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Allergen-specific immunotherapy in children. Standardization of approaches to assessing the effectiveness

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The article is concerned with the issue of a standardized approach to determining the effectiveness of allergen-specific therapy (AST) in children. AST has a special role in treating allergy: only this method can induce clinical and immunological tolerance to the cause-significant allergen; is safe enough and highly effective; reduces the duration of acute conditions; reduces the necessity for both basic therapy medicines and additional symptomatic therapy; is capable of preventing the progression of allergic diseases by reducing the sensibility spectre and the formation of bronchial asthma in those suffering from allegic rhinitis; improves the control over the disease and has a positive effect on the patient's and his family quality of life. At the moment evaluating the effectiveness of medical technologies is one of the most important tasks in medicine while the effectiveness and safety of any medical intervention should be obtained in accordance with the requirements of evidence-based medicine. In order to determine the effectiveness of AST in children, a combined clinical and pharmaceutical evaluation should be performed and as a second point — determine the patient's life quality and also evaluate the gravity of symptoms according to the visual analogue scale, and to count the number of days with the symptoms and without them.

Key words*: children, allergic rhinitis, allergic rhinoconjunctivitis, allergen-specific immunotherapy, evaluating the effectiveness of medical intervention, standardized AST evaluation.*

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INTRODUCTION

In recent decades, there was an upward trend in the prevalence of allergic diseases, which led to the emergence of a sustainable concept of "allergy epidemic". This is confirmed by the annual increase in the number of children suffering from allergic rhinitis (AR). However, different centers' data vary greatly [1].

Thus, according to the International study of asthma and allergies in childhood (ISAAC), the prevalence of AR symptoms on average is 8.5% (1,8-20,4) in 6-7-year-old and 14.6% (1,4-33,3) in 13-14-year-old children [2].

The frequency of AR symptoms in children in the Russian Federation ranges from 18 to 38%. In the age group of up to 5 years, the prevalence of AR is the lowest; the rise of incidence is noted during early school years [3]. According to results of the Russian research conducted in accordance with the protocol of Global Allergy and Asthma European Network (GA_2LEN), the prevalence of the allergic rhinitis symptoms in adolescents of 15-18 years was 34.2%. During in-depth survey of 1/3 of adolescents, the AR diagnose was confirmed in 10.4% of cases, which is significantly higher (up to 20 times) than the official statistics [3].

There is data confirming that the AR presence in children under the age of 5 years is a risk factor for later asthma development (especially in case of sensitization to household and epidermal allergens). In patients with newly diagnosed asthma, in 41.5% of cases (95% confidence interval 20,0-61,3), there is a concomitant AR. Moreover, if the AR therapy is assigned promptly (immediately after diagnosis), the risk of asthma development is relative (3,79; $p < 0,001$) [4].

However, despite the proven intercommunication and influence on bronchial asthma, the AR problem is often given too little attention [4, 5]. As a result, the majority of pediatric patients either do not receive the necessary therapy, or are treated inadequately, randomly taking symptomatic medications or medications that do not meet current recommendations for AR treatment.

The participation of different pathogenetic mechanisms in the implementation of the allergic inflammation causes the common goal of therapeutic approaches - achievement of the disease control [3-5]. The links of the allergic diseases complex treatment's composite chain, besides adequate basic treatment and immunological tolerance, consist of preventive measures and elimination of triggers impact. Herewith the choice of drug therapy can be both focused at the blockade of certain key inflammation mediators, and to be caused by a broad spectrum of anti-inflammatory action, disconnecting the chain of cytokine activation, that reinforce and support allergic reactions [3-5].

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Characteristics. There is no doubt that allergen-specific immunotherapy (ASIT) takes special place in the treatment of allergy. ASIT is capable of inducing clinical and immunological tolerance to the cause-significant allergen. ASIT has a long efficiency; is capable of preventing the progression of allergic diseases, reducing the likelihood of the sensitization specter spreading and of the asthma formation in patients with AR and conjunctivitis, and also improves the disease control [3-5]. ASIT also has positive influence on the life quality of the patient and his/her family [3-5].

Today, ASIT is one of the most effective treatment methods for AR, which is confirmed by numerous randomized double-blind placebo-controlled clinical studies. This is the only pathogenetic etiotropic publicly available immunomodulatory therapy for patients suffering from allergic diseases caused by IgE-mediated immune inflammation [3-7].

Conditions of the ASIT appointing is the presence of clear evidences of a link between the allergen exposure, symptoms of the disease, and IgE-dependent mechanism (the results of skin tests and / or level of specific IgE of 2 and above reaction class), subject to all the elimination measures, without exacerbation of comorbidities [3-7].

ASIT classification. ASIT can be pre-season, pre-season-seasonal, and year-round. There are injecting (subcutaneous, when the allergen is injected subcutaneously to the shoulder) and non-

injecting (sublingual, when the allergen dissolves in the sublingual region; or oral, when the allergen is swallowed) ASIT methods [6, 7].

ASIT **maintaining protocol** includes two stages:

1) reaching the maximum therapeutic dose (dose escalation phase);

2) maintenance therapy (the main treatment phase).

ASIT is **contraindicated** in the following cases:

- Severe immunopathological conditions and immunodeficiencies;
- oncological diseases;
- Severe mental disorders;
- Treatment with β-blockers, including topical forms;
- Receiving monoamine oxidase inhibitors in combination with sympathomimetics;
- Exacerbation of any concomitant disease;
- Any intercurrent diseases in the acute stage;
- Vaccination (at dose escalation phase of ASIT).

Temporary contraindications for ASIT are:

- Exacerbation of underlying disease;
- Exacerbation of any concomitant disease;
- Any intercurrent diseases in the acute stage;
- Vaccination.

Immunization under ASIT. The issue of active immunization in long-term ASIT conditions is especially important for pediatric patients. Of course, it is desirable to carry out routine vaccination 1 month before the ASIT or, if possible, after the end of treatment [7].

When indicated, vaccination is carried out at the supporting (main) treatment phase under the following conditions:

- Not earlier than 7-10 days after the allergen injection;
- Regular injection of the allergen is carried out not earlier than 3 weeks after vaccination.

Vaccination is not carried out in case of injecting ASIT during the dose escalation phase [7]. When non-injecting (sublingual) ASIT, for active immunization, allergenic drug reception is temporarily interrupted 3 days prior to the proposed vaccination, on the day of vaccination and for 10-14 days after the preventive vaccination.

Furthermore, during sublingual ASIT, you should remember the additional temporary contraindications, which are [7]:

- Damage and injuries of the oral mucosa;
- Persistent ulcers and erosion;
- Periodontal disease;
- A recent tooth extraction and other surgical procedures in the oral cavity;
- Severe inflammatory diseases of the oral mucosa (lichen planus, fungal infections, etc.).

Clinical results. During the period of ASIT use, we accumulated a long experience in both adult patients and in children, which allows to consider this method safe enough and highly effective [3-7]. ASIT reduces the duration of exacerbations, lowers the need for not only preparations of basic therapy but also for additional symptomatic therapy. ASIT use can significantly reduce the severity of clinical symptoms with natural allergen exposure, and prevent the transformation of AR in asthma and increase the sensitization spectrum [3-7]. By acting on both early and late allergic response phases, ASIT leads to inhibition of not only the allergen-specific reaction but also of tissue hyperreactivity, manifesting itself in increased sensitivity to the allergy mediator - histamine. The suppression of effector cells migration in the allergic inflammation zone leads to generation of regulatory T-lymphocytes, which promotes the induction of immunological tolerance, which is manifested in the proliferative and cytokine response decrease in answer to cause-significant allergens exposure.

Currently, there is a huge amount of both researches conducted on the protocol of blind randomization with placebo-control, and long-term observation studies using various agents and methods of injection. However, the difficulty is the lack of a common methodological approach to

the ASIT efficiency evaluation [8]. A variety of approaches to address this issue in both adults and children patients is being discussed. The world's leading professional associations and agencies (WAO, EAACI, FDA, IMEA), and expert communities are discussing the possibility of using different analysis scales of symptoms, quality of life assessment questionnaires, and use of drugs questionnaires. European Academy of Allergology and Clinical Immunology has formed a target group to create a position document on standardization of the ASIT results evaluation (for allergic rhinoconjuctivitis syndrome) [8]. However, not all the criteria in this document, unfortunately, can be widely used in all cases by experts in the regions of the Russian Federation - as a consequence of both regional (mainly linguistic) and age features of patients. There is no doubt that in randomized studies and observations in real life conditions, it is essential to use a unified methodological approach. Therefore, it is urgent to develop a unified algorithm that takes into account the particular patient population's features.

Today, the clinical results of conducted ASIT can be evaluated using the following criteria [8]:

- Overall assessment of symptoms;
- Evaluation of drugs used;
- Combined clinical and pharmacotherapeutic evaluation;
- Assessment of the patient's life quality at the background of ASIT;
- Assessment of the symptoms severity on a visual analog scale (VAS);
- The number (count) of days without symptoms and exacerbation days;
- Overall assessment and satisfaction of patients;
- The rhinitis symptoms control;
- Provocation tests with allergens.

Table 1. Symptoms evaluation

Score	Symptoms	Score	Symptoms
Nasal		0	No
0−3	Itchiness	1	Mild (symptom is present, but is minimal; easily tolerated)
0−3	Sneezing		
0−3	Coryza	2	
0−3	Nasal obstruction	3	Moderate (sign / symptom of medium heaviness that worries; tolerable)
Ocular			Severe (sign / symptom that is hard to tolerate; impairs the quality of life and / or sleep)
0−3	Itchiness / Red eyes		
0−3	Lacrimation		
Average daily score = [(0−3) + (0−3) + (0−3) + (0−3) + (0−3) + (0−3)] / 6			

OVERALL SYMPTOMATOLOGY ASSESSMENT

Clinical symptoms severity assessment

Allergic rhinoconjunctivitis, or rhinoconjunctivitis syndrome (RCS), is manifested by a combination of ocular and nasal symptoms [9]. It would be logical to hold the assessment of these symptoms after a qualitative and quantitative cause-significant allergen impact assessment. However, in real life, it is extremely difficult to implement this - the duration and intensity of such effects may vary. For example, in case of pollinosis, the beginning, duration and intensity of the pollen season, depending on weather conditions, is important, while in case of sensitization to domestic allergens, the presence of trigger factor is typically annual [8].

As an evaluation criterion, you can use a *total average RCS symptoms assessment* for the entire period of the allergen exposure. The total average RCS symptoms assessment is calculated by virtue of the daily point counting of symptoms severity for a period of the allergen exposure.

Ocular (itching / irritation / hyperemia, lacrimation) and nasal (itching, sneezing, rhinorrhea, nasal congestion) manifestations of RCS are estimated separately [8, 10].

The severity of each symptom is evaluated on a scale from 0 to 3 points [8].

- 0 - no signs, no symptoms;
- 1 - mild symptoms (minimal symptoms; easy to carry);
- 2 - moderate symptoms;
- 3 - severe symptoms (symptoms that are difficult to tolerate; impair the quality of life and / or disturb the sleep; Table.1).

Used pharmacotherapy evaluation

Drugs for symptomatic relief such as antihistamines, topical glucocorticoids or antileukotriene receptor blockers (ALTR) can be appointed to patients with allergic RCS receiving an ASIT course [5-7]. ASIT use reduces the RCS symptomatology, however, so does the use of symptomatic therapy [3]. In that way, the use of drugs affects the extent of symptoms, which should be reflected on the ASIT impact point evaluation [10, 11].

Currently, comparative data on the use of symptomatic treatment for RCS is insufficient, and therefore we propose to use a graded approach:

- 1st stage: systemic and / or local (ocular or nasal) antihistamines of II generation;
- 2nd stage: if stage 1 is insufficient, prescribe intranasal glucocorticoids;
- 3rd stage: if step 2 is insufficient, add ALTR blockers.

This graded approach is based on clinical guidelines on maintaining the allergic rhinitis and rhinoconjunctivitis [4-5] and is conventional by efficiency (activity) of the used drugs [12]. In order to standardize the used pharmacotherapy assessment, we recommend using the total daily dose of the proposed groups of drugs [8].

The estimation of daily drug use, which is used in accordance with the graded approach is conducted (table 2).

Table 2. ***Used drugs evaluation***

Drugs	**Score**
System and / or local (ocular or nasal) antihistamines of II generation	1
Add intranasal corticosteroids if phase 1 is insufficient	2
Add ALTR blockers (or a combination of AH / ALTR) if phase 2 is insufficient	3
Average daily score = 0−3	

Note. *AH — antihistamines, ALTR — antileukotriene receptors*.

Combined (total) clinical and pharmacotherapeutic evaluation

Previously, there was no common approach to the clinical symptoms severity assessment and a simultaneous analysis of the used drugs number [13]. Therefore, the initiation of a balanced system creation is a natural stage of the approach to the ASIT effectiveness evaluation standardization [8]. Total score consists of counting the daily symptomatology scores and the used pharmacotherapy scores. Thus, the combination of clinical and pharmacotherapeutic score is the total evaluation of clinical symptoms severity and used drugs [10-12].

Calculation of the combined clinical and pharmacotherapeutic assessment is based on the summation of the number of points which reflect the severity of 6 daily observable clinical symptoms (4 nasal, and 2ocular). The maximum number of points for each symptom is 3 (on the basis of 18 ÷ 6 = 3). In addition, the outcome scores include the assessment scores of the drugs usage (in accordance with a graded approach).

The overall clinical and pharmacotherapeutic rating: (0 - 3) + (0 - 3) = 0-6.

In case of the year-round allergies' study (e.g., allergic rhinitis caused by sensitization to house dust mites in the absence of ocular manifestations), assessment of symptoms is carried out only by 4 nasal symptoms. Herewith the maximum total score is also 3 (on the basis of of 12 ÷ 4 = 3).

Quality of life evaluation

Quality of life is one of the most important criteria when evaluating therapy effectiveness. To determine it, various questionnaires are developed and widely used [14, 15]. They assess to analyze common, including psychological and social, aspects of the criteria for any patient groups in case of different nosologies, including allergic disease. Appropriate questionnaires for patients suffering from AR are developed and validated. For example, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [16], with the help of which it is possible to assess the challenges faced by patients due to the presence of AR, to determine how the ASIT course can prevent the condition's deterioration and quality of life reduction during the period of the cause-significant allergen exposure. There are variations of this questionnaire for different age groups: for adults [17], a mini-RQLQ [18], for children [19] and adolescents [20]. These questionnaires are widely used in studies of ASIT.

In addition, a questionnaire combining rhinitis and asthma assessment – RHINASTHMA, - is being developed now [21], however, it is still under study [22, 23].

Advantages of quality of life questionnaires are that they are quite sensitive and reflect minimal changes in the course of the disease during therapy. This is extremely actual for the further analysis of the criteria, particularly in clinical studies of new drugs for confirming their efficacy and safety. Another their advantage is that questionnaires are translated into different languages, so that their everyday use does not cause linguistic problems [8].

Visual analogue scale

The visual analog scale is an demonstrative subjective assessment of the overall patient discomfort due to symptoms of allergic RCS. It reflects not only the severity of each symptom, but also the effectiveness of the therapy [24]. This method is widely used in the evaluation of subjective symptoms such as pain [25].

During the psychometric test, the patient and / or his parents (or legal representative) evaluates the RCS symptoms severity on the vertical scale of 10 cm height, where the value 0 corresponds to the symptoms absence, and 10 – to the sharply pronounced manifestations [11]. Thus, an "analog" form of this method differs it from the others and makes possible to conduct a "quantitative" assessment of the disease manifestations severity [24] in comparison with the common symptoms evaluation indexes and results of quality of life questionnaires (RQLQ) [26].

The number of days with / without symptoms

Counting days without symptoms ("good") and days with pronounced clinical manifestations ("poor / heavy") is an auxiliary criterion [27-34]. It is optimal to carry out simultaneously evaluation of the number of days without clinical manifestations, number of days with controlled manifestations, and days without emergency medication in parallel with the symptoms assessment scales that have been listed above [8]. The presence of any 3 of 6 allergic RCS symptoms is considered to be the definition criterion for days with pronounced / severe clinical manifestations [34, 35]. It is easy to analyze this criterion subject to the availability of the data on the overall assessment of symptoms and the results of drugs use analysis.

Patient's satisfaction with treatment

Previously, the patient was asked only one question: "How do you assess your symptoms, compared with the previous season, and how do you feel in general in this season?" [31].

Now, to assess the patients' with allergic rhinitis satisfaction with treatment, a questionnaire containing 16 paragraphs is developed - Satisfaction Scale for Patients Receiving Allergen Immunotherapy (ESPIA) [36]. There is also the Patient Benefit Index (PBI) [37]. It consists of 25

questions which the patient should answer twice - before and after the therapy. Questionnaires give the opportunity to evaluate response to therapy for a particular patient retrospectively; they are simple and quick to use, validated, and correlate with clinical improvement and with quality of life indexes [36-38].

Controlling symptoms

Today, at the stage of treatment, the disease control level is seen as an alternative to the severity of the disease assessment. Questionnaires to assess the severity of allergic rhinitis are developed and validated: Control of Allergic Rhinitis and Asthma Test (CARAT10), Allergic Rhinitis Control Test (ARCT), and Rhinitis Asthma Patient Perspective, (RAPP) [23, 38-41]. Some of these new tests, such as CARAT, are submitted electronically, easy and quick to fill, and take into account the psychometric characteristics. Unfortunately, questionnaires for the control of allergic RCS are not used in the ASIT studies and are not confirmed in the pediatric population.

Provocative tests with allergens

Provocative tests with allergens consist of one or more allergen concentrations topical impact on the skin or mucosa of the target organ (conjunctiva, nose or bronchi), and cause both subjective and objective symptoms of allergic inflammation. In ASIT evaluating studies, different researchers used the following provocative tests: skin test, conjunctival, intranasal and endobronchial provocations, as well as ecological simulation room test. For some of them, methodological approaches were described and efforts to standardize the obtained results were made [8]. However, of all of these, it is possible to use only a skin test as an auxiliary criterion in pediatric practice. Herewith, some studies have shown that the result of the skin test does not always correlate with the ASIT therapeutic action [42-47].

DISCUSSION

Despite the simplicity of use, the final result of the RCS symptoms evaluation by 6 manifestations can be interpreted in different ways in the absence of universal terminology and a common severity gradation scale. Therefore, probability of discrepancies between the conclusions to researches conducted in different organizations, or to inhomogeneous indicators in the ASIT efficiency analysis, is fairly high. In addition, the average daily figures score calculating may lead to underestimation of the condition severity in days when symptoms are less pronounced.

Use of drugs evaluation on the background of ASIT is not only a course effectiveness indicator, but also can be used in pharmacoeconomic analysis. However, it should be remembered to prescribe the drugs not only as required, but in accordance with the graded scheme, and to count the scores during taking each drug. At the same time, children patients may respond differently to the reception of some drug even within the same pharmacotherapeutic group, due to the peculiarities of the drug metabolism and / or individual response to pharmacotherapy.

The benefits of a combined approach are indisputable: parallel evaluation of symptoms and the used drugs will provide an opportunity to carry out a standardized analysis of ASIT in case of allergic RCS and compare the results of clinical trials directly in the future [6].

The study of patients' with allergic RCS receiving ASIT quality of life reflects even minimal changes in the disease course, which is necessary for a complete analysis of the disease clinical manifestations. Weakness of this method is quite high number of questions, as well as the fact that the questionnaire RQLQ evaluates the disease's symptomatology for a short period (1 week), so there is a natural risk of a possible underestimation of the state, as the difficult days can be skipped.

A visual analog scale is used for ASIT studies in both adults [48, 49] and children, but it is not fully validated yet [50, 51] and can be used as an additional criterion. VAS has broad prospects for further applications using the new technologies, especially for remote monitoring of the patient, due to the ease of use and accessibility, and to the absence of discrepancies in the terminology and interpretation of results.

Portable mobile telemedical monitoring tools could help further development of postmarketing studies, especially in the prospective efficacy and safety studies of long-term year-round ASIT schemes in the context of the expressive information and communication technologies development and widespread communication networks use.

Counting the number of days with / without symptoms was implemented previously in a sufficiently large number of studies [27, 30-32, 52, 53], but the results of criteria's "clinically permissible value" are heterogeneous [54]. It should be noted that the prospects of counting "good / bad" days remain the same: according RQLQ, there is a direct correlation between the number of days with severe symptoms and poor quality of life [8].

Currently, the absence of children's versions, translations and validations of questionnaires hamper the determination of patient' satisfaction with treatment. A similar situation is with questionnaires of RCS symptoms control for children. The use of provocative tests to assess the ASIT effectiveness in children is difficult for several reasons, and the skin testing use as a criterion does not have a confirmed correlation with ASIT therapeutic efficacy.

CONCLUSION

Great hopes are now pinned on the development of information and communication technologies, capabilities of telemedicine and clinical decision support systems both in order to assess the medical technology (ASIT), and for simultaneous monitoring of the patient's condition. Their use will help to assess the prevalence and severity of allergic diseases; to determine the phenotypes of patients with allergies; to select from the group and to evaluate patients with uncontrolled severe persistent course of allergy; to monitor patients during the ASIT and after the courses. In addition, the application of these methods will provide an opportunity to make the selection of patients who will response to ASIT with the highest likelihood based on predetermined and proved criteria, which is especially actual from the pharmacoeconomic point of view.

Today, health technology assessment is one of the most important problems in health care. Proof of the efficacy and safety of any medical intervention should be obtained in accordance with EBM requirements. The solution to this crucial task is to develop and implement a common methodological approach to carrying out a standardized assessment of the results obtained in the studies.

There are a number of criteria for allergen-specific immunotherapy that have obtained confirmation of sensitivity and positive correlation, which have been used for over a hundred years. Because of the already mentioned good reasons, not all of them can be used in the pediatric population of patients with allergic RCS.

We should follow a common methodology in assessing the effectiveness of the ASIT course in children with allergic rhinoconjunctivitis syndrome of both seasonal and year-round flow. We should carry out a combined clinical and pharmacotherapeutic assessment as the primary endpoint in the analysis; and as the secondary, we should determine the patient's quality of life, score of the symptoms severity on a visual analog scale, and count the number of days with symptoms or without them.

CONFLICT OF INTEREST

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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