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Efficacy and safety of allergen-specific immunotherapy in children

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Abstract

Atopic diseases are one of the most common chronic diseases in children and adolescents. They lead to a significant deterioration in the quality of life of patients and their families. The only strategy for the treatment of atopic diseases that has a disease-modifying effect is allergen-specific immunotherapy. The purpose of this review is to summarize the literature data on the practical aspects of allergen-specific immunotherapy use in children and adolescents with allergic rhinoconjunctivitis and atopic bronchial asthma. An analysis of scientific articles has shown that allergen-specific immunotherapy can reduce the severity of symptoms of allergic rhinoconjunctivitis and/or atopic bronchial asthma and reduce the amount of pharmacotherapy, as well as reduce the risk of bronchial asthma developing in patients with allergic rhinoconjunctivitis. The current evidence of the preventive effect of allergen-specific immunotherapy in relation to the development of new sensitizations in monosensitized patients is unconvincing, and, according to many authors, new randomized clinical trials are needed. According to most experts, allergen-specific immunotherapy should be started in children from 5 years of age in the presence of proven immunoglobulin E-mediated sensitization to one or more allergens, carried out for at least 3 years, using preparations in which the presence of major allergens is documented. At the same time, both subcutaneous and sublingual administration of allergens has comparable effectiveness. Allergen-specific immunotherapy is a safe and well-tolerated treatment for children, but currently there is no generally accepted classification of possible adverse events, as well as a standardized and uniform system for assessing their severity.

Keywords: allergy, allergen-specific immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy, allergic rhinitis, bronchial asthma, review.

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Background

Allergic diseases are among the most common chronic diseases and include atopic dermatitis, bronchial asthma (BA), allergic rhinitis/rhinoconjunctivitis, food allergies, and insect venom allergies. Allergic diseases can cause a significant deterioration in the quality of life of patients and their families and can become a serious burden for patients, healthcare system, and society.

Allergy onset is often in early childhood, continues throughout adulthood, and is characterized by a high degree of comorbidity. Accordingly, therapeutic strategies aimed at the pathological mechanisms of allergic diseases, leading to symptom alleviation, reduction of pharmacotherapy used, and realization of a disease-modifying effect. One such attractive treatment is allergen-specific immunotherapy (ASIT).

ASIT is a unique etiopathogenetic immunomodifying method for the treatment of allergic diseases mediated by immunoglobulin E (IgE), which includes administration of increasing doses of the allergen responsible for the clinical manifestations of the disease [1].

ASIT is aimed at inducing and maintaining immune tolerance [2, 3]. Immune tolerance, a state of active immune response, results in insusceptibility to allergens and a gradual reduction in the symptoms of allergic diseases.

During ASIT, a special immunosuppressive environment is formed as a result of a complicated interaction of immune cells, tissues, and mediators, which is represented by populations of regulatory cells, such as regulatory T cells (Tregs) [4–6], regulatory B cells (Bregs) [7–9], tolerogenic dendritic cells (tDCs) [10–12], regulatory innate lymphoid cells type 2 (ILCregs2s) [13, 14], and natural killers with regulatory functions, which are called regulatory NK cells [15]. All these regulatory cells produce inhibitory cytokines, such as interleukin-10, transforming growth factor, and interleukin-35 [8, 9, 13, 16, 17], which ultimately leads to

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switching of B cells to the synthesis of IgG_4, reduction in the formation of allergen-specific IgE, and suppression of T-cell proliferation and synthesis of interleukins−4, −5, and −13 [18–20].

Given the predominance of inhibitory cytokines and low levels of allergen-specific IgE, the activation threshold of mast cells and basophils increases for their degranulation; consequently, the response to allergens decreases. This effect of ASIT on mast cells and basophils is called early desensitization. Late desensitization involves reduced tissue infiltration by allergic inflammatory cells and their production of inflammatory mediators [4].

Effects of allergen-specific immunotherapy

Two groups of effects from ASIT in allergic diseases can be distinguished, namely, therapeutic and prophylactic. Currently, convincing evidence reveals the clinical efficiency of ASIT in allergic rhinoconjunctivitis (AR), which involves reducing the severity of disease symptoms and consequently the amount of pharmacotherapy required. Thus, when the European Academy of Allergy and Clinical Immunology prepared a guideline on ASIT for AR, a systematic review of studies on this issue was performed. In total, the review included 61 randomized clinical trials (RCTs) of subcutaneous ASIT, which analyzed 6,379 patients, and 71 RCTs, within which 13,679 patients received sublingual ASIT. These RCTs assessed the severity of clinical symptoms and the amount of drug therapy received during ASIT. RCTs used various protocols and products containing tree, grass, and weed pollen allergens, cat and dog dander, and house dust mites. The authors concluded that ASIT reduces effectively the severity of AR clinical manifestations and reduces the amount of drug therapy received [21]. Some evidence reveals that these benefits persist after the discontinuation of ASIT.

The use of ASIT for the treatment of pediatric patients with BA remains a debatable issue because of several factors [22]. First, most data on the clinical efficacy of ASIT in BA are obtained from studies designed to evaluate the efficacy of immunotherapy in AR, where a subset of participants also had atopic BA. Second, meta-analyses of ASIT efficiency in BA revealed multidirectional results because of methodological problems in the integration of data obtained from RCTs, use of various products for ASIT, and lack of standardized approaches to assessing the severity of clinical symptoms and volume of pharmacotherapy received [23–26]. Third, the number of RCTs studying the efficiency of ASIT in BA in pediatric patients is extremely low [26, 27].

In a meta-analysis that was included in the Cochrane database, Normansell et al. evaluated the efficiency of sublingual ASIT in patients with BA based on an analysis of 52 RCTs involving 5,077 patients [26]. Although the general trend indicated a positive effect of sublingual ASIT in patients with BA compared with placebo, the authors concluded that the analysis of RCTs regarding BA symptoms and amount of pharmacotherapy received had very low-quality findings; therefore, an unambiguous conclusion on the positive effect of ASIT on the BA course could not be made.

However, some other RCTs have demonstrated the efficiency of ASIT in reducing the severity of BA symptoms and/or reducing the volume of its therapy [28–30].

In addition, to the well-documented clinical efficacy of ASIT in the treatment of AR, RCT data suggest that ASIT can alter the natural course of respiratory allergy and prevent the occurrence of new BA in pediatric patients with pollen-induced AR [31, 32]. The results of one of these large RCTs on the preventive effect of sublingual ASIT were published relatively recently [3, 32]. The study included a total of 812 pediatric patients aged 5–12 years with seasonal AR. All children included in this RCT had no BA symptoms and/or wheezing episodes. After randomization in a 1:1 ratio, ASIT was initiated with lyophilized tablets containing timothy grass pollen allergen extract for 3 years, followed by another 2 years. This large RCT revealed that ASIT reduced significantly the risk of BA symptoms. In addition, the severity of symptoms of seasonal rhinoconjunctivitis and the amount of pharmacotherapy used to relieve it have significantly decreased.

In addition, to the effect on the natural course of allergic respiratory diseases, ASIT prevents the emergence of new sensitizations. However, some authors believe that the current evidence for this is insufficient [33, 34]. For example, Gabrielle Di Lorenzo et al. conducted a meta-analysis that included eight RCTs investigating the efficiency of ASIT in reducing the risk of the development of new sensitizations in pediatric patients' monosensitized to house dust mites allergens. In this review, which combined the treatment results of 721 pediatric patients with BA, 330 of them received subcutaneous ASIT with house dust mite allergens, and 331 patients received only pharmacotherapy [33]. The authors concluded that the analyzed RCTs had insufficiently high quality, which led to inconsistent results and insufficient credibility of the preventive effect of ASIT on the emergence of new sensitizations. Danilo Di Bona et al. drew similar conclusions following a systematic review of 18 RCTs involving 1,049 pediatric patients and 10,057 adults who received subcutaneous or sublingual ASIT against house dust mites and pollen from trees, grasses, and weeds [34].

The authors stated the need for more high-quality RCTs to analyze the preventive effects of ASIT.

Based on the above data, ASIT may reduce the severity of AR and/or BA symptoms and the amount of pharmacotherapy received for respiratory allergy symptoms. ASIT also reduces the risk of BA in patients with AR.

Selection of patients for allergen-specific immunotherapy

Current international clinical guidelines recommend including ASIT in the treatment of pediatric patients with AR with or without BA in the presence of proven IgE-mediated sensitization to one or more clinically significant allergens [22, 35–38]. When deciding whether to perform ASIT, important factors such as the preferences of the child and/or caregiver, ability to adhere to the treatment plan, severity of symptoms of an allergic disease, need for pharmacotherapy, efficiency of elimination measures, and presence or absence of BA must be considered.

From the standpoint of indications for ASIT and the appropriateness of using this treatment method, the severity of AR symptoms is a decisive aspect. According to the ARIA[1] classification [39, 40], ASIT is currently recommended for patients with moderate-to-severe AR. However, ASIT can be also a treatment option in patients with mild AR to prevent the onset of BA and/or new sensitizations [39–41].

The most important parameters for assessing the severity of BA include the need for additional visits to the doctor, calls for emergency medical care, response to pharmacotherapy, efficiency of measures to prevent exposure to cause-significant allergens, and recurrence of symptoms of allergic disease that impairs the child's daily living activities (attendance at school and sporting activities) and the quality of sleep [22].

ASIT should be also considered a treatment option for patients who experience frequent and/or severe drug side effects or who wish to avoid long-term pharmacotherapy.

Before initiating ASIT, any relative or absolute contraindications should be carefully assessed [22, 42]. Absolute contraindications for ASIT include uncontrolled severe BA, active severe systemic autoimmune disease, active malignancy, and poor adherence to therapy. Relative contraindications include partially controlled BA, β-blocker therapy, systemic autoimmune disease in remission, severe mental disorder, immunodeficiency, and serious systemic reaction during ASIT. Additional contraindications for sublingual ASIT include persistent damage to the oral mucosa, persistent periodontal disease, open wounds in the oral cavity, recent tooth extraction, other surgical procedures in the oral cavity, gingivitis accompanied by bleeding gums, and severe inflammatory diseases of the oral mucosa, for example, lichen ruber planus and mycoses.

Choice of drugs for allergen-specific immunotherapy

A prerequisite for the correct selection of drugs for ASIT is the identification of the symptom-causing allergen(s). Accordingly, first-line tests are usually employed in routine clinical practice, which includes skin prick tests and measurement of the levels of allergen-specific IgE. However, in patients with polysensitizaton, first-line diagnostic tests may not be sufficient to identify the key allergen. In these cases, molecular allergodiagnosis methods can help distinguish primary sensitization from cross-reactions and select correctly the allergen for ASIT [43–47].

According to modern concepts, allergens for ASIT are drugs that can cause specific acquired changes in the immunological response to a sensitizing agent and are manufactured industrially. Their sale requires authorization in accordance with the procedures established for all drugs after RCTs [48, 49].

In ASIT preparations, the presence of major allergens must be documented by quantitative methods such as radioimmunoassay, enzyme immunoassay, radial immunodiffusion, and immunoelectrophoresis. Preparations contain 5–20 μg of allergens for subcutaneous ASIT and 15–187 μg for sublingual ASIT [50]. In pediatric practice, water-salt extracts of allergens, modified allergens, and sublingual allergens are usually used, which are produced in the form of drops, instant sublingual tablets, and lyophilisate tablets.

Allergens for ASIT can be modified chemically or physically to reduce the drug allergenicity for ASIT while maintaining immunogenicity. Chemical modification is performed by treating allergens with binding molecules such as formaldehyde, glutaraldehyde, and alginate or by replacing one functional group of the allergen with another, such as potassium cyanate. Chemically modified extracts of allergens are called allergoids. Physical modification involves the adsorption of allergens on tyrosine, suspension of calcium phosphate or aluminum hydroxide, and alginate [48, 51].

Allergen-specific immunotherapy in pediatric practice

Traditionally, in pediatric practice, subcutaneous and sublingual methods of ASIT are used. Sub-

[1] ARIA, allergic rhinitis and its impact on asthma.

cutaneous ASIT involves weekly escalating injections of the allergen(s), followed by maintenance injections for at least 3 years [22, 38]. In sublingual ASIT, the patient takes drops or tablets daily by placing them under the tongue [37, 38].

The efficiency of these ASIT methods has been confirmed in several clinical studies. Subcutaneous ASIT is effective in patients with AR caused by grass pollen and house dust mite allergens, resulting in the reduction of the severity of disease symptoms, need for antiallergic drugs, and improvement in the quality of life of patients [22, 52]. Similar results have been obtained with the use of subcutaneous ASIT in the treatment of allergic BA; however, this method was more effective in seasonal BA than in persistent asthma [52, 53].

RCTs have also demonstrated the long-term clinical benefit of subcutaneous ASIT. Thus, the severity of clinical symptoms and consumption of drugs for their relief remained low for at least 3 years after subcutaneous ASIT [54, 55]. In addition, a prospective RCT conducted in pediatric patients with AR showed that subcutaneous ASIT can prevent the occurrence of BA and new sensitizations [30]. Despite its proven efficacy, subcutaneous ASIT is associated with poor compliance, with only 25% of patients completing the 3-year course because of the inconvenience associated with injections and treatment costs [56].

Sublingual ASIT has been developed as an alternative to subcutaneous ASIT, particularly in pediatric patients. Numerous RCTs have evaluated the efficiency of sublingual ASIT and showed that this method also leads to a reduction in the severity of symptoms of an allergic disease and amount of pharmacotherapy [57–62].

In pediatric practice, three RCTs have directly compared the efficacy and safety of subcutaneous and sublingual ASIT with house dust mite allergens in pediatric patients with BA with or without AR [2, 63]. These studies have revealed that after 3 years of both ASIT methods, the severity of respiratory allergy symptoms and the need for pharmacotherapy decreased.

Thus, when choosing the ASIT method (sublingual or subcutaneous), factors such as the availability of ASIT drugs, treatment cost, safety of various ASIT methods for pediatric patients, ease of use, and personal preferences of the patient and parents must be considered.

Initiation of allergen-specific immunotherapy in pediatric patients

According to numerous RCTs, ASIT is the only treatment method for allergic diseases that leads to a decrease in symptom severity, need for pharmacotherapy, risk of developing BA in patients with AR, and new sensitizations in patients with monosensitization. Given the potential of ASIT to alter the natural disease course, ASIT must be initiated during childhood when BA is either absent or less severe, and there is only one or a few sensitizations [22, 64].

Modern international regulatory documents recommend stating ASIT at the age of 5 years, primarily for safety reasons. Young children cannot accurately describe subjective symptoms, such as itching of the skin and mucous membranes, nausea, dysphagia, headache, dizziness, and shortness of breath; thus, the risk of the onset of adverse reactions, both local and systemic, may be missed. In this regard, European experts believe that in children aged <5 years, ASIT can be considered a treatment method on a limited and individual basis [22, 35–39].

The current federal clinical guidelines for ASIT and the Consensus Document of the Association of Paediatric Allergists and Immunologists of Russia "Allergen-Specific Immunotherapy in Children" specify that ASIT should be started from the age of 5 years, which, in addition to practical considerations, has a legal justification. As in Russia, no medicinal allergen preparations were approved for use in children aged <5 years [1, 64].

Duration of allergen-specific immunotherapy

Modern international guidelines recommended an ASIT duration of at least 3 years [21, 22, 35–39, 64]. Thus, Arroabarren et al. demonstrated comparable efficiency of ASIT with house dust mite allergens in patients with AR for 3 and 5 years [65].

On treatment initiation and the patient has reached a maintenance dose, the efficiency of ASIT should be assessed, and whether there are any side effects, treatment adherence, and possibility of modifying the current dosing regimen should be evaluated. Clinical improvement through a decrease in the severity of symptoms of an allergic disease and a decrease in the need for drugs can be expected within the first year of ASIT.

Several reasons underlie the poor or absence of clinical improvement, such as incorrect identification of clinically significant allergens, inadequate allergen dose, very short duration of therapy, and poor adherence to the treatment regimen.

As stated above, the correct identification of the key symptom-causing allergen(s) in an allergic disease is important. Moreover, in patients with polysensitization, the choice of allergens for ASIT may present a certain difficulty. According to current recommendations, either a single allergen or a mixture of homologous allergens from the same family should be selected for ASIT in patients with poly-

sensitization to taxonomically related homologous allergens [35].

Patients who are polysensitized to non-homologous allergens may be advised to either start ASIT with the allergen responsible for most of their allergic disease symptoms or perform ASIT with the two clinically most important allergens.

For mixtures of allergens, current guidelines recommend mixing only homologous allergens that are usually taxonomically related and not including allergens with enzymatic activity, such as house dust mites, in such mixtures [22, 38, 64].

Treatment adherence is another important problem that affects ASIT efficiency. Education of an allergic child and family should be considered the main aspect of increasing adherence to ASIT [66, 67]. The standardization of allergens used in both the diagnostics and treatment of allergic diseases is another factor that can influence significantly the efficiency of ASIT.

Once clinical benefits have been confirmed, ASIT should be continued for at least 3 years. After 3 years of treatment, ASIT can be continued for another ≥2 years, depending on individual treatment outcomes and family consent [22, 51].

After ASIT, some patients experience long-term remission in terms of symptoms of allergic disease, whereas others have a relapse [2, 58, 65]. Unfortunately, at the present stage, no laboratory tests or biomarkers can distinguish patients who will relapse from patients who will have long-term remission [68].

Safety of allergen-specific immunotherapy

Numerous clinical studies have evaluated the safety profile of both subcutaneous and sublingual methods of ASIT [51, 64, 69–71]. Both ASIT methods are safe and well-tolerated treatments in pediatric patients with AR and controlled BA. However, during ASIT, both local and systemic side effects may occur.

Local side effects during subcutaneous ASIT include itching, redness, and swelling at the injection site [21, 63]. In children, local responses in the shoulder area can be bothersome. In the event of such reactions, the injection site can be cooled, and topical glucocorticoids or oral antihistamines can be used. In the case of a pronounced local reaction, when the diameter of the focus of redness and/or edema exceeds 10 cm, the possibility of changing the mode of further subcutaneous ASIT should be considered [21, 22].

Local side effects during sublingual ASIT are quite common, which include itching, swelling, paresthesia in the mouth, and swelling of the lips [62, 72].

Systemic side effects of ASIT are manifested as generalized urticaria, angioedema, acute bronchospasm, abdominal pain, diarrhea, and anaphylaxis. Based on a prospective survey of physicians, Rodriguez Del Rio et al. conducted a large-scale clinical study of systemic adverse reactions during ASIT in children and adolescents [73].

A total of 19,699 subcutaneous doses of allergen extracts and 131,550 sublingual doses of allergens were administered. In this study, the incidence of systemic adverse reactions during subcutaneous ASIT was 0.11%, 90% of adverse systemic responses occurred during the allergen dose induction phase, and >80% of adverse systemic reactions developed in the first 30 min after the allergen administration.

The incidence of systemic adverse reactions in sublingual ASIT was significantly lower, with 0.004%, whereas 80% of adverse reactions were registered with the use of drops [73, 74]. Such a significant difference in the frequency of systemic adverse reactions during subcutaneous and sublingual ASIT can be due to the amount of immunologically active allergen.

Although the total amount of allergen in a sublingual ASIT formulation is higher than the doses used for subcutaneous ASIT, allergens administered sublingually are diluted and washed out with saliva, resulting in much less actual amount of allergen, which has penetrated the oral mucosa and is recognized by the antigen-presenting cells, than the initially introduced amounts [75]. Conversely, dendritic cells in the oral mucosa were more tolerogenic than those in the skin [76, 77].

However, at present, no classification of adverse events during ASIT and no standardized and homogeneous system are generally accepted for the assessment of their severity. This becomes a significant limiting factor in the reporting of adverse events in various clinical trials and influences their prevalence rates during ASIT. However, Passalacqua et al. proposed a classification of adverse events in both routes of allergen administration and options for assessing their severity (Tables 1 and 2) [78, 79].

To minimize the probability of side effects during ASIT, the following rules must be observed.

1. ASIT must not be used in exacerbated BA, urticaria, atopic dermatitis, and severe exacerbation of AR.

2. The allergen dose must be adjusted, or ASIT must be temporarily discontinued in the case of systemic reactions such as BA, urticaria, or rhinitis.

3. ASIT must be terminated in the case of a confirmed anaphylactic reaction.

4. ASIT must not be started during the blossom season (when there is a risk of symptom exacerba-

Table 1. Evaluation of the severity of local side effects during sublingual allergen-specific immunotherapy (ASIT)

Characteristics	Mild	Moderate	Severe
Itching, swelling of the mouth, tongue, and lips; throat irritation, rhinorrhea, abdominal pain, heartburn, vomiting, staphyloedema	No discomfort; does not require treatment, and cessation of ASIT	Causes discomfort, requires symptomatic therapy, and no need to stop ASIT	Causes discomfort, requires symptomatic therapy, and cessation of ASIT

Note: ASIT, allergen-specific immunotherapy.

Table 2. Evaluation of the severity of systemic side effects during allergen-specific immunotherapy

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms and signs from one organ or system. Skin: generalized itching, urticaria, hyperemia, or angioedema (except for the larynx). Respiratory symptoms: rhinitis and cough. Conjunctivitis	Symptoms and signs from one organ or system. Respiratory: asthma attacks, wheezing cough, chest-compressing pain, shortness of breath (dyspnea), FEV_1 decrease by 40%, and positive response to emergency bronchodilators. Gastrointestinal symptoms: abdominal cramping, vomiting, diarrhea. Uterine spasm	Bronchial asthma symptoms (decrease in FEV_1 or PEF by >40%), no response to emergency bronchodilators, or swelling of the larynx, uvula, and tongue with or without stridor	Respiratory failure with or without loss of consciousness, or arterial hypotension with or without loss of consciousness	Patient death

Note: FEV_1, forced expiratory volume per 1 second; PEF, peak expiratory flow.

tion). However, a study reported that ASIT initiation during the blossom season does not increase the risk of adverse events [11].

5. The allergen dose must be temporarily adjusted during peak blossom season if symptoms of allergic disease worsen.

6. Subcutaneous ASIT must be performed by a trained physician/nurse, and the patient should be followed up closely for at least 30 min after the injection.

7. For subcutaneous ASIT, the allergen dose should be temporarily adjusted in the case of the occurrence of granulomas at the injection site.

8. In the presence of any ulcers in the mouth or dental procedures and manipulations, sublingual ASIT should be temporarily discontinued.

9. Patients and their parents should be provided with full and clear information about the rules for self-administration of drugs for sublingual ASIT; however, the initial drug administration should be performed in a medical institution under the supervision of a physician.

Conclusion

ASIT is a unique etiopathogenetic therapeutic strategy for allergic diseases, which aimed at reducing the severity of the disease symptoms and decreasing the use of necessary pharmacotherapy. In addition, ASIT has a proven disease-modifying effect and can prevent the progression of respiratory allergies and emergence of new types of sensitization.

ASIT is currently indicated primarily for children and adolescents with moderate-to-severe AR/rhinoconjunctivitis with or without BA, in which symptoms interfere with daily living activities or sleep despite regular and appropriate pharmacotherapy and/or an allergen-avoidance strategy. The documented IgE-mediated mechanism of allergy underlying the allergic disease is an important aspect.

For ASIT, registered medicinal products containing sufficient doses of major allergens, properly standardized, should be used. In addition, the efficacy and safety of these drugs must be proven in RCTs. The decision to start ASIT depends on various factors. ASIT must be combined with pharmacotherapy and performed for at least 3 years.

At present, both subcutaneous and sublingual allergen administration can be used in pediatric practice. Moreover, evidence on the preferential use of one method of introducing the allergen over another is not convincing. However, significant advantages of sublingual ASIT include a higher safety profile and an easier route of administration that does not require a doctor or other qualified medical professional, except for the administration of the initial dose of the drug. ASIT is a safe treatment method, and in the vast majority of cases, it is well tolerated by pediatric and adolescent patients.

In recent decades, extensive clinical and scientific research has been conducted on various aspects of ASIT. However, despite significant progress, many questions remain unresolved, par-

ticularly in pediatric practice. These include the following:

– discovery of new biomarkers of allergic inflammation, which will help determine better the disease mechanisms and optimize significantly the selection of patients for whom ASIT will be most effective.

– development of new hypoallergenic, but immunogenic peptides with high efficiency and a limited potential for side effects.

– development of strategies for the use of ASIT to prevent the development of a new allergic disease in different populations and at different life stages.

In addition, issues of harmonizing the design of RCTs on ASIT must be further elaborated. At present, comparing the results of individual studies is extremely difficult because of the heterogeneity of the studied populations, drugs used for ASIT and protocols for their administration, and methods for evaluating the results of this type of treatment. In addition, the description and classification of side effects vary significantly in different studies, and the overall quality of life of patients is not assessed. Therefore, eliminating gaps in the evidence base of ASIT is an important aspect in the development of personalized treatment strategies for patients with allergic diseases.

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