Review paper

Oral immunotherapy in children for the most common food allergy

Doustna immunoterapia u dzieci w najczęstszych alergiach pokarmowych

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Medical Studies/Studia Medyczne 2022; 38 (3): 210–220
DOI: https://doi.org/10.5114/ms.2022.119920

Key words: immunotherapy, allergy, desensitization.

Słowa kluczowe: immunoterapia, alergia, odczulanie.

Abstract

Nowadays, the incidence of food allergies is increasing. While strict allergen avoidance remains the most important therapeutic approach, oral immunotherapy is increasingly being used to desensitize and induce tolerance in children. Oral immunotherapy is a possible treatment for food allergies, which includes the administration of gradually increasing doses of the allergen. While most children can be desensitized, or even gain sustained unresponsiveness, oral immunotherapy involves a high risk of side effects or allergic responses with a need to use epinephrine, and the long-term effectiveness is unknown. In this paper, we summarize recent clinical trials in which oral immunotherapy has been used to treat common food allergies: to cow's milk, peanuts, and chicken eggs.

Streszczenie

Częstość występowania alergii pokarmowych wzrasta w dzisiejszych czasach. Wydaje się, że jedyną aktualnie możliwością terapeutyczną dla pacjentów jest ścisłe unikanie alergenów. Immunoterapia doustna zaczyna być coraz częściej stosowana do odczulania i tworzenia tolerancji u dzieci. Immunoterapia doustna to leczenie alergii pokarmowych, które obejmuje podawanie stopniowo rosnących dawek alergenu. Gdy większość dzieci udaje się odczulić, a nawet można uzyskać u nich trwałą tolerancję na alergen, terapia ta wiąże się z wysokim ryzykiem wystąpienia działań niepożądanych oraz reakcji alergicznych, z koniecznością zastosowania adrenaliny, a długoterminowa skuteczność jest nieznana. W artykule podsumowano ostatnie badania kliniczne, w których zastosowano immunoterapię doustną w leczeniu powszechnych alergii pokarmowych – na białka mleka krowiego, orzeszków ziemnych i jaja kurzego.

Introduction

These days, especially in developed countries, the frequency of food allergies (FA) appears to be increasing. Evaluating its prevalence is elusive because many factors influence the appraisal including age, ethnicity, dietary exposures, and methodology used by each author. Based on multitudinous studies, the prevalence estimates range from 1–2% to 10% [1]. According to EAACI, allergic hypersensitivity to food occurs in 0.1–6.0% of European citizens [2].

The main risk factors for developing the disease are a family history of atopy, male sex, a history of eczema, Asian and Afro-American ethnicity, obesity, low consumption of essential fatty acids and antioxidants, increased use of proton pump inhibitors, early or late broadening of the infant diet, and vitamin D insufficiency. The last factor needs further exploration [3]. There are also environmental factors associated with a lower risk of the disease like having siblings and pets in the house and increased diversity of food in infancy. The most common food allergens are peanuts, cow's milk, shellfish, tree nuts, chicken's eggs, finfish, strawberries, and wheat [4].

Recent research, recommendations, and resources give insight into enhancing the safety and well-being of patients and their families, and current care depends mainly on avoidance and emergency preparedness. Rather than rigorous abstinence, incorporating heat-denatured versions of milk and egg into the diets of children who tolerate these items indicates a fun-

damental shift in treatment strategy [1]. While rigorous allergen avoidance remains the most important therapeutic approach, oral immunotherapy (OIT) is increasingly being used to desensitize and induce tolerance. Allergen-specific immunotherapy (AIT) can have 3 main outcomes: desensitization, sustained unresponsiveness (SU), and failure. Desensitization is a temporary suppression of the immune response to an antigen and persists only during constant exposure to the allergen. Sustained unresponsiveness, on the other hand, is a persistent state of clinical nonreactivity achieved after successful immunotherapy, which is independent of constant dosing of allergens [5]. AIT is the most effective method of causal treatment in pollen, insect, and venom allergy, but it is still a non-established method and thus a medical experiment in food allergy. The oral (OIT), subcutaneous (SCIT), sublingual (SLIT), and epicutaneous (EPIT) routes may be used. SCIT consists of a series of injections of allergen extract. Injections are performed by medical professionals due to their possible adverse effects. SCIT protocols involve weekly injections with an increasing amount of allergen in subsequent doses during the first phase (3–6 months), followed by the second phase, when injections are performed once a month and the amount of allergens is constant. The total duration of SCIT is 3–5 years. SLIT involves putting drops or a tablet with allergen extracts under the tongue. SLIT is given in several doses over a 12-week period. The highest effectiveness is achieved when given 12 weeks before the start of the pollen season. The first dose is given by a physician to monitor for any rare adverse reactions. Subsequent doses can be taken at home, which is very convenient. EPIT has gained a lot of interest recently. This method allows for needleless administration of an antigen to the surface of the epidermis, which contains Langerhans cells. An additional advantage of this immunization method is the lack of vasculature in the place of antigen application, which minimizes the risk of a systemic reaction. The surface of the epidermis is additionally superficially damaged by adhesive tape to increase the epidermis permeability for the antigen. This procedure acts also as an activator of the keratinocytes to release interleukins, thus contributing to the maturation of DC cells and their migration from the skin to the lymph nodes. OIT is the subject of various clinical research trials [6]. OIT is a possible treatment for food allergies that include the administration of gradually increasing doses of the allergen under medical monitoring. Following that, the food allergen must be consumed every day. The Polish Society of Allergology has not yet developed an OIT recommendation; however, a group of experts considers OIT to be the most effective and safest method in children and adults and emphasizes the urgent need to establish clear clinical and immunological indications as well as an immunotherapy regimen [7]. The study's goal is to create proven techniques for maximizing benefit while minimizing the danger of potential damage in patients with severe food allergies. The kind of food used in OIT protocols varies, with some utilizing commercially accessible products in their natural forms (for example, cow's milk, eggs, or peanut flour) and others using specially manufactured items like dried egg white or hydrolysed milk proteins.

Immunological mechanisms

The whole molecular process of gaining a DS or SU during allergen-specific immunotherapy has not been discovered yet. However, there have been many interesting observations of immune mechanisms both during and after therapy. Initial changes in immune reply consist of an increase in specific IgG4 and a decrease in specific IgE. Clinically, at this stage, skin test responses are reduced. A possible mechanism assumes that these fluctuations contribute to the blockage of mast and basophil cell transduction pathways, responsible for degranulation, which leads to their weakened inflammatory backlash. It was also proven that MCs hinder allergic reactions by the output of immunosuppressive cytokines such as IL-2 and IL-10 [8].

On the other hand, some studies reveal that at the beginning of AIT levels of allergen-specific IgE were elevated. Despite that fact, desensitization could be achieved. Changes in cellular response include allergen-specific T-cell anergy, the proliferation of induced Tregs (iTregs), which limits immunological hypersensitivity by direct suppression, production of IL-10, IL-35, and TGF-B, and depletion of T-effector cells. Within 3–6 months of therapy, there is a switch, and Th-2 declines in favour of Th1 and its anti-inflammatory cytokine profile. iTregs also dampen humoral response by suppression of B cells. As early as the end of the second month of peanut OIT, allergen-specific class-switched B cells that generate IgG and IgA emerge. Regulatory clones of OIT-induced B cells that produce IL-10 are linked to IgG4 production. Within a few months of starting, IgG4 levels rise dramatically as a result of the therapy and may continue to be higher than the baseline level even after the OIT comes to an end. It is worth mentioning that part of these immunological changes are transient and fade even during therapy, which might have an impact on the efficacy of this method. More investigations must be done to discover factors that enable desensitization and unresponsiveness to food allergens [9].

OIT protocol

Because there are no defined standardized OIT methods for patients with FA (the way to consume the allergen – liquid, powdered, etc., the initial and final

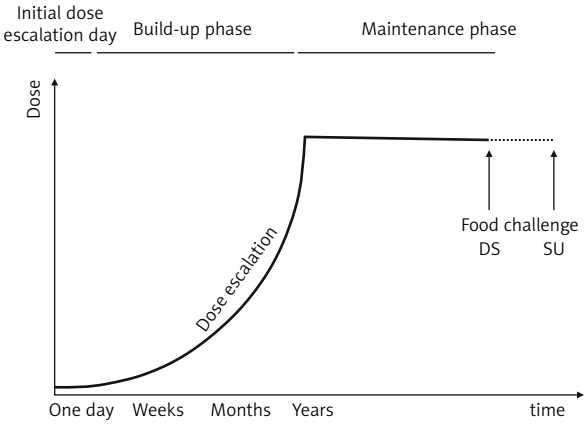

Figure 1. Typical scheme of the OITs. Generally, most of the treatments start with a few months of dose escalation after the initial dose administration, and then after reaching the maximum dose of the allergen, the maintenance dose phase starts, and continues for the next few months

dosages, and the therapy duration), the details vary between studies. Firstly, the participants are chosen based on defined criteria, such as a confirmed history of allergies, as well as test findings supporting the history of the allergy. Patients have often been excluded if they had a record of a life-threatening response, a suspicion of eosinophilic gastrointestinal illness, poorly managed asthma, or other conditions that would make participation in the trial difficult. In general, the desensitization protocol starts with an initial dose escalation (1–2 days), and the doses are very small (a few milligrams); then there is a dose build-up phase where dose-doubling is carried out gradually with increasing amounts of the antigen in every administration (it lasts around 3–9 months). After 6–12 months there is a maintenance dose which usually is around 4000 mg of the antigen, and the final step is the oral food challenge (OFC) (Figure 1). There is no evidence of the required minimum duration of the maintenance phase [10].

Effectiveness of therapy in different studies

Internationally, there is great interest in OIT, with numerous clinical trials of OIT in different types of food, especially peanuts, sesame, wheat, and eggs. These clinical trials have established the efficacy of OIT in inducing desensitization and sustained unresponsiveness, mostly in paediatric patients. Predominantly, apart from some differences, the clinical trials consisted of daily administration of the allergen in increasing doses for a certain amount of time.

Milk OIT

In developed countries, the prevalence of cow's milk allergy (CMA) and intolerance is believed to be between 1% and 7.5%, and it is one of the most prevalent triggers of food-induced anaphylaxis [11]. Through a study of the literature, we reviewed past OIT for CMA and summarized the effectiveness of this therapy. This procedure is associated with significant adverse responses, including anaphylaxis in some patients.

Meglio *et al.* were among the first authors when they attempted to desensitize 21 children with severe IgE-mediated CMA within 6 months by increasing the daily dose of the whole cow's milk. The children admitted to the survey had to be at least 6 years old, to be sure that oral tolerance to cow's milk was not spontaneously attained. The protocol consisted of providing increasing amounts of cow's milk beginning with around 0.06 mg of cow's milk proteins and then doubling the doses every day for about 6 months to obtain the maximum dose of 200 ml of cow's milk. During the procedure, all of the children were given medicinal prophylaxis – cetirizine at a dose of 0.25 mg/kg/day *per os* – and subsequently, the treatment was discontinued. After 6 months of desensitization, the cutaneous sensitivity for both casein and β-lactalbumin declined significantly ($p < 0.001$) in the children who completed the protocol. Three of the 21 children did not have the double-blind, placebo-controlled food challenge (DBPCFC) because of a compelling history of severe reactions after ingesting small doses of CM. Fifteen of the 21 (71.4%) children reached the daily consumption of 200 ml. Moreover, 8 of the 15 children received the entire cow's milk dose without experiencing any adverse reactions. The remaining 7 of the 15 youngsters experienced symptoms that began quickly after ingesting cow's milk and lasted for 2 h. Cetirizine was not combined with any other medication to manage these symptoms. All these children had no difficulties 2 months after discontinuing cetirizine and continuing to take the whole cow's milk. Three of the 21 (14.3%) children were able to tolerate 40–80 ml/day of undiluted cow's milk [12].

Longo *et al.* achieved very promising results in open-label experiments of milk OIT. For 1 year, 60 OFC-proven milk-allergic children aged 5 to 17 years were randomly assigned to milk OIT or avoidance. The OIT therapy was given in graded doses of whole milk up to a maximum of 150 ml, and to attain doses greater than 150 ml, milk-containing meals were administered. The OIT dose reached over the 1-year therapy period was used to assess response. After 1 year, 11 (36%) of 30 participants maintained a daily consumption of cow's milk of 150 ml or more, the majority of them with the addition of other dairy products, good enough to allow an unrestricted diet. Sixteen (54%) patients were able to consume a small amount of milk, ranging from 5 to 150 ml, while 3 (10%) children were unable to continue in the trial due to allergic reactions such as respiratory or stomach issues. After 12 months, no patients in the

avoidance group could tolerate 5 ml of whole milk. However, adverse symptoms were quite common in the milk OIT group, prompting 10% of individuals to withdraw from the research [13].

Skripak *et al.* published the findings of the first double-blind, placebo-controlled trial of OIT in 2008. Twenty OFC-proven milk-allergic children aged 6 to 17 years were randomly assigned to receive milk powder OIT or placebo (2 : 1 ratio). The patients began treatment with a dosage of up to 50 mg, which was followed by dose escalation up to a maintenance dose of 500 mg. After 23 weeks of maintenance, a DBPCFC of 8 g of milk protein was used. After milk OIT, the average cumulative reactive dosage rose from 40 to 5140 mg, and the placebo group showed no change from their 40 mg average initial threshold. Local (mainly oral pruritus) and gastrointestinal symptoms were the most common types of reactions in the active group. Symptoms from the lower respiratory system and skin were less frequent [14].

Pajno *et al.* conducted a trial including 30 children aged from 4 to 10 years, with IgE-mediated CMA, verified by a double-blind placebo-controlled food challenge. They were randomly assigned to CM desensitization or soy milk as a control. The dose was doubled every week for 18 weeks, and the maintenance dose was 200 ml of CM. The prevalence and seriousness of symptoms were monitored after each dose administration, and desensitization was discontinued if serious symptoms occurred. After desensitization was achieved or after premature termination, the double-blind food challenge was repeated. Ten out of 13 active patients acquired full tolerance to CM (200 ml) and one obtained partial tolerance. Two active participants ended the desensitization after experiencing severe responses; however, no reactions occurred in the controls, whose sensitivity to CM remained unaltered. Specific IgE and IgG4 levels in response to CM were assessed at the start of the trial, after 8 weeks, and at the end of the trial. Only the active group showed a substantial rise in specific IgG4 levels [15].

Martorell *et al.* administered OIT for 24–36 months to toddlers who were allergic to cow's milk. 90% of the youngsters in the OIT group were able to consume 200 ml of cow's milk without experiencing any adverse responses after 1-year follow-up. The rate of outgrowth in the OIT group was greater than in the spontaneous tolerance group. Eighty percent of the OIT group experienced allergic responses – 14 (47%) children developed moderate reactions (generalized urticaria, facial angioedema, cough, and mild bronchospasm), 10 (33%) developed mild reactions (localized erythema, urticaria, vomiting, rhinitis, and conjunctivitis), and 1 patient required adrenaline [16].

Salmivesi *et al.* conducted a randomized, double-blind, placebo-controlled trial of 28 children aged 6–14 years old and divided them into an active-treatment group and a placebo group. For 23 weeks, the amount of CM protein in the active group was increased from 0.06 mg to a total of 6400 mg (200 ml of milk). The protocol was completed by 24 (86%) patients – 16 (89%) in the active group and 8 (80%) in the placebo group. Due to gastrointestinal symptoms, 2 children in the active treatment group dropped out of the research. The parents of 27 children, 17 from the initial active treatment group and 10 from the original placebo group, were contacted 12 months after the placebo-controlled OIT (6 months after the open OIT). Thirteen children in the active treatment group, as well as all 10 children in the original placebo group, ingested 6400 mg of cow's milk protein daily. Three of the protocol's children did not consume cow's milk or cow's milk products. At 6–12 months after desensitization, 23 (82%) of the 28 children were able to consume large quantities of cow's milk. There was no need for any of the children to be treated in an emergency department, and no asthma aggravation was linked to milk drinking. The most prevalent symptoms were itching and stinging in the mouth. Also, many children experienced intestinal, oral, nasal, and dermal adverse effects. Only 1 child experienced regular symptoms (eczema flare-ups). As a result, CM-induced symptoms were evident in 13 of 23 (57%) individuals who continued to consume CM. Around 3 years later, one more youngster had stopped drinking milk daily. As a result, the long-term success rate was 22 of 28 (79%) [17].

Keet *et al.* investigated the effectiveness of SLIT alone or SLIT followed by OIT in the treatment of CMA by the double-blind, placebo-controlled food challenge. Thirty children with CM allergy, aged 6 to 17 years, were involved in the study. Patients maintained SLIT escalation to 7 mg daily or began OIT to either 2000 mg (the OITA group) or 1000 mg of milk protein (the OITB group). After 12 and 60 weeks of maintenance, they were challenged with 8 g of milk protein. The 8 g milk protein challenge was passed by 1 of 10 patients in the SLIT group, 6 of 10 subjects in the SLIT/OITB group, and 8 of 10 subjects in the OITA group after the treatment. SLIT accompanied by OIT was more successful than SLIT alone for desensitization to CM; however, it was associated with higher systemic adverse effects [18].

Inuo *et al.* conducted a randomized, double-blind, controlled single-centre trial, and 25 children, aged 1–9 years, were randomized into partially hydrolysed cow's milk protein-based formula (pHF-pHF) and extensively hydrolysed cow's milk protein-based formula (eHF-pHF) groups. All participants consumed the assigned formula in an amount that met the pHF threshold in the baseline food challenge. OIT was given to participants who were unable to ingest 20 ml of regular cow's milk protein-based formula (rCMF). In the baseline food challenge, all individuals ingested

the allocated formula in amounts equal to the pHF threshold. During the blind phase, participants were given unlabelled milk formula cans containing pHF or eHF. Participants in the pHF-pHF group consumed 20 ml of pHF containing the amount required for the pHF threshold once per day, while participants in the eHF-pHF group consumed 20 ml of eHF containing the amount required for the pHF threshold, but not eHF thresholds, during the first 8 weeks of the trial (the double-blind phase). All participants took 20 ml of pHF at the quantity necessary for pHF thresholds throughout the second 8 weeks of the study (the open phase). Twenty children finished the program. Ten were from the pHF-pHF group and 10 from the eHF-pHF group. The primary endpoint in the pHF-pHF group was a substantial rise in the threshold, but not in the eHF-pHF group. After taking formulas in both phases, no one experienced significant systemic allergic responses that necessitated the administration of adrenaline or systemic corticosteroids [19]. A summary of the recent studies is shown in Table 1.

Milk OIT combined with omalizumab

Omalizumab is a monoclonal antibody that binds to free IgE and inhibits it from binding to the IgE receptor, blocking the allergic reaction [9]. Hence, it may be a potential therapeutic target for children with severe allergies, including food allergies. In one of the first randomized, double-blinded, placebo-controlled trials, the safety and effectiveness of OIT in combination with omalizumab was measured. Omalizumab therapy started 4 months prior to the start of cow's milk OIT. Wood *et al*. discovered notable improvements in safety, but there was no discernible difference in the rate of desensitization or SU. Overall, 91.5% of omalizumab patients experienced symptom-free doses during dosage escalation, compared to 73.9% of placebo individuals [20]. According to Takahashi *et al*., desensitization was obtained in every patient who received OIT together with omalizumab. In this study, children who received omalizumab followed by 24 weeks of OIT with microwave-heated cow's milk achieved desensitization 8 weeks after the drug was stopped, and none of the 6 children in the untreated group did [21]. Although the results are promising in both studies, there is still little known about the long-term effectiveness, and this method remains experimental.

Peanut OIT

In 2009, the first open-label trial of peanut OIT was published in the form of a prospective cohort study, which demonstrated effective desensitization and an encouraging safety profile. At 36 months, 93% of the 29 patients who completed the program could endure an oral challenge with a cumulative dosage of 3900 mg of peanut protein on a maintenance dose of 1800 mg of peanut protein [22]. As peanut OIT became more and more popular, many new studies were published every year.

In 2017, Kukkonen *et al*. included 60 patients between the ages of 6 and 18 years, who experienced a moderate-to-severe response to peanuts in a double-blind, placebo-controlled peanut challenge (DBPC): during an 8-month build-up and maintenance period, 39 received OIT, whereas 21 controls avoided peanuts. The majority of OIT patients (85%) completed the build-up phase, and 67% tolerated 5.0 g of peanuts at the post-treatment challenge. There were no desensitized controls [23].

In 2018, Bird *et al*. conducted the first phase 2 multicentre research to evaluate AR101, a new oral biologic therapeutic product, for safety and effectiveness in OIT. A total of 55 participants were included in the study (29 AR101 and 26 placebo). In the intention-to-treat analyses, 23 of 29 (79%) and 18 of 29 (62%) AR101 participants tolerated > 443 and 1043 mg, respectively, at exit DBPCFC, compared to 5 of 26 (19%) and 0 of 26 (0%) placebo participants. AR101 substantially decreased symptom severity during exit DBPCFCs when compared to placebo [24]. The same year, the PALISADE group in the phase 3 trial, at a challenge dosage of 100 mg or less of peanut protein, examined individuals 4 to 55 years old with peanut allergies for allergic dose-limiting symptoms. At the exit food challenge, 250 of 372 participants (67.2%) who received active therapy, compared to 5 of 124 participants (4.0%) who received a placebo, were able to consume a dosage of 600 mg or more of peanut protein without experiencing dose-limiting symptoms. Efficacy was not proven in those aged 18 years and older [25]. In research by Nagakura *et al*., 24 children with anaphylaxis to peanuts were progressively administered increasing quantities of peanut powder up to 133 mg/day, and as a premedication, the patients were given 10 mg of loratadine. A year later, after 2 weeks of peanut abstinence, individuals were given an oral food challenge. Within a year, 22 (92%) of the children in the OIT group had desensitized, and 8 (33.3%) of the children in the OIT group had sustained unresponsiveness (asymptomatic after eating 795 mg of peanut protein), but none of the children in the control group achieved this [26].

Blumchen *et al*. tested 62 children with a peanut allergy. Peanut OIT with a maintenance dosage of 125 to 250 mg peanut protein was given to the patients in the active group. After 16 months, 23 of 31 (74.2%) of the active group's children were able to tolerate at least 300 mg of peanut protein at final OFC, and 13 of 31 were able to take the maximum dose of 4.5 g peanut protein [27].

The most recent study, conducted by Jones *et al*., tried the OIT for peanut allergy in children aged from 1 to 3 years with a maintenance dose of 2000 mg of

Table 1. Summary of recent studies about OIT for cow milk allergy

Research	Age range	Maintenance dose	Therapy duration	OFC dose at the end of the treatment	Participants	Active group	%DS among active group	Medical prophylaxis
Meglio *et al.*	6–10	200 ml of CM	6 months	200 ml of CM	21		71.4%	Cetirizine 0.25 mg/kg/day
Longo *et al.*	5–17	150 ml of CM	1 year	150 ml or more of CM	60	30	36%	Oxatomide 1 mg/kg/day
Skripak *et al.*	6–17	500 mg of milk powder	23 weeks	Cumulative doses 8 g of milk protein	20	13		None
Pajno *et al.*	4–10	200 ml of CM	18 weeks	Increasing doses of 0.1, 0.3, 1, 3, 10, 30, and 100 ml	30	15	77%	None
Martorelet *et al.*	24–36 months	200 ml of CM	1 year	200 ml of CM	60	30	SU 90%	None
Salmivesi *et al.*	6–14	6400 mg CM proteins (200 ml of cow milk)	23 weeks of dose escalation 12 months of maintenance	–	28	18	81%	None
Keet *et al.*	6–17	OITA-1000 mg OITB-2000 mg Slit 7 mg	60 weeks	8 g of milk protein	30	30	10% SLIT 60% OITB 80% OITA	None
Inuo *et al.*	1–9	All participants consumed the assigned formula in an amount that met the pHF threshold in the baseline food challenge	16 weeks	A total volume of 20 ml of pHF, eHF, or rCMF was administered every 30 min in 5–7 instalments, 8 and 16 weeks after treatment	25	25 (13 pHF-pHF, 12 eHF-pHF)	–	None
Takahashi *et al.*	6–14	200 ml of CM combined with omalizumab	24 weeks	Cumulative doses of 6 g milk powder	16	10	100%	None
Wood *et al.*	7–32	520 mg of milk protein	Treatment was unblinded after 12 months of combined OIT, and omalizumab was maintained for another 12 months in the active group while injections were stopped in the placebo group	10 g of milk protein	57	28	At month-28, 24 (88.9%) omalizumab-treated subjects and 20 (71.4%) placebo-treated subjects; At month – 32, SU was demonstrated in 48.1% in the omalizumab group and 35.7% in the placebo group	None

CM – cow's milk, OIT – oral immunotherapy, pHF – partially hydrolysed cow's milk protein-based formula, eHF – extensively hydrolysed cow's milk protein-based formula, rCMF – regular cow's milk protein-based formula, DS – desensitization, SU – sustained unresponsiveness, SLIT – sublingual immunotherapy.

Table 2. Summary of recent studies about OIT for peanut allergy

Research	Palisade group 2018	Nagakura 2018	Blumchen 2019	Kukkonen 2017	Fleischer 2019	Bird 2018	Edwin H. Kim 2019	Jones *et al.* 2022
Delivery method	OIT	OIT	OIT	OIT	EPIT	OIT	SLIT	OIT
Age	4–55	5–18	3–17	6–18	4–11	4–26	1–11	1–3
Maintenance dose	300 mg	795 mg	125–250 mg	100–2000 mg	250 µg	300 mg	2 mg	2000 mg
Therapy duration	24 weeks	2 years	16 months	8 months	12 months	20–34 weeks	Up to 5 years	134 weeks followed by 26 weeks of avoidance
OFC dose	≥ 600 mg	795 mg	DS ≥ 300 mg SU 4500 mg	5 g	I. ≥ 300 mg II. ≥ 1000 mg	I. ≥ 443 mg II. 1043 mg	750 mg for DS 5000 mg for SU	5000 mg
Participants	496	33	62	60	356	52	48	146
Active group	372	22	31	39	238	29	48	96
%DS among active	250/372 (67.2%)	SU 15/22 (68.1%)	DS 23/31 (74.2%) SU 13/31 (41.9%)	67%	84/238 35%	DS I. 23/29 (79%) II. 18/29 (62%)	DS 32/48 (67%) SU 10/48 (20.8%)	After 134 weeks – 71% After avoidance – 21%
Medical prophylaxis	–	Loratadine, montelukast	–	Antihistamines were taken daily during the build-up phase	–		–	–

EPIT – epicutaneous immunotherapy, OIT – oral immunotherapy, DS – desensitization, SU – sustained unresponsiveness, SLIT – sublingual immunotherapy.

peanut protein, which is the highest dose that has been administered in the last few years, which resulted in 68 (71%) children becoming desensitized. After 26 weeks of avoidance, only 20 (21%) children met the remission criteria. At weeks 134 and 160, peanut OIT increased peanut-specific and Ara h2-specific IgG4, while it decreased peanut-specific and Ara h2-specific IgE, skin prick test, and basophil activation when compared to placebo. Younger age and lower baseline peanut-specific IgE were predictive of remission in subjects undergoing peanut oral immunotherapy [28].

While oral immunotherapy is well described, less is known about sublingual and epicutaneous immunotherapy. The PEPITES randomized clinical trial consisted of 356 children allergic to peanuts, who were given treatment with a peanut patch providing 250 µg of peanut protein daily for one year. After 12 months of treatment with peanut-patch therapy vs. placebo, the difference in treatment response rate (percentage of subjects meeting a defined eliciting dosage to peanut challenge) was statistically relevant, but it did not fulfil a predefined requirement for a positive trial outcome (≥ 15% lower bound of the confidence interval) [29]. Kim *et al.* described their long-term peanut sublingual immunotherapy (SLIT) for children aged from 1 to 11 years for up to 5 years duration. Thirty-seven of 48 participants finished 3 to 5 years of peanut SLIT, with 67% (32/48) ingesting 750 mg or more during the food challenge. Moreover, 25% (12/48) of the participants passed the 5000 mg food challenge without experiencing any of the clinical symptoms, and 10/12 revealed SU after 2–4 weeks [30]. A summary of the recent studies is shown in Table 2 [31].

Egg OIT

Schofield published the first report of egg OIT in *The Lancet* in 1908, after successfully desensitizing a 13-year-old child with egg allergy [30]. It was the first randomized, double-blind, placebo-controlled research by Burks *et al.* [32], in which 55 children with egg allergies aged 5 to 11 years were given OIT or a placebo. Following the first dose-escalation, build-up, and maintenance phases, an oral food challenge with egg-white powder was administered at 10 and 22 months. After 10 months of therapy, none of the children who got a placebo and 55% of those who received OIT completed the oral food challenge, indicating that they were desensitized, and after 22 months, 75% of the children in the OIT group were desensitized. Children who passed the test at 22 months ceased OIT and eliminated egg consumption for 4 to 6 weeks. At 24 months, 28% of the OIT group passed the oral food challenge and were confirmed to have SU. All children who had passed the oral food challenge at 24 months were ingesting eggs at 30 and 36 months.

Staden *et al.* studied 45 children who were given either egg or milk OIT at maintenance doses of

1.6 g/day for the egg or 3.3 g/d for the milk. The control group had an avoidance diet. Although the milk and egg results were not reported independently, 16 of 25 (64%) children were able to bring the allergenic food into their diet after a median of 21 months of therapy, 9 with complete tolerance and 7 with partial tolerance, compared to 7 of 20 children (35%) in the control group. Twenty-one children had minor symptoms including tingling in the mouth, vomiting, or eczema exacerbation, which were effectively treated with oral antihistamines if necessary. Four children had severe side effects such as generalized urticaria, bronchial obstruction, or angioedema, which were effectively managed with antihistamines and steroids [33].

Buchanan *et al.* described 7 children, ranging in age from 14 to 84 months, who received 24 months of egg OIT at a maintenance dosage of 300 mg daily, with 4 (57%) passing an oral food challenge at the end of therapy. After a 3–4-month period without OIT, during which they maintained an egg-restricted diet, those who passed the first challenge performed a second DBPCFC. Only 2 children passed their second DBPCFC [34].

After 8 months of therapy, 40% of 50 participants were desensitized and 46% were somewhat desensitized, according to Palosuo *et al.* in their findings from a randomized, open-label trial of egg OIT. After 18 months of OIT, 44 of 50 patients (88%) were consuming eggs; 36 of 50 (72%) were considered desensitized and 8 of 50 (16%) were partially desensitized. After 3 months of maintenance therapy at the intended dosage, all 36 children who were considered desensitized passed the oral food challenge. They discovered that high baseline egg-white-specific IgE levels and polysensitization to the egg allergen molecules Gal d 1–4 were linked to treatment cessation and the necessity for individualized, long-term treatments [35].

Maeta *et al.* investigated the safety and effectiveness of low-egg-allergen cookies (LAC) as low-dose OIT in children with severe egg allergy. Seven of the 11 individuals progressed to the point where they could commence OIT with hard-boiled egg white. They were able to ingest 0.5 g of hard-boiled egg white following the OIT without experiencing an allergic response. As a result, they suggest that low-dose OIT can lower the likelihood of allergy symptoms caused by accidental ingestion of food containing eggs, as well as enhance the quality of life of the patients [36]. In another study, designed by Escudero *et al.*, after one month of egg avoidance following 3 months of egg OIT with a maintenance dose of at least one uncooked egg every 48 h, rates of SU were assessed. When challenged, 11 out of 30 children (37%) were able to complete the OFC without experiencing any side effects, as opposed to only one out of 31 (3%) children in the control group [37]. A summary of the recent studies is shown in Table 3.

Summary

FA is a serious health issue that is becoming more prevalent. Dietary restriction is the principal treatment option for FA, with rescue epinephrine use in the presence of serious allergic responses. Although the findings of current OIT trials are promising, the key concern with OIT is the variability of research protocols, which includes patient selection, the length of maintenance doses (identifying the predictive factors in order to pick those who require a longer maintenance phase), primary end objectives, desensitization definition, OFC procedures to measure desensitization, SU, identifying biomarkers, and safety profiles. There are several barriers to the use of OIT daily. One of them is the fact that the long-term effectiveness is unknown. OIT in general leads to desensitization, but it has a limited capacity to lead to long-term tolerance once continual exposure has ended. For instance, in one of the most recent trials, just 21% of children reached the remission criteria after 134 weeks of daily exposure to the allergen and 26 weeks of avoidance, as opposed to 71% of the children who desensitized immediately after the maintenance phase ended [28]. Secondly, even while anti-IgE and OIT have great potential, additional investigation is essential to clarify several unresolved difficulties before they may be used in situations other than research. First, more research is needed to determine OIT's long-term effectiveness after anti-IgE therapy is discontinued. Further study is required to determine the potential biomarkers to forecast each patient's response to treatment. Finally, some healthcare systems may find anti-IgE therapy to be unaffordable due to its high cost. What is more, adverse effects are very common, and even though they are mostly mild, there is a risk of acute responses at any time throughout the desensitization procedure, such as anaphylaxis, with the need for an epinephrine injection [38]. Lately, there have been fears about the safety and therapeutic value of OIT participation because according to Chu *et al.* peanut OIT procedures increase the incidence and probability of major adverse events such as anaphylaxis and the requirement for epinephrine similarly during the build-up and maintenance phases. The most frequent and milder side effects and the main reason for discontinuation of the treatment are gastrointestinal symptoms (i.e. abdominal pain, vomiting, nausea, dysphagia, and reduced appetite), asthma, urticaria, and rhinitis [39]. There is also a risk of the development of persistent non-IgE-mediated food allergies, such as eosinophilic esophagitis, which is a rare but concerning side effect of OIT [40]. It is important to note that patients who completed their OIT protocols and even became desensitized might have a false sense of security because, for the time being, they can consume the allergen without experiencing any symptoms. However, little is known about the long-term effectiveness, and

Table 3. Summary of recent studies about OIT for egg allergy

Research	Burks *et al.* 2012	Buchanan *et al.* 2007	Staden *et al.* 2007	Palosuo *et al.* 2021	Maeta *et al.* 2018	Escudero *et al.* 2015
Delivery method	OIT	OIT	OIT for egg and milk separately	OIT	OIT	OIT
Age	**5–11**	14–84 months	0.6–12.9	6–17	3–8	5–17
Maintenance dose	2 g	300 mg	1.6 g – egg 3.3 g – CM	1 g	10 LAC, each containing 79–110 mg of egg white protein	1 undercooked egg every 48 h
Therapy duration	I: 10 months II: 22 months	24 months	11–59 months	8 months	3–4 months	3 months
OFC dose at the end of the treatment	5 g of egg – white powder after 10 months 10g of egg – white powder after 22 months 10 g of EWP after 24 months (4–6 weeks of avoiding eggs)	8 g of egg protein	Egg – 4.6 g, and if no reaction was observed – 6.2 g milk – 3.3 g, and if no reaction was observed – 4.77 g	1.5 g	2 g of hard-boiled egg white protein	
Participants	55	7	45	50	11	61
Active group	40	7	Milk – 14 Egg – 11	50	11	30
%DS among active	55% after 10 months 75% after 22 months (28% with SU after 24 months)	57%	16/25 (64%)	44%	7 subjects tolerated 2 g of hard-boiled EW after the OIT. Four of the subjects showed no improvement in response to OIT.	93% 37% SU
Medical prophylaxis	None	None	Antihistamines and steroids if needed	None	None	None

OIT – oral immunotherapy, DS – desensitization, SU – sustained unresponsiveness, EW – egg white.

after some time, they might become susceptible to that allergen once more. In addition, besides the objective results, the patient's opinion about the treatment should also be considered. To summarize, OIT is a potential therapy for FA, and it will be critical to developing standardized protocols. Understanding the process underlying complete recovery or SU is essential to achieving the aim of the treatment. Future research is required before OIT can be used more frequently in FA. Although AIT is a promising technique for treating FA, it is not currently advised in clinical practice because it is still considered to be an experimental treatment for the patients.

Conflict of interest

The authors declare no conflict of interest.

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