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Пищевая аллергия: тренды развития технологий аллергенспецифической иммунотерапии

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АННОТАЦИЯ

Обоснование. Пищевая аллергия остаётся актуальной проблемой современного мира, ухудшает качество жизни пациентов и членов семьи. Одним из наиболее перспективных методов терапии пищевой аллергии является аллергенспецифическая иммунотерапия.

Цель — анализ результатов клинических исследований эффективности и безопасности современных технологий аллергенспецифической иммунотерапии в лечении пищевой аллергии, опубликованных за последние три года.

Материалы и методы. Проведён поиск и анализ научных публикаций с использованием ресурсов PubMed и eLibrary, каталогизирующих биомедицинскую научную литературу. В обзор включены оригинальные исследования, опубликованные за период с 1 января 2020 года по 31 декабря 2022 года.

Результаты. Обзор позволил систематизировать данные, накопленные за последние три года, отражающие основные тенденции в аллергенспецифической иммунотерапии пищевой аллергии. Анализ исследований продемонстрировал современные подходы к аллергенспецифической иммунотерапии в виде оральной и эпикутанной иммунотерапии и затронул аспекты эффективности и безопасности данных методов. В когортах пациентов с пищевой аллергией оральная и эпикутанная технологии показали высокую эффективность в достижении толерантности и десенсибилизации к пищевому триггеру. В ходе проведённого анализа выявлено, что эпикутанная иммунотерапия характеризуется высоким уровнем приверженности пациентов к лечению.

Заключение. Необходимы дальнейшие масштабные клинические исследования по изучению современных методик аллергенспецифической иммунотерапии у пациентов с пищевой аллергией для формирования стандартизированных протоколов терапии.

Ключевые слова: пищевая аллергия; лечение; иммунотерапия; аллергенспецифическая иммунотерапия; АСИТ.

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Food allergy: Trends in the development of allergen-specific immunotherapy technologies

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ABSTRACT

BACKGROUND: Food allergy is an urgent problem for public health around the world. One of the most promising methods of food allergy treatment is allergen-specific immunotherapy.

AIM: to analyze the results of clinical studies on the effectiveness and safety of modern allergen-specific immunotherapy technologies in the treatment of food allergies published over the past three years.

MATERIALS AND METHODS: A search and analysis of scientific publications was carried out using resources cataloging biomedical scientific literature: PubMed and eLibrary. The review includes original studies published between January 1, 2020 and December 31, 2022.

RESULTS: The review made it possible to systematize the data accumulated over the past three years, reflecting the main trends in allergen-specific immunotherapy of food allergy. The analysis of studies showed modern approaches to oral and epicutaneous immunotherapy and affected the efficacy and safety of these types of treatment. In food allergy cohorts, the allergen-specific immunotherapy approach of oral and epicutaneous allergen-specific immunotherapy has been shown to be highly effective in achieving tolerance and desensitization to the food trigger it was revealed that epicutaneous allergen-specific immunotherapy is characterized by a high level of adherence of patients to treatment.

CONCLUSION: It is necessary to continue conducting large-scale clinical studies on modern methods of allergen-specific immunotherapy in patients with food allergies to form standardized therapy protocols.

Keywords: food allergy; treatment; immunotherapy; allergen-specific immunotherapy; ASIT.

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List of abbreviations

AIT: allergen immunotherapy
CMP: cow's milk protein
OIT: oral immunotherapy
FA: food allergy
SCIT: subcutaneous immunotherapy
SLIT: sublingual immunotherapy
EPIT: epicutaneous immunotherapy

BACKGROUND

Food allergy (FA) remains a challenge for modern clinical medicine. FA prevalence has been increasing and is clinically characterized by severe reactions, including anaphylactic shock [1, 2]. The global prevalence of FA is ~4% in children and 1% in adults and had increased significantly over the last decades [1]. FA is cost-intensive for both the healthcare system and patient [3]. Additionally, FA causes to the need to comply with elimination measures, and also reduces the quality of life of patients and family members [1].

Currently, no standard FA treatment that can induce lifelong tolerance to food triggers and cure FA has been established. The main treatment for FA is strict elimination diet with exclusion of trigger allergens [4]. However, this approach is challenging owing to hidden allergens in food products. Current data on the early introduction of allergenic foods to infants to reduce FA incidence have no standardized treatment protocols and cannot be widely implemented in the routine clinical practice [4]. Thus, the scientific community should develop effective and safe therapeutic approaches for FA treatment.

Allergen immunotherapy (AIT) is used to treat IgE-mediated allergic diseases, including FA. AIT has a wide range of effects on the immune system. Particularly, AIT reduces the activation of mast cells and eosinophils, promotes the formation of allergen-specific regulatory T-cells and B-cells, and changes the IgE and IgG4 levels [5]. Immunotherapy with food allergens includes the administration of increasing doses of a specific food to achieve a maintenance dose for desensitization [2, 5, 6]. To study the treatment of FA, researchers have evaluated the main AIT methods: oral (OIT), sublingual, subcutaneous, and epicutaneous immunotherapy (EPIT) [5].

Therefore, **this systematic review aimed** to analyze the effectiveness and safety of modern AIT methods in the treatment of FA using clinical studies published in the last 3 years.

MATERIALS AND METHODS

The search and analysis of scientific publications was conducted using resource cataloging of biomedical scientific literature: PubMed and eLibrary. The present study includes original studies published between January 1, 2020, and December 31, 2022.

Analysis was performed using the following steps. First, publications were searched using keywords and titles. The search in PubMed and eLibrary was performed with the keywords "food allergy" and "treatment." At this stage, 779 articles from PubMed and 124 articles from eLibrary were analyzed. Second, the publications obtained during the initial search were analyzed, and articles (*n*=861) that did not meet the selection criteria and duplicates were excluded. Third, the full text of 42 publications was analyzed. During this stage, review publications and retrospective studies were excluded, and 15 publications containing data from clinical studies that met the inclusion criteria were included in the review.

RESULTS

Characteristics of studies

Randomized double placebo-controlled studies (*n*=4), open randomized studies (*n*=8), and meta-analyses of previously performed studies (*n*=3) were included in the review, according to the methodology. Most studies were performed on pediatric populations, with one study recruiting a group of adults. Samples included different ethnic groups, both European and Asian.

The reviewed studies examined current AIT strategies for a range of culprit allergens, such as peanuts (*n*=10), cow's milk protein (*n*=2), chicken egg white (*n*=4), and wheat (*n*=1). The observation period for patients receiving AIT lasted for 6 months to 5 years.

The studies included in the review examined current approaches to immunotherapy, including oral (*n*=10) and epicutaneous (cutaneous) (*n*=5) immunotherapy.

Oral immunotherapy

OIT studies are based on the concept that constant intake of allergens in small doses over a long period of time results in the development of tolerance to these allergens [1]. Thus, tolerance induction in OIT is associated with antigen-specific suppression of cellular or antibody immune response after antigen exposure through oral administration [7]. Early antigen exposure through the gastrointestinal tract decreases reactivity to local or systemic exposure to allergens [8].

OIT is not widely implemented in the treatment of FA in several countries, despite the extended period of its evaluation [9]. Currently, a single OIT drug is officially

registered globally. This drug targets peanut allergy and has proven to be successful in double placebo-controlled studies. Twelve months after the treatment initiation, 67.2% of recipients tolerated 600 mg of peanut protein in the OIT group and 4% in the placebo group [1].

The effectiveness and safety of this treatment method has been actively studied, introducing OIT into clinical practice [10].

Food allergy to peanuts

Peanuts remain one of the common causes of allergic reactions in patients with FA worldwide. Sensitization to peanuts usually develops in childhood and persists into adulthood [11, 12]. Peanuts are the main cause of severe anaphylactic reactions [11, 13, 14].

OIT had been proven to be effective for peanut allergy treatment. A specialized powder containing peanut protein was used to study OIT with peanut allergen [15, 16]. Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE), a placebo-controlled randomized clinical trial, was performed in patients aged 4–55 years (*n*=551). The study has shown the safety and effectiveness of the peanut powder AR101 during an observation period of 12 months [15, 16]. Further, 67.2% of participants who received AR101 were able to tolerate ⩾600 mg of AR101 compared to 4% of participants in the placebo group [15]. This drug is the standard oral biologic approved in the United States and Europe and registered by the US Food and Drug Administration (FDA) for reduction of severity of allergic reactions in patients with peanut allergy [16, 17].

An open-label follow-on study (PALISADE follow-on study) examined the effects of long-term maintenance dose (300 mg/day) of AR101 in children aged 4–17 years. Two dosage regimens were studied: 1.5 years (group A, *n*=110) and 2 years (group B, *n*=32). Novel approaches to allergen dosing regimens that are highly safe and more effective in achieving tolerance have been explored. Daily use of a maintenance dose (300 mg/day) of peanut allergen powder for 1.5 years (group A) or 2 years (group B) resulted in persistent tolerance to 2000 mg of peanuts, followed by desensitization in 48.1% and 80.8% of subjects, respectively. The overall incidence of adverse events decreased throughout the intervention period (from the treatment initiation in PALISADE study and at its end point, in the open-label study after 2.5 and 3 years of follow-up) [16].

A phase III, randomized, double-blind, placebo-controlled study of AR101 examined the effectiveness of maintenance doses of AR101 (300 mg) in children aged 4–17 years with documented peanut allergy. Participants increased their dose of peanut powder from 0.5 mg to a target dose of 300 mg over 40 weeks. Patients were followed up in a subsequent open-label 6-month study, wherein they continued to take a maintenance dose (300 mg) throughout the trial period. During this period, most adverse reactions were assessed as mild or moderate. The most common adverse reactions were gastrointestinal symptoms [18].

In two meta-analyses, the risk of potentially life-threatening reactions during OIT was similar at different stages of treatment, despite the good rates of desensitization. The frequency of epinephrine use was low since the subjects reached long-term treatment phase. In most studies, severe reactions were observed during the first stage of immunotherapy [19, 20]. For example, in a meta-analysis aimed to assess OIT with peanut allergen, adverse reactions requiring epinephrine treatment occurred in 7.6% of participants, with a frequency of 2.0 per 10.000 [19]. Another meta-analysis including 12 randomized trials of OIT with peanut allergen has found that a higher proportion of patients receiving OIT achieved desensitization (OR=12.4; 95% CI, 6.8–22.6) compared with controls. However, an increased risk of anaphylaxis (OR=3.1; 95% CI, 1.8–5.6), epinephrine use, and severe adverse reactions (OR=2.2; 95% CI 1.3–3.8) was noted. The median follow-up duration was 1 year [20].

Food allergy to cow's milk

Cow's milk protein (CMP) allergy is a reproducible reaction to one or more milk proteins, occurring via different immune mechanisms, both IgE-mediated and cell-mediated [21–23]. CMP allergy has a significant impact on the physical and mental health of infants and is thus crucial in pediatric practice [24].

Cow's milk contains proteins from the casein fraction (αs1-, αs2, β- and κ-caseins) and whey protein (α- and β-lactoglobulin), which contain sequential and conformational epitopes [25]. Thermal treatment of cow's milk changes the conformational structure of the protein, which causes a change in the allergenicity of products containing CMP [25]. In a study, more than a half of the children with IgE-mediated allergy to CMP can tolerate thermally processed (baked) milk, which is included in muffins, cakes, and breads [26]. A milk ladder concept has recently appeared in the literature. Milk ladder is an approach wherein products containing CMP are gradually introduced to expand the diet of patients with CMP allergy [25, 27]. An open randomized controlled trial explored the safety, effectiveness of the milk ladder approach and quality of life of patients with CMP allergy. In this study, the value of a single intake of whole cow's milk was assessed in children aged <12 months before introducing baked cow's milk into the diet based on the milk ladder. Before treatment initiation, the first group of patients received a one-time CMP dose of 0.5 mg under the physician's supervision, followed by the introduction of baked milk into the diet at home in accordance with the milk ladder. The control group did not receive a one-time CMP dose before treatment initiation. Patients were observed for 12 months [27]. After 6 months of observation, 73% of children in the first group, compared to 50% of children in the control group, reached level 6 (the upper) of CMP tolerance on the milk ladder. By the 12th month of observation, 65% of patients in the first group, compared to 35% in the control group, had completed the milk ladder (step 12: the introduction of pasteurized cow's

milk into the diet). Furthermore, it was found that a single intake of a low-dose of cow's milk in the presence of a researcher increased the parents' commitment to continue the introduction of dairy products and achieve the final step of the milk ladder. Moreover, the progress made starting with the introduction of baked milk significantly reduced the level of mother's anxiety, which improved the family's overall quality of life [27].

The principle of introducing cow's milk through the milk ladder is gaining popularity in therapy. However, questions regarding the timing of the introduction of dairy products and the possibility of expanding the diet remain. Thus, further evaluation of the safety and effectiveness of various treatment regimens is warranted.

Food allergy to chicken egg

In addition, chicken egg is a common allergen in childhood, and egg allergy can persist into adulthood [23, 28]. Along with peanuts, egg is considered one of the main triggers causing anaphylactic reactions [29]. Egg white is widely included in the modern human diet. Chicken egg allergy significantly reduces the diet diversity and quality of life of patients [28].

An egg contains >30 protein molecules. However, sensitization to each egg protein has different clinical significance, which is associated with different molecular physicochemical properties. The main egg allergens are ovalbumin, conalbumin, ovomucoid, and lysozyme in the egg white and alpha-livetin in the egg yolk. All these proteins have different resistance to temperature and digestive enzymes [30].

A multicenter, randomized, open-label, placebo-controlled study in children aged 3–16 years (*n*=96) has examined the safety and effectiveness of products containing cooked (baked) chicken eggs and compared them with those containing raw egg white powder. Patients who were tolerant to baked chicken eggs but allergic to uncooked chicken eggs were included in the study. The food ingredients were prepared according to pre-developed recipes, with a typical dose of baked chicken egg around 2000 mg (one muffin or 1/3 of a whole egg). The second group received standardized dried egg white powder (pasteurized, raw egg), starting at 0.1 mg; the dose was gradually increased to a target of 2000 mg over 2 years [31]. Adherence to treatment was high in both groups of patients (89.7% and 95.1%, respectively).

Moreover, 11% of patients achieved stable tolerance after receiving baked chicken eggs compared to 42% of patients taking egg powder. Thus, a weak clinical effect of OIT was observed in patients tolerant to processed (baked) egg but sensitive to raw egg. Further, a reduction in egg white-specific IgE levels and in wheal diameter in skin testing were more pronounced in patients taking egg powder [31].

A randomized placebo-controlled study has examined the effect of egg powder on tolerance and desensitization. Children aged 5–18 years with an egg white allergy (*n*=55) were observed for 4 years, and 75% of patients receiving OIT achieved desensitization to egg allergens after 22 months of treatment. At the end of the 4-year protocol, 50% of children achieved stable tolerance to egg white, and 28% achieved desensitization; 95% of patients who achieved stable tolerance did not exclude either chicken eggs or products containing eggs from their diet [32].

Additionally, a non-randomized controlled clinical trial studied Asian children with egg allergy (*n*=113). The effectiveness and safety of "slow" OIT with low doses of egg allergen (from 0.2 g to 5.0 g, the total course dose of protein was 980 mg egg white) was evaluated [33]. A positive effect after 12 months of therapy was achieved in 34.7% of patients receiving egg whites and in 11.1% of controls.

In a study conducted in Iran, patients received low doses of egg white for 6 months. The patients from the group with FA to chicken egg (*n*=8) have developed tolerance to egg white. Additionally, their specific IgE levels and blister diameter after a skin prick test decreased compared with those in the control group [34]. However, the study has significant limitations because of its small sample size (*n*=11).

An egg ladder principle is applied when expanding the diet containing egg protein. Egg ladder includes different levels of heat treatment of egg-containing products and their gradual introduction into the diet [31]. However, there are no standardized approaches to the exact timing of introduction of egg whites into the diet.

Food allergy to wheat

Wheat is one of the widely consumed food grains worldwide because of its widespread occurrence in various climatic zones and its widespread use in the food industry. Wheat is one of the main food triggers in the structure of allergic sensitization [35]. The prevalence of wheat intolerance with IgE-dependent mechanism varies from 0.2% to 4% in different regions [36–38].

A Japanese study has assessed the effectiveness of OIT in patients with wheat anaphylaxis. The effectiveness of low-dose wheat allergen for the treatment of severe wheat allergy was evaluated. The study included 27 children aged 5–18 years with a history of anaphylaxis to wheat and a wheat allergy confirmed by an oral challenge test with 53 mg of wheat protein. In this study, OIT with low doses of wheat (50–75 mg) safely induced immunological changes and provided desensitization, resulting in tolerability of 400 mg of wheat. In addition, the risk of adverse symptoms caused by accidental allergen ingestion was reduced. OIT did not induce severe symptoms and improved the patients' quality of life.

An open-label, non-randomized study of Asian children with wheat allergy (*n*=42) has evaluated the efficacy and safety of low-dose slow-infusion OIT (starting wheat

protein dose from 0.2 g to 5.0 g; cumulative dose, 226 mg). After 1 year of low-dose treatment, the effect was noted in 37.5% of patients in the OIT group and 10% of patients in the control group [33].

Epicutaneous immunotherapy

EPIT is one of modern AIT approaches gaining popularity in FA treatment. This method is based on skin application of the allergen with a patch. The main advantage of EPIT is non-invasive administration of the trigger allergen orally or via injection. In a study in mice, skin-applied peanut antigen induced T-cell tolerance, promoted a shift in the immune response from Th2 to Th1, increased the number of regulatory T-cells, decreased IgE levels, and induced the formation of long-term tolerance [40]. Previous studies have confirmed the effectiveness and safety of EPIT with peanut allergen [41–43].

In a multicenter, randomized, prospective, double-blind, placebo-controlled study, EPIT with a patch (Viaskin Peanut) containing peanut allergen was evaluated in a group of patients aged 4–25 years. Patients were randomized into three treatment groups and followed for 52 weeks: allergen patches with 100 mcg and 250 mcg and placebo patch. On week 53, all participants switched to 250 mg patch regimen for 130 weeks [44]. After 130 weeks of therapy, desensitization occurred in 5% of participants in the placebo group, in 20.8% in the group starting with 100 mg, and in 36% in the group starting with 250 mg and persisted throughout the entire observation period. The median of successfully tolerated dose changed to 11.5 mg, 141.5 mg, and 400 mg, respectively.

Another randomized, multicenter, placebo-controlled, phase III clinical trial examined the safety of EPIT with a patch containing peanut allergen (250 mg dose) in children aged 4–11 years over the period of 6 months. In the study, 72.3% of children had a history of anaphylaxis to peanuts. At least one episode of local skin reaction during treatment was reported by 100% of subjects in the 250 mg group and 83.8% of patients in the placebo group. Moreover, in the study, the same frequency of adverse reactions was observed in all patients, regardless of them having a history of anaphylaxis or not [45]. Further, initiation of therapy at an early age was a predictor of tolerance and desensitization [44, 46, 47].

A high level of adherence to treatment (>90%) was noted in studies on EPIT made in the past 3 years [44, 45, 47, 48]. In addition, EPIT improved the quality of life of patients and their parents. The number of EPIT adverse effects was significantly lower compared to OIT [44, 48]. EPIT remains understudied; however, it has great prospects and warrants further research on the effectiveness and safety to establish treatment standards for actual clinical practice.

CONCLUSIONS

The rapid increase of global FA prevalence requires further clinical studies assessing the effectiveness and safety of modern approaches to FA treatment with a high level of patient adherence to treatment.

Published clinical trials and meta-analyses in cohorts of patients with FA were analyzed. OIT and EPIT showed high efficiency in achieving tolerance and desensitization to food triggers.

In all OIT studies, receiving allergens in low doses caused desensitization and fewer adverse reactions. The analysis revealed a high level of patient adherence to treatment with EPIT.

Certain studies have examined OIT and EPIT, considering various ethnic characteristics in different geographical regions (USA, Japan, and European countries); however, no published clinical studies have been performed in a Russian population. Thus, large-scale clinical studies of OIT or EPIT should be conducted on Russian patients with FA.

ADDITIONAL INFORMATION

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