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REVIEW PAPER/*PRACA POGLĄDOWA*

Food allergies, searching for rescue therapy: a literature review

Alergie pokarmowe – w poszukiwaniu skutecznego leczenia – przegląd piśmiennictwa

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ABSTRACT

Introduction: Food allergy is a severe, potentially life-threatening condition. Its prevalence has increased dramatically in recent years. Complete avoidance of triggered food and usage of rescue medication in case of accidental ingestion is the current standard procedure. However, food allergy immunotherapy, especially oral immunotherapy (OIT) is now recognized as a new active alternative treatment in patients with IgE-mediated food allergy. Introducing this therapy into clinical practice has been a very significant advancement. Many studies show that OIT can lead to protective levels of desensitization in patients with food allergy. Hence, significant questions concerning the treatment remain.

Aim: This literature review aims to provide an overview of continuously developing therapies in food allergy treatment.

Material and methods: The review was designed to assess the data on food allergen immunotherapy (FA-AIT), especially oral immunotherapy (OIT). We searched the following sources: National Library of Medicine PubMed, Google Scholar, Science Direct and Cochrane databases with keywords: food allergy, OIT, immunotherapy, efficacy, guidelines, and Palforzia.

Results: We found 7938 articles. We limited the search to data published in the last 5 years to obtain the latest information. Only one article used to prepare this literature review was published 9 years ago. We excluded duplicates and articles out of topic. Then, we chose meta-analyses, reviews, randomized controlled trials, controlled clinical trials, multicenter studies and guidelines with free full text. We also used Palforzia product characteristics to prepare this article.

Conclusions: Treatment of food allergies is changing. Active treatment is necessary to reduce the burden of food allergies. The efficacy of OIT in desensitization has been confirmed. The transition of oral immunotherapy in peanut allergy to clinical practice has been a significant advancement. However, in some patients, the disadvantages of therapy including mainly mild allergy reactions, long treatment, and high costs of the therapy can overweigh the advantages. When proposing food allergy immunotherapy, a shared decision process

should be implemented. Many issues of food allergy immunotherapy still need to be clarified in coming years to optimize the role of the therapy for food allergy.

KEY WORDS

food allergy, food allergen immunotherapy, oral immunotherapy, Palforzia, desensitization.

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INTRODUCTION

The occurrence of food allergies is increasingly growing [1]. It has become a significant medical problem in the last decades [2]. It applies to 5% of adults and 8% of children in developed countries [3]. Discovering new therapies for this potentially life-threatening condition is a public health priority [2]. The elimination diet is the main method of dealing with food allergies. This method can be difficult and frustrating especially for commonly consumed foods and eating in restaurants. The patients are also trained to use adrenaline as a rescue medication in case of dangerous allergic reactions after accidental exposure. Allergen immunotherapy for food allergies is another alternative option of the treatment being discussed around the world. This therapy is an immunomodulatory intervention for IgE-mediated food allergy. It evolves regular exposure to growing doses of the allergen at regular intervals. It increases the amount of food that the patient can consume at the same time preventing allergic symptoms and finally establishes immune tolerance of food allergens [2].

The most common allergens that cause allergy are: cow's milk, hen's egg, and peanuts [3, 4]. Majority of children (60–80%) spontaneously recover from allergy to cow's milk and eggs, but only 10–20% of children recover from allergy to peanuts [5]. Avoiding food allergens can be very difficult. It reduces the quality of life and in some cases, it can cause anxiety, stress, nutrition deficiencies, or even death. The study shows that accidental exposure to food allergens can be very frequent. It occurs in 12.4–23.5% of allergic children in North America and 41.9% in Japan [5]. Severe reactions occur in one-third of allergic children and can be life-threatening [1]. Food allergy is the main cause of anaphylaxis in children in Europe [5] and incidence is still increasing [4]. For those reasons another treatment option besides the elimination diet is needed.

FORMS OF FOOD ALLERGEN IMMUNOTHERAPY

Various forms of food allergen immunotherapy (FA-AIT) have been tested around the world: subcutaneous immunotherapy (SCIT), oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) are continuously being studied. SCIT involves administering the allergen by injection, OIT involves immediately ingesting the food allergen, SLIT involves keeping the allergen under the tongue and EPIT involves application of the patch containing allergens onto the skin. OIT is the most commonly used and most studied method, due to the best results in desensitization of OIT particularly for cow's milk, hen's egg, and peanut allergies [2]. A typical oral immunotherapy protocol consists of 3 phases: initial dose escalation, up-dosing, and maintenance [6].

EFFICACY

Recently a lot of studies have confirmed desensitization during therapy [2, 7] however, if the administration of the allergen is discontinued the symptoms may return [2]. The studies consider mainly cow's milk, egg, and peanut allergy. Some studies confirm the effectiveness of oral immunotherapy for other foods such as walnut, pecan, cashew nuts [8] and sesame seeds [9]. The primary aim of OIT is the increase of reactivity threshold to prevent patients from life-threatening events caused by accidental ingestion. The final effectiveness of OIT is commonly evaluated in terms of desensitization and sustained unresponsiveness. Desensitization is increasing the reactivity threshold of an allergen allowing the patient to eat the culprit food during the treatment. The other endpoint – sustained unresponsiveness also known as tolerance or post-discontinuation effectiveness – is the possibility to eat any amount of culprit food without any symptoms even a long time after therapy discontinues. The ultimate

goal of FA-AIT is to achieve post-discontinuation effectiveness. The time to reach this purpose for many allergens has not been defined yet. It has not been established in most allergens how long and how often allergic food should be ingested to keep desensitization after therapy [10]. After discontinuation a benefit is confirmed in some patients [11, 12]. The meta-analysis from 2022 shows that peanut oral immunotherapy may induce tolerance of peanuts in children after stopping the therapy. The long-term effectiveness depends on the OIT protocol (the speed of up-dosing, the maintenance dose, dose intervals, the duration of treatment) and allergen ingestion regimes after the discontinuation of OIT. Unfortunately, a complete tolerance in some patients may be impossible to achieve. In comparative studies of OIT and SLIT it was proven that OIT is more effective than SLIT in desensitization [2]. There are no sufficient data to assess effectiveness of other routes of FA-AIT [13]. Taking into consideration multiple food OIT, the time to desensitize is suggested to be only a few months longer than for single food [11].

SAFETY

The safety of the treatment is still being examined. No deaths connected with therapy have been reported [2]. The meta-analysis from 2022 shows that OIT does not increase frequency of mild and severe adverse reactions in peanut allergy, but it may enhance mild adverse reactions to cow's milk and hen's egg allergy. In this study, no increase in anaphylaxis or life-threatening conditions has been reported [13]. Another meta-analysis from 2019 shows that OIT can increase rather than decrease the risk of allergic reactions and anaphylaxis during the treatment [14]. According to the Canadian Society of Allergy and Clinical Immunology (CSACI) guidelines from 2020, patients undergoing OIT will more likely experience allergic reactions than those who avoided triggered food. Although allergic reactions may be more frequent during OIT, anxiety associated with this therapy is manageable. The patients are aware of the adverse reactions risk and are prepared for such situations. This gives the patient a little control. The burden of unexpected reactions is bigger than the burden of expected ones [11]. Standardized strategies and algorithms are needed to improve the safety of the therapy. SLIT and EPIT are associated with a lower risk of significant adverse events than OIT. The safety of SCIT with modified allergens has been not reported yet. Regarding EAACI Guidelines, FA-AIT should be performed in specialized clinical centers with experienced professionals who can manage any complications [2]. Well-tolerated doses, without any allergic reaction, can be later administered at home. However, every dose increase should be performed in a specialist setting. Every patient should be equipped with adrenaline auto-injectors fur use at home and also must know how to recognize an allergic reaction. It seems that there are no differences in safety between administering various types of allergens (e.g. milk and egg) [2]. Recent studies revealed that using anti-IgE – omalizumab can increase the safety of OIT, especially at the beginning of the process [15, 16]. The use of omalizumab with OIT allows for up-dosing more quickly and with fewer allergic side effects. Another option to improve safety is low-dose OIT. It is an effective treatment with a very good safety profile that prevents anaphylactic reactions after incidental ingestions [17]. It can be an option, particularly in the heavily sensitized patients. The efficacy of low-dose OIT is suggested to be similar to OIT [17].

SIDE EFFECTS

There are disadvantages of OIT. In most cases we can observe side effects, usually mild. However, life-threatening conditions such as anaphylaxis also can occur [1]. Meta-analysis suggests that mild and severe allergic reactions can occur more frequently in patients on OIT compared to the patients without therapy [5]. The most common side effects are urticaria, angioedema, itching in the mouth, atopic dermatitis, coughing, wheezing, and rhinitis. Vomiting, diarrhea, abdominal discomfort, and eosinophilic esophagitis are also well-known side effects [13, 18]. It has been reported that the new onset of eosinophilic esophagitis appears in about 2.7% of patients after OIT [4]. Most OIT studies included patients with controlled asthma and excluded patients with uncontrolled asthma. Patients with asthma are suggested to have a higher risk of adverse reactions and some of them may experience a worsening of the illness [11]. The risk of side effects is generally greater in connection with infections, empty stomach, irregular intake, exercises, menses, and insufficient control of allergic rhinitis or asthma.

CONTRAINDICATIONS

The lack of cooperation between the patient and the physician, severe asthma, active malignant neoplasia, pregnancy, active systemic autoimmune disorders, active eosinophilic esophagitis, and other eosinophilic disorders are contraindications for FA-AIT [1, 5]. A history of moderate-to-severe anaphylaxis to food is associated with more side effects, but it is not a contraindication. The patients who have experienced an anaphylaxis reaction require close supervision. Uncontrolled atopic dermatitis, chronic urticaria, systemic or organ-specific autoimmune disorders in remission, mastocytosis, using β-blockers and ACE inhibitors can be relative contraindications [2].

The final decision whether the patient can be treated with food allergen immunotherapy is taken individually.

QUALITY OF LIFE (QOL)

It is expected that patients will be less scared during the therapy after allergen exposure than before. The social life will improve and so the quality of life will be better, which is confirmed by many studies. However, the data are not sufficient to make definite conclusions about the impact of OIT on QoL [19]. The patients less affected by FA at the beginning of the treatment may perceive deterioration in the quality of life, because of adverse effects during the escalation phase [5]. The trend subsequently reverses and the QoL starts to improve as the patient gets more desensitized. The initial difficulties can have an impact on the patient's motivation, compliance and lead to therapy discontinuation. Long-term compliance is a tough challenge. The difficulties that can emerge during the treatment are taste aversion, incorporating the treatment with daily routines, using adrenaline, and side effects [10]. OIT is time-consuming because of the many visits to the clinic necessary to up-dosing. However, the data show that patients do not feel oppressed by the therapy [11].

ALLERGENS

The quality of the allergen is crucial for the treatment. Unfortunately, allergens used in FA-AIT have not been standardized in all allergies yet. Fresh food, powdered or lyophilized products, dilutions of unprocessed food, or crude extracts have been used in recent studies. The variety of products may contain diverse amounts of allergens. There is the only one drug – called Palforzia – used for peanut oral immunotherapy that received the US Food and Drug Administration (FDA) approval in January 2020 [5] and was also authorized for use in the European Union (European Medicines Agency approval) [20].

PALFORZIA

The transition of OIT to clinical practice is a significant advancement in food allergy treatment. Palforzia is a peanut-allergen powder. It is the first product approved by the FDA for the treatment of children from 4–17 years old with peanut allergy [6]. The therapy can be continued in patients after 18 years of age. Palforzia is a powder derived from roasted peanuts packaged in capsules or sachets at varying doses. Instead of swallowing, it is opened and mixed with semisolid food like fruit puree or pudding. Liquids must not be used [12]. It is given according to the first defined protocol. The initial dose escalation phase starts with 0.5 mg, then the dose is increased up to 6 mg. Every dose should be separated by an observation period of 20 to 30 min. During this time patients ought to be carefully observed by a practitioner trained to manage adverse effects, especially anaphylaxis. A patient must be under supervision for at least 60 min after the last dose. The treatment is discontinued if allergic symptoms require medical intervention. The up-dosing phase should begin the day after the initial dose escalation phase. It consists of 11 dose levels and it starts with 3 mg dose. The first dose is administered in a healthcare setting. After that, a patient continues to take it at home until the up-dosing appointment. An up-dosing appointment takes place every 2 weeks. Then a patient receives a higher dose and is carefully observed. The biggest total daily dose is 300 mg and is administered at the 11th dose level [12]. The maintenance is the last phase that requires daily administration of 300 mg of the allergen. This treatment is intended to reduce allergic reactivity to peanuts. The sustained efficacy has been confirmed in patients who completed 12 or 18 months of Palforzia maintenance treatment [12]. Palforzia costs about $800 a month in the United States.

PATIENT'S SELECTION

Confirming the patient's diagnosis and considering the advantages and disadvantages of the treatment are the most important factors before starting OIT. The diagnosis consists of the history of the acute reaction after eating triggered food and the presence of antigen-specific IgE [1]. When the diagnosis is unclear, an oral food challenge is needed. According to the European Academy of Allergy and Clinical Immunology (EAACI), the right age to start the treatment may be around 4–5 years old. This is because of the possibility of developing spontaneous tolerance in younger patients [2]. However, there are several studies suggesting greater efficacy and tolerance of OIT when starting before this age. Spanish and Canadian Society of Allergy and Clinical Immunology guidelines suggest starting the treatment in toddler age because it is best tolerated then. To start therapy patients and their caregivers should understand the principles and risks of the method. They ought to be informed on how to deal with adverse events and be educated on how to inject adrenaline. The guidelines emphasize the importance of shared decisions before starting therapy.

BIOMARKERS IN OIT

The POISED study was conducted to try to define biomarkers that might be useful for identifying the best responsive patients for the therapy in peanut allergy. Some biomarkers identified at baseline may be associ-

ated with an improved success rate. These biomarkers include: lower IgE to Ara h1-3, lower peanut sIgE, lower peanut IgE to IgG4 ratio, and a lower basophil activation test response to peanut. According to the study, a higher ratio of peanut-specific IgE to total IgE, higher peanut-specific IgE, Ara h1 IgE, Ara h2 IgE, and Ara h1 IgE to peanut-specific IgE were significantly associated with an increased frequency of adverse events during active OIT. Patients with high levels of these biomarkers have a lower probability to benefit from treatment because of side effects. In the study, lower Ara h2 IgE and peanut-specific IgE were related to successful therapy. Higher Ara h2 IgE to peanut-specific IgE was associated with a higher risk of therapy failure. On the contrary, gender, age, years with peanut allergy disease, and atopic comorbidity did not enhance the risk of treatment failure. These data need further investigation to find the criteria that might allow us to identify the most and the least responsive patients [21]. Other studies concerning other allergens are required.

FUTURE

There is still an urgent need to define: the dosage and duration of the therapy for allergens other than peanut, standardized products used in therapy, treatment of multiple allergies, effectiveness after discontinuation of the treatment for most allergens, cost-effectiveness, advanced insight into mechanisms of action, identification markers of response, identification of the most suitable candidates for treatment and identification of factors and biomarkers to predict good response to treatment [2, 5]. In the future, allergies to foods other than milk, eggs, and peanuts should be further studied.

There have been many attempts to modify allergen structures to provide safer tolerance induction. The new biological ideas such as anti-IgE, epithelial cytokines, Th1 adjuvants, DNA vaccines, and microbiome interventions are studied [22]. *Lactobacillus rhamnosus* supplementation has been suggested as an adjuvant treatment for OIT in peanut allergy and *Bifidobacterium bifidum* in cow's milk allergy with improved safety outcomes [5]. These studies are promising alternatives, but they are in preclinical and animal studies and so far cannot be clinically used [23].

CONCLUSIONS

Treatment of food allergies is changing. Active treatment is necessary to reduce the burden of food allergies. The efficacy of OIT in desensitization has been confirmed. The transition of oral immunotherapy in peanut allergy to clinical practice has been a significant advancement. However, in some patients, the disadvantages of therapy including mainly mild allergy reactions, long treatment, and high costs of the therapy can overweigh the advantages. When proposing food allergy immunotherapy, a shared decision process should be implemented. Many issues of food allergy immunotherapy still need to be clarified in coming years to optimize the role of the therapy for food allergy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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