Peanut allergy immunotherapy: review of current treatment options

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SUMMARY

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Peanut allergy is the most common food allergy in developed countries of Europe and America, affecting nearly 2% of children. Ingestion of peanut proteins even in the minimal amount may result in a dangerous to life or health anaphylactic reaction, thereby being one of the most common causes of anaphylaxis with fatal effect. Possible therapeutic methods for peanut allergy are sought to achieve patients' desensitization and antigen tolerance. Among currently considered therapies there are oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT), however all of them are still in clinical trials. The most effective immunotherapy is OIT, resulting in higher tolerated antigen doses in comparison to sublingual and epicutaneous therapy, though oral immunotherapy has a higher risk of adverse reactions, mostly gastrointestinal and oropharyngeal. It may be advantageous to fuse several immunotherapy methods into sequential schemes. Future studies are required to furtherly evaluate effectiveness and compare mentioned immunotherapy methods of peanut allergy.

Key words: *food hypersensitivity, immunotherapy, peanut hypersensitivity, sublingual immunotherapy*

STRESZCZENIE

Immunoterapia alergii na orzechy ziemne: przegląd aktualnych metod terapeutycznych

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Alergia na orzechy ziemne jest najczęściej występującą alergią pokarmową w krajach rozwiniętych Europy i Ameryki, dotykając 2% dzieci. Przyjęcie nawet znikomej ilości białek orzechów ziemnych może skutkować groźną dla zdrowia i życia reakcją alergiczną, przez co alergia na orzechy ziemne jest jedną z najczęstszych przyczyn anafilaksji ze skutkiem śmiertelnym. Poszukuje się możliwych metod terapeutycznych, umożliwiających osiągnięcie desensetyzacji i tolerancji antygenowej na białka orzechów ziemnych. Spośród obecnie rozważanych terapii wymienia się immunoterapię doustną, podjęzykową oraz naskórną, z których wszystkie są nadal na etapie badań klinicznych. Najskuteczniejszą metodą jest immunoterapia doustna, pozwalająca na osiągnięcie wyższych tolerowanych dawek antygenów, w porównaniu do immunoterapii podjęzykowej i naskórnej. Immunoterapia doustna jest jednak obarczona najwyższym ryzykiem występowania niepożądanych reakcji, głównie w obrębie układu pokarmowego i nosogardzieli. Korzystne może okazać się połączenie kilku metod immunoterapii w następujących po sobie schematach. Konieczne są jednak kolejne badania oceniające skuteczność i porównujące ze sobą możliwe metody immunoterapii u pacjentów z alergią na orzechy ziemne.

Słowa kluczowe: *alergia pokarmowa, immunoterapia, immunoterapia podjęzykowa, alergia na orzechy ziemne*

In recent decades, allergic diseases have become one of the most profound health problems of societies in developed countries. Food allergies concern 2-5% of the world population. In Poland 4-8% of children and 2-3% of adults are diagnosed with food allergy, however these numbers are continuously increasing

[1]. Among food products which intake may result in an emergence of the allergic reaction, the most common ones are peanuts – responsible for ca. 2% of allergies in children [2]. Contrary to cow milk allergy (68%) and chicken egg allergy (79%), there is only a 27% chance to outgrow the peanut allergy [3]. Since allergies significantly impair social and professional life, increase stress response in patients and devalue the standard of their lives, numerous studies have been conducted to evaluate treatment possibilities. Therefore, peanut allergy is one of the well-studied and best-known food allergies [4]. Presently, food allergy treatment consists of the allergens elimination in patients' diet. This is however difficult to comply with due to the peanut allergens prevalence in food products, even in residual amounts. Studies show over 75% of patients with peanut allergy have unintentionally ingested peanuts in their life despite complying to the strict eliminative diet [5]. In order to improve patients' prospects to control their disease, studies over various immunotherapy methods are conducted including oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT). The essence of these immunotherapies is administration of increasing in time doses of allergens, which should result in desensitization and thereby an antigen tolerance acquisition. In this paper we submit presently considered methods of peanut allergy immunotherapy, which are in distinct phases of clinical trials, focusing on their effectiveness, advantages and potential adverse effects.

PATHOGENESIS

Ara h 1-9 antigens are involved in the pathogenesis of the IgE-mediated allergic reaction to peanuts (*Arachis hypogaea*). The first three of them (vicillin, congultin and glycine) are the most common allergens (in 25-77% of allergic individuals) and together with Ara h 4, 6 and 7 belong to the group of seed storage proteins. Ara h 2 is also particularly associated with systemic reactions. In turn, Ara h 5, 8 and 9 are allergens associated with the so-called Oral Allergy Syndrome (OAS), which occurs in people previously allergic to tree pollen (especially birch pollen), after contact by the mouth or eating a particular food. These individuals develop contact urticaria with clinical signs of allergic rhinitis as a result of cross-reactions [6].

Peanut allergy is the most common food allergy, with the greatest prevalence in the populations of developed countries in Europe and America (up to 2% in the United States) [7] and much less common in Asia [8]. There are several hypotheses as to why peanut allergy is so common. One of them is the high proteolytic stability of proteins due to the presence of disulfide bridges and significant glycation of spare proteins, such as Ara h proteins, increasing allergen exposure and induction of a stronger immune response. Moreover, Ara h 1 may act as an adjuvant for T helper cells, which enhances the production of IgE immunoglobulins [9].

Among the risk factors for peanut allergy, there are family factors (siblings of allergic individuals have an increased risk of developing allergies compared to the population risk), genetic factors (mutations causing loss of filaggrin function are associated with oral allergy syndrome), use of skin care products containing proteins derived from peanuts, especially in children with atopic dermatitis, and age of first exposure to allergens (prior exposure reduced the risk of allergy by 11.8% or 24.7%, respectively, in children with negative or positive skin tests) [10]. The consumption of nuts by pregnant women is also considered as a risk factor, although the results of some studies suggest a protective effect of low doses of allergens during pregnancy and breastfeeding on the incidence of allergies in the offspring [11].

In patients with severe allergic reactions, the threshold dose for initiating symptoms is usually lower than in mild patients group, typically one to three nut equivalents (although the lowest threshold dose reported was 0.05 mg peanut protein) [8]. Approximately 25% to 50% of patients with a peanut allergy have a coexisting allergy to other types of nuts. Some of them occur as a result of the cross-reaction of homologous IgE antibody binding epitopes (e.g. with hickory, almond, Brazil nut and hazelnut allergens). In the studies, the patients also showed concomitant allergies to eggs, cow's milk, fish and soybeans. Moreover, 75% of patients have accompanying atopic diseases – most often asthma, atopic dermatitis or allergic rhinitis. Special attention should be paid to the coexistence of asthma, which is a risk factor for anaphylactic reaction [7,12].

THE COURSE OF THE DISEASE

Most patients are exposed to Ara h antigens for the first time and develop an allergic reaction within the first two years of life. The symptoms of the first allergic reaction are usually milder than with subsequent exposures. The median time from diagnosis to accidental allergen exposure was 4 months in the study by *Wen Cin Chiang et al.* [13]. Another study concluded the average annual rate of allergen exposure was 14.3% [14].

The most reliable predictor of persistence or resolution of allergy is the level of specific anti-Ara h IgE antibodies and the dimensions of the reaction area in skin tests. However, up to 25% of children may have a bubble diameter >10mm, a high level of specific

IgE >15 kU/L, and not respond to an oral challenge. Therefore, clinical signs of allergic reactions are not reliable prognostic factors for persistence of sensitization [15].

The most common allergic reaction occurs as a result of the ingestion of an allergen. It can present as IgE-mediated anaphylaxis, but most people will experience milder symptoms and never experience an anaphylactic reaction. Anaphylaxis, caused by physical contact with the antigen through the skin or the inhalation of antigen particles, is much less common [16]. Symptoms of an anaphylactic reaction after consuming an over-threshold dose of nuts appear within seconds to two hours after consumption. It is believed to be caused by the massive release of inflammatory mediators from mast cells and basophils. The median onset of reaction after exposure is 3 minutes in the United States [17], and in European registries, the onset of symptoms was less than 10 minutes in 50% of the subjects. A biphasic reaction is much less common, where symptoms recur after the initial anaphylactic event is allegedly resolved [18].

Peanut allergy is one of the most common causes of fatal anaphylaxis [19]. Its risk is increased by a lower dose threshold causing an allergic reaction, a history of anaphylactic reactions in the patient and allergy to birch pollen [20].

The symptoms of an anaphylactic reaction after exposure to peanuts are similar to an anaphylactic reaction due to other factors; mild to severe and include itching, facial flushing, hives or angioedema, periorbital edema, runny nose, nasal congestion, cough, wheezing, shortness of breath, change in voice quality, choking feeling, tachycardia (or less commonly bradycardia), dizziness, hypotension, sense of anxiety and cardiovascular collapse. However, when peanuts are eaten, gastrointestinal symptoms are more pronounced, including among others nausea, vomiting, upper abdominal pain, colic pain and diarrhea [21].

ORAL IMMUNOTHERAPY

Oral immunotherapy (OIT) of peanut food allergy is a supportive treatment aimed at mitigating symptoms of the allergy. OITs main goal is the induction of a state of desensitization in the patient, which is defined as an increase in the reactivity threshold for the allergen administered by the oral route. This is accomplished by a daily stimulation of the immune system with doses of antigen lower than the reactivity threshold (that do not initiate an allergic reaction) and gradual increase of doses until the desired reactivity threshold is reached. OIT does not cure allergies and requires long-term, daily intake of low doses of the allergen. The clinical goal is to alleviate the symptoms of hypersensitivity following accidental ingestion of the allergen.

OIT is currently the most clinically verified method of peanut allergy immunotherapy, and the only form which has a commercially available formula in the US and EU. The largest clinical trials conducted on OIT include the PALISADE study (USA – adult population) [22] and the ARTEMIS study (EU – pediatric population) [23].

The mechanism of action of OIT has not been fully understood yet. Most studies investigate the effects of oral immunotherapy on peripheral immune structures, mainly tissue basophils and mast cells. The phenomena occurring in the gastrointestinal immune system (GALT) combined with interactions with the microbiome remain largely unexplored, although most authors suspect that the effects of OIT are most pronounced in these structures and have the greatest impact on the clinical outcomes of treatment.

The regulation of the allergic response under the influence of low doses of the allergen takes place in two, difficult to separate, stages: initiation and consolidation.

Initiation

The duration of this period varies individually, usually lasting several months. In the initial weeks of OIT, plasma levels of specific IgE (sIgE) increase due to the continued activation of allergen specific Th2 cells, which stimulate B cells to produce type E specific immunoglobulins. At the same time, the Th2 lymphocyte subpopulation grows by promotion of the differentiation of naive T lymphocytes to Th2 and blockage of IL-4 modulated pathways that suppress the action of regulatory lymphocytes, which leads to an escalation of the allergen response. Chronically elevated levels of serum sIgE are compensated by basophils and mast cells in three main mechanisms: 1) the endocytosis of IgE, 2) down-regulation of membrane FcεRI receptor and 3) the actin cytoskeleton rearrangement and the resulting stabilization of secretory granules. Mentioned processes lead to desensitization and increased tolerance to the antigen (allergen). Along with the prolonged time of exposure and increasing dose of the allergen, Th2 lymphocytes change the spectrum of synthesized cytokines. The clonal expansion of the cells producing IL-10 begins to prevail. The exact mechanism leading to the change of the response remains unknown. IL-10 is a potent suppressor of pro-inflammatory activity of lymphatic cells as it inhibits the activity of Th2 lymphocytes, stimulates the differentiation of regulatory lymphocytes, and stimulates B lymphocytes to produce allergen-specific IgA and IgG type 4 immunoglobulins, which weaken IgE-modulated reactions.

Consolidation

It occurs mainly as a result in changes within individual subpopulations of T lymphocytes. Prolonged exposure to the allergen leads to depletion and deletion of reactive Th2 lymphocytes. The concentration of allergen-specific plasma IgG4 increases up to 10 times compared to the input level. High IgG4 levels inhibit the allergic reaction in two main mechanisms: 1) competition for the IgE epitope that prevents FcεRI from activating basophils and mast cells; 2) The Fc region of IgG4 binds to the FcgRIIb receptor on the surface of basophils, the activation of which stabilizes the cell, preventing the release of secretory granules. The changes in the concentrations of individual immunoglobulin classes are presented in figure 1.

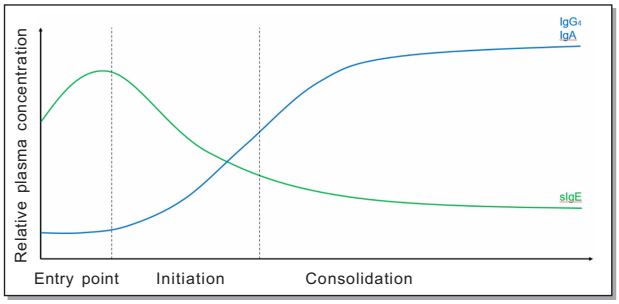

Figure 1. Preview of the change in blood plasma concentrations of individual immunoglobulin classes depending on the phase of the immune response
Rycina 1. Podgląd zmian stężenia w osoczu krwi poszczególnych klas immunoglobulin w zależności od fazy odpowiedzi immunologicznej

OIT is a new and experimental method of treatment, therefore there are no uniform and universal criteria on how the therapy should be conducted. In most cases, classification for treatment consists of confirmation of peanut allergy and exclusion of the presence of potentially serious comorbidities: poorly controlled bronchial asthma, eosinophilic gastroenteritis, past or present severe mast cell disorders or other conditions that make the requiring close cooperation treatment impossible (e.g. psychiatric disorders). OIT is also contraindicated if a patient experienced a severe anaphylactic reaction in the last 60 days prior to the start of treatment. The baseline level of both total and specific IgE in the plasma is irrelevant. The minimum age for starting therapy is 4 years [23].

The only FDA and EMA-approved peanut allergy OIT medication is PALFORZIA®, manufactured by Aimmune Therapeutics Ireland Limited. The active substance in PALFORZIA is peanut protein in the form of a defatted powder from the seeds of *Arachis hypogaea L.* (peanut), which is the main allergen of peanuts. The manufacturer's recommended dosing schedule consists of three consecutive steps: an initial dosing phase, an escalation phase, and a maintenance dosing phase.

The first step – the initial dosing phase – takes place one day in a treatment facility capable of treating potentially severe allergic reactions, including anaphylaxis. It is performed by administering the allergen to the patient in increasing doses, starting from a dose of 0.5 mg. While being observed, every 20 to 30 minutes the patient is given the next dose, successively 1 mg, 1.5 mg, 3 mg and 6 mg. The procedure is considered successful if no severe symptoms of an allergic reaction requiring medical intervention occur after the administration of a dose of at least 3 mg. Treatment should be discontinued immediately if the above reaction occurs after any dose that has been administered. The occurrence of a mild reaction is not a contraindication to continuation. Patients who tolerate a dose of at least 3 mg within a maximum of 4 days should start the next treatment phase.

The escalation phase has 11 levels and consists of a daily single administration of an increasing dose of the peanut allergen, starting with an initial daily dose of 3 mg. The dose is increased at 2-week intervals until the tolerated daily dose of 300 mg is reached. In the event of severe allergy symptoms occurrence, it is permissible to extend the period corresponding to a given level. The first dose of each subsequent level should be taken in a healthcare facility and if the dose has been well tolerated, the remaining doses are taken by the patient at home.

The maintenance phase, which is the last step in treatment, the patient maintains a daily dose of 300 mg of the allergen. Treatment of this scheme is indefinite [23].

Various adverse effects occur in 85% of patients undergoing OIT. In studies, 85% of observed reactions were classified as mild, the remainder ranged in severity from moderate to severe, however, life-threatening reactions were rare, affecting 1.1% of patients. The most common OIT side effects and their frequency are summarized in table 1. The highest incidence of

Table 1. Most common OIT adverse effects
Tabela 1. Najczęstsze działania niepożądane OIT

Adverse effect	Frequency
Abdominal pain	49,4%
Throat irritation	40,7%
Itching	33,7%
Nausea	33,2%
Vomiting	28,5%
Urticaria	28,5%
Itching of the oral mucosa	26,0%
Upper abdominal pain discomfort	22,8%
Systemic allergic reactions • Including anaphylaxis	15,1% 1,1%

adverse effects is in the initial dosing phase, including life-threatening reactions. The incidence of treatment side effects is much higher in patients with other allergic conditions – e.g., allergic conjunctivitis (2.9 times higher) or asthma (2.3 times higher) [22].

OIT efficiency is defined as a sustained increase in allergen tolerance, referred to as desensitization. In terms of laboratory measurements and clinical indicators of therapy effectiveness, i.e., an increase in the daily tolerated dose of an allergen, a decrease in specific IgE concentration and an increase in IgG4 concentration, the effectiveness of OIT therapy has been confirmed in numerous clinical trials. However, most of the measures described apply only the controlled conditions of a clinical trial, while the assessment of the impact of OIT on the daily functioning of patients shows inconclusive results. In addition, due to the severity of side effects, 10.5% to 21% of patients had to discontinue treatment prior to entering the maintenance phase. Compared to the classic therapeutic approach, which consists of an avoidance of peanut-containing products, the treatment is associated with a greater frequency of anaphylactic reactions resulting in increased consumption of adrenaline and other side effects (nausea, vomiting, abdominal pain, angioedema and throat irritation). The impact on the quality of life (QoL) of patients is also difficult to assess due to the low quality of many studies using non-standardized questionnaires and the potential bias in the results. Some standardized studies of the impact of OIT on QoL indicate a slight increase in the quality of life in the groups using OIT compared to placebo, however, it should be mentioned that the increase in QoL is variable during the course of therapy and concerns only some aspects of quality of life, mainly those assessed by patients' caregivers [24]. Extensive meta-analyzes indicate the need for further evaluation of the impact of OIT on the patients' functioning and quality of life. ICU should be considered as a supportive treatment, which does not discharge the patient from having to comply with an elimination diet and only mitigates potential, unintentional intake of the allergen [25,26].

SUBLINGUAL IMMUNOTHERAPY

Sublingual immunotherapy (SLIT) is another considered therapy for peanut allergy. Primarily it was applied in treatment of allergic rhinitis [27], however due to the easier way of administration in comparison to other immunotherapy methods and a better safety profile, it is currently studied to be used in food allergies therapy as well [28]. In sublingual immunotherapy a patient is given peanut proteins administered sublingually in a form of drops or, less often, tablets. This solution should be kept sublingually for 2 minutes and then swallowed. Sublingual immunotherapy dosage consists of phases of escalating doses followed by a maintenance phase. Dosage is dependent from the amount of peanut proteins and the volume in which they were dissolved – usually the maximal amount practicably holdable sublingually by a patient [29]. Up to now, results of two studies evaluating SLIT usage in peanut allergy treatment are available.

In 2011 *Kim et al.* [29] conducted a double-blind, placebo-controlled study over SLIT in which 18 children aged 1-11 years (median 5.2) were being given crude peanut extract or placebo for a total time of 12 months. For the first 6 months doses were increased by 25-100% biweekly, from the starting dose of 0.25 mg to reach the final maintenance dose of 2000 mg. After every dose escalation patients were to administer the new dose at home for 2 weeks by themselves. Thereafter for the next 6 months during the maintenance phase patients were given 2000 mg (maintenance dose) of peanuts proteins daily. In the result, 18 patients finished the protocol without doses missed, where 11 subjects from the group receiving the active SLIT therapy achieved desensitization. After total of 12 months since the beginning of the treatment patients underwent a DBPCFC (double-blind, placebo-controlled food challenge), in which 11 subjects from the active SLIT group safely ingested a median cumulative dose of 1710 mg – 22 times more than the median cumulative dose in the placebo group (85 mg). In patients from active SLIT group changes in immunologic response were noted as there was a statistically significant increase in peanut-specific IgG4 levels, decreased peanut-specific IgE levels, decreased basophil responsiveness as well as a decrease in skin prick test wheal size. During the follow-up study [30] a dose of 2000 mg of peanut proteins has been continued to be administered daily for the next 3-5 years. In the result 67% of subjects succeeded to pass DBPCFC with median cumulative dose of 750 mg and 25% of subjects with 5000 mg without allergic response. In 4.8% of patients adverse events were reported. The most common adverse reaction in the active SLIT therapy group was transient oropharyngeal itching (3.6%), representing 75% of all adverse events, and its intensity decreased as the therapy was continued. This study concluded SLIT can be a safe and effective therapy of peanut allergy in children. Adverse reactions were limited with the majority of oropharyngeal and gastrointestinal symptoms [31]. Extended time of the therapy resulted in increased modulation of allergic response, whereas a low median of patients' age suggests that starting the treatment when children are younger may lead to a greater effectiveness [30].

In 2013 a randomized, double-blind, placebo-controlled study by *Fleischer et al.* [32] took place, in which 40 subjects aged 12-37 (median 15) were given placebo or peanut protein in the dose starting from 0.000165 mg up to 660 mg. Dosing was continued for the next 2 weeks by patients themselves at home after every dose escalation similarly to the *Kim's* study above, reaching the maintenance dose of 1386 mg. After 44 weeks of the study patients underwent an oral food challenge (OFC), where 5 g or at least 10-fold more than the baseline intake of peanut proteins were ingested. In the result 14 out of 20 subjects (70%) from the active SLIT group were considered as responders to the therapy with a median successful dose of 496 mg, compared to 3 out of 20 (15%) in the placebo group. The study was continued for the next 24 weeks and in Week 68, at the maintenance dose of 3696 mg, OFC was performed again using 10 g of peanut protein powder. Median successful consumed dose increased up to the 996 mg, which was statistically significant compared to the week 44. The clinical response was associated with the increase of peanut-specific IgG4 levels and decrease in basophil reactivity. The most common adverse reactions were related to the oropharyngeal mucosa (37%), and after exclusion of these symptoms 94.7% of subjects were considered symptom-free in the active SLIT group. Even though a clinical desensitization has been achieved in some subjects, immunomodulatory effects of the peanut SLIT were modest, as authors of the study concluded [33].

SUBCUTANEOUS AND EPIDERMAL IMMUNOTHERAPY

Subcutaneous immunotherapy (SCIT), which consists of administering small doses of peanut antigens under the skin, is also considered in immunotherapy. Such therapy is successfully used in the case of allergy to house dust mites, pollen of grasses, grains and other plants, both in children and adults. Unfortunately, despite the potential to induce tolerance to peanut proteins, subcutaneous therapy turned out to be dangerous and provoked increased systemic reactions [34,35]

Epidermal therapy is developed in many clinical trials (including PEPITES randomized clinical trial, multicentre trials conducted by CoFAR). It uses an epicutaneous delivery system (EDS). As a result of the action of sweat, allergens are dissolved and pass through the stratum corneum [36]. The patches are applied to the area of unchanged skin, between the scapulas in children under 11 years old or on the medial surface of the arm in the elderly. Their position changes every day. Skin patches are a less invasive form of therapy and may pose a lower risk of systemic reactions than oral (OIT) or sublingual (SLIT) therapies. It also uses lower doses than the rest of the treatments, and the maintenance dose is identical to the starting dose [37,38].

Initial reports suggest that EDS may lead to desensitization to a higher dose that normally causes an allergic reaction, and in a small percentage of patients it may result in long-term (4 to 8 weeks) antigen non-response after discontinuation of therapy (SU – sustained unresponsiveness). The therapy is most effective in children <11 years of age [37].

In a multicentre study in Europe and North America, the threshold dose of nut protein was more than 10 times higher than the dose before treatment and/or exceeded 1000 mg in 25% of placebo patients, 45% of patients with EPIT 0.05 mg, 41% with EPIT 0.1 mg and 50% from EPIT 0.250 mg. However, only the 0.25 mg dose produced an effect significantly different from placebo (25% absolute difference, 95% CI 7.7-42.3%). Almost all of the patients had side effects such as mild local skin reactions [38].

DISCUSSION

All of the described therapeutic methods in peanut allergy are at the initial stage of evaluating their effectiveness and safety. To date, no large-scale clinical trial has been conducted that would allow a reliable comparison of the described treatment approaches. The performed comparative analyzes, based on a small number of participants, confirm the results obtained in the studies of individual therapies [39]. The most effective method of desensitization is oral therapy (OIT), which in the maintenance phase allows tolerance of an average dose of 7246 mg of peanut protein, and the percentage of patients in whom treatment is successful is close to 100%. In the case of SLIT, the average tolerated dose of antigen equals 496 mg, while the percentage of patients who develop tolerance oscillates around 70% [3]. Epidermal therapy allows to achieve clinical tolerance of a higher dose of the allergen (5044 mg orally), but in only 48% of patients, and the percentage of positive responses is higher in the group of younger children [37]. The results clearly show that the OIT allows both to achieve the highest tolerance threshold and the greatest effectiveness of therapy. However, at the same time, OIT is a method with the biggest proportion and intensity of adverse effects – they occur many times more often than in other methods (e.g., 4 times more often than in SLIT). 18% of people participating in the study were forced to discontinue the trial during the escalation phase, and another 12% in the maintenance phase. 23% of patients required at least one administration of epinephrine to control the response

to increasing doses of the allergen [39]. The other methods are safer and the side effects are milder in the case of SLIT, in vast majority of cases, they are limited to symptoms from the nasopharynx, the most frequent being pruritus. EPIT very rarely causes symptoms other than local skin reactions in the area of application. One of the most important factors taken into account when assessing immunotherapy is its potential to produce a patient's sustained unresponsiveness (SU) to an allergen. SU occurs in most patients undergoing OIT but fades with time after discontinuation of treatment or reduction of the dose to less than 300 mg per day. There are no analyzes thoroughly assessing the potential of SLIT and EPIT to generate SU. However, based on the available studies, the percentage of patients achieving SU in these therapies is small – not exceeding a few percent. It would be clinically valuable to find a parameter, whose monitoring would allow to assess the effectiveness of the therapy and accordingly modify its course. Unfortunately, at the time of this article creation no parameter, which would be characterized by high sensitivity and specificity with simultaneous easy measurement, has been discovered. In recent years, it has been shown that a therapeutic protocol initially consisting of SLIT or EPIT, which after a certain period of time, e.g. 6 months, is changed to OIT, allows for a significant reduction in the severity of side effects, but does not completely eliminate them, and some patients are still forced to drop out of the therapy. Nevertheless, this sequential approach appears to be the most promising treatment scheme [39].

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