunotherapy for food allergy. Immunol Allergy Clin N Am 2020; 40: 135-48.
42. Wang J, Sampson HA. Safety and efficacy of epicutaneous immunotherapy for food allergy. Pediatr Allergy Immunol 2018; 29: 341-9.
43. Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. JAMA 2019; 321: 946-55.
44. Fleischer DM, Shreffler WG, Campbell DE, et al. Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results. J Allergy Clin Immunol 2020; 146: 863-74.
45. Chu DK, Freitag T, Marrin A, et al. Peanut oral immunotherapy with or without H1 and h2 antihistamine premedication for peanut allergy (PISCES): a placebo-controlled randomized clinical trial. J Allergy Clin Immunol Pract 2022; 10: 2386-94.
46. Brandström J, Vetander M, Sundqvist AC, et al. Individually dosed omalizumab facilitates peanut oral immunotherapy in peanut allergic adolescents. Clin Exp Allergy 2019; 49: 1328-41.
47. Andorf S, Purington N, Kumar D, et al. A phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued vs discontinued dosing in multifood allergic individuals. EClinicalMedicine 2019; 7: 27-38.
48. Tang ML, Ponsonby AL, Orsini F, et al, Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 2015; 135: 737-44.e8.
49. Loke P, Orsini F, Lozinsky AC, et al. Probiotic peanut oral immunotherapy versus oral immuno-therapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, random-ised, phase 2b trial. Lancet Child Adolescent Health 2022; 6: 171-84.

50. Shaker M, Chan ES, Protudjer JLP, et al. The cost-effectiveness of preschool peanut oral immunotherapy in the real-world setting. J Allergy Clin Immunol Practice 2021; 9: 2876-84.
51. Shaker M, Greenhawt M. Estimation of health and economic benefits of commercial peanut immunotherapy products: a cost-effectiveness analysis. JAMA Network Open 2019; 2: e193242.
52. Patrawala S, Ramsey A, Capucilli P, et al. Real-world adoption of FDA-approved peanut oral immunotherapy with palforzia. J Allergy Clin Immunol Pract 2022; 10: 1120-2.e1.