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The efficacy of modern allergy diagnostic and allergen specific immunotherapy in children

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Introduction. Allergy can be named how disease of the XXI century. There are numerous manifestations and treatment options for allergic diseases. Every year the number of patients, especially pediatric turns to doctors with complaints of allergy.

According to the World Allergy Organization (WAO) (2015) 150 million Europeans suffer from allergic diseases, and the beginning of 2025 half-population of Europe will have an allergic pathology. Asthma and allergic rhinitis cause 100 million absences from work and at school. Also of great importance to quality of life, patientes often suffer even beyond episodes of exacerbation. At the same time, European experts insist that the use of advanced cost-effective methods of diagnosis and treatment of allergic diseases can save up to 142 billion euros per year.

And all this despite the fact that the attention of scientists around the world riveted to questions for diagnosis and treatment of allergy for more than 100 years, when John Bostock first described the symptoms of hay fever, which he suffered. And in 1880 William Fares Blakely first applied skin applications pollen in patients with seasonal rhinitis and wrote the first recommendations on the use of this technique, opening a new era in the treatment of allergic diseases and the modern principle laid allergen-specific immunotherapy. (ASIT). I'd like to add that in the last international consensus of allergen-specific immunotherapy (updated document containing allergen-specific immunotherapy: American Academy of Allergy, Asthma and Immunology / European Academy of Allergy and Clinical Immunology / consensus PRACTALL 2013) as a new strategy to conduct treatment is considered an allergen-specific immunotherapy through the skin!

General position of allergen immunotherapy were formulated in 1914, after research, that did L. Freeman J. Noonan: during three years they were administered to patients with hay fever plant extracts and got a successful result in a decrease in sensitivity to antigen almost a year. At that time it contained the following recommendations: the efficacy of treatment depends on the dose of allergen, the interval between injections should not exceed 2 weeks, the dose of antigen excess can lead to systemic reactions.

Today ASIT is the treatment for only IgE-dependent allergic reactions, which has pathogenetic substantiation. Its treatment is focused primarily on the pathogenesis of the disease and not its symptoms. For several decades, scientists studying detail of the pathogenesis ASIT. According to the results of recent studies of children with asthma sublingual immunotherapy of house dust mites leads to lower levels of allergen-specific IgE in serum significantly, and slightly increased levels of allergen-specific IgA, and the level of IgG4 and IgG1 remains unchanged. A number of studies show that the effect of ASIT affects the formation of inflammatory mediators both in early and in late phase allergic responses. ASIT inhibits involvement in allergic reactions (artificially provoked or caused by natural allergen exposure) precisely those cell units, which mediates effector stage allergies. Successfully held ASIT matches with a decrease of eosinophils in nasal mucosa. In addition, evidence that after ASIT noted switching of the T lymphocytes. Changing the response of T lymphocytes to the allergen is observed against the background of a positive clinical effect of holding ASIT and includes a reduction of proliferative response of T cells and IL-4 forming, simultaneous increase levels of IL-10 and TGF-β. Also take place increased expression of receptors for IL-2 (CD25), HLA-DR (antigen presenting cells) and increased content of IL-12, through which support is provided by Th-1-dependent cell response. More than half of patients after ASIT were found a significant increase in mRNA expression of IL-2 and IFN-γ (Th1-cell markers that are involved in launching and maintaining production of IgG antibodies, which belong to blocking

antibodies). Thus, holding the allergen-specific immunotherapy results in switching immune response with IgE to IgG response and provides tolerance of T lymphocytes. ASIT affects for all stages of an allergic response and immunological phase including, resulting in switching immune response from Th2 to Th1, inhibits both early and so late phase allergic responses.

According to different authors clinical efficiency of ASIT is achieved in 70-90 %. Patients marked decrease in activity of disease symptoms, reducing consumption necessary medicines. This therapy leads to lower tissue and organ sensitivity regarding the impact of the allergen reducing nonspecific hyper reactivity tissue, reducing signs of allergic inflammation. The resulting effect lasts for several years. The fundamental difference of pharmacotherapy is to preserve the long-term effect, the effect immediately in all parts of allergic inflammation. The effectiveness of the method ASIT confirmed by numerous randomized double-blind placebo-controlled studies conducted in different ways as parenteral and sublingual, against various allergens (household, pollen, epidermal, insect and molds) [1,6, 8, 9, 10 12, 14].

A very important issue is quality assessment of drugs for allergen-specific diagnostics and therapy. For a long time these drugs are treated mainly through extraction from different raw materials (allergens of plant and animal origin) of active principles which cause allergic reactions. Unfortunately, such water-salt extracts were difficult to control the content of the ballast or excipients, which are not only functionally active, but can, cause negative side effects, thus significantly affecting the quality of the drug. Therefore, one of the most important problems of modern science is to improve treatment methods and standardization of allergenic drugs. At this stage the priority task – is to form the overall World standardization of allergenic drugs strategy, which provides for the mandatory standardization of allergens by following three criteria: total allergenic activity; biological activity; Content in preparation of main and minor allergens in mass units. Today, modern technology allowed to examine and synthesize the structure of allergenic proteins – thus began a new era in allergy. Epoch of molecular (component) diagnostics of allergy (MD). These technologies are actively used in the standardization of allergenic drugs and can determine the number of major and minor allergens [1, 4].

Despite the rather considerable amount of information on the efficacy and safety ASIT, in Ukraine, this method is not widely used by a number of objective and subjective circumstances. However, it is clear that ASIT is quite expensive treatment and it is carried out for a long time (3-5 years). Because a clear verification of diagnosis, selection of patients and identify initial sensitizing allergen or allergens play a significant role in optimizing the treatment process, in including and considering its pharmacy-economic feasibility. In the world the comfortable therapy is crucial for patient, over the last 20 years in Europe actively studied efficacy of sublingual forms ASIT – SLIT [8, 7, 9, 11, 12,13].

So our purposes of study: early diagnostics to determine the population of children, which necessary appointment sublingual immunotherapy (SLIT), improvement of prediction algorithms of efficacy of treatment, assessment of the efficacy and safety mark SLIT in children up to 5 years.

Materials and methods. Based on studies and data analysis of the literature [1, 3, 5] algorithm was proposed for selecting patients for SLIT and monitoring its performance in children with asthma and allergic rhinitis [1, 3, 5, 8, 13]. The first phase included a screening method of allergic skin prick tests. We used diagnostic allergens with controlled major allergen in content – «Diater» (Spain). 260 children aged 26 months. 5 years, including 180 patients with a diagnosis of atopic asthma and 80 children with AR in combination with BA were examined. Patients had high incidence heredity to atopy (74 %) and wheezing-syndrome (57 %) in the first years of life. Payed attention of the relatively low levels of total IgE in children of this age period (average 75.6 IU / ml at age norm of 50 IU / mL), indicating a very approximate its value

Table 1

Clinical characteristics of examined children

Average age, year	4,2 (1,1)
Gender # male (%)	145 (55,8)
Atopic hystory, children(%)	192 (73,8)
Artificial feeding, children (%)	84 (32,3)
Passive smoking, children (%)	34 (13,1)
Cough, children (%)	165 (63,5)
Wheezing, children (%)	57 (21,9)
Rhinitis, children (%)	174 (66,9)
Breathlessness, children (%)	112 (43,1)
IgE , UE\ml	75,6 (11,4)
Eosinophilia in peripheral blood,%	2,3 (1,1)
Eosinophilia (nasal mucus), %	21 (8,9)

Table 2

Character sensitization according to skin prick test

1 group 180 children – BA, (%)	2 group 80 children – з AR, (%)	Inhaled allergens, title
156 (86,7)	71 (88,8)	*Dermatophagoides pteronyssinus*
134 (74,4)	55 (68,8)	*Dermatophagoides farinae*
94 (52,2)	43 (53,8)	Timothy
65 (36,1)	35 (43,8)	Ragweed
86 (47,8)	52 (65)	Birch
32 (17,8)	12 (15)	Molds
56 (31,1)	19 (23,8)	Epidermal allergens (cat)

in the diagnosis of atopy in children Clinical characteristics of patients in Table 1.

Results. The results showed the prevalence polysensitization in children up to 5 years. At the same time, among surveyed children found a high percentage of children sensitized to ragweed pollen. It is characterized by extremely unfavorable situation in Kyiv and region.. Found a relatively high frequency of children during the first years of life with sensitization to epidermal allergens (cat) in patients with asthma and asthma in combination with RA (31 % and 24 % respectively), which was not confirmed in the history of most children. A high proportion of children with significant sensitization to birch pollen were detected. And by cross-reactions to a variety of family trees fagales, which corresponds to these data, a high degree of pollination in Europe and in Ukraine.

For the differential diagnosis of false positive results of skin prick tests (SPT) with the possibility of cross-reactions and improvement prognosis SLIT next step was the use of molecular diagnostics (tab. 3).

Analysis of the results showed a high straight correlation coefficient (2,1> r <8,4) between «positive» skin prick test and sensitization of class 2-5 according to molecular diagnostics in the examined children. Our results of molecular diagnostics formed the basis of our proposed and the following algorithm which allows identifying patients with optimal indications for ASIT and predicting the degree of efficiency (Table. 4).

If data SPT and molecular diagnostics are conformed – the result SLIT will be excellent. If the presence of positive minor allergen expected effect of therapy with the worse prognosis, which is associated with the modern requirements that apply to medicinal extracts (high degree of concentration of major allergens), as described above. And in the absence of major allergens in molecular diagnostics ASIT is considered inappropriate. (tab.4)

The final stage of the study it had its own unique experience (due to the small age of the examined children) of the destination SLIT in patients with AR and asthma who have been diagnosed by skin prick testing and molecular diagnostics and detected with sensitization to house dust mites. A relatively small number of children surveyed, due, above all, the age characteristics and small term study. The analysis of international and Ukrainian literature data that indicate search for specific biomarkers to assess the efficacy ASIT and SLIT is the absence of data based medicine. And also, given the economic situation and international recommendations – evaluating the effectiveness of SLIT was carried out using 5-point visual analogue scale VAS (all) and (up): before treatment; after 4 months of treatment, after 12 months of therapy (tab. 5).

By the beginning of children in both groups were more clinical symptoms of these diseases, and against the background of the reliable SLIT decrease severity of symptoms. Thus, children with AR 1 year after the start

Table 3

Character sensitization according to molecular diagnostics

Patients with MD (selection and prediction SLIT)	Match results SPT and sIgE (%)	sIgE molecules allergens
20 children «+» SPT *D. pteronyssinus*	16 (80)	rDer p1, rDer p 2
20 children «+» SPT *D. pteronyssinus*	1 (5)	rDer p10
20 children «+» SPT Timothy	12 (60)	rPhl p1, rPhl p5b
20 children «+» SPT Ragweed	13 (65)	rAmb1
20 children «+» SPT Birch	9 (45)	rBet v1
10 children «+» SPT children Alternaria alternata	4 (44)	rAlt a1

Table 4

SLIT prediction algorithm

SPT «+»	SPT «+»	SPT«+»/«-»
The major allergen «+»	The major allergen «+»	The major allergen «-»
The minor allergen «-»	The minor allergen «+»	The minor allergen «+»/«-»
HIGH	AVERAGE	LOW

Table 5

Evaluating the effectiveness of sublingual allergen-specific immunotherapy

Symptom	Children I group , n=12			II group(BA+AR), n=6		
	Prior therapy (points)	After 4 months. (points)	After 12 months. (points)	Prior therapy (points)	After 4 months. (points)	After 12 months. (points)
Difficulty nasal breathing	4,01 ± 0,05	0,57 ± 0,1	0,21 ± 0,2	4,18 ± 0,07	0,47 ± 0,12	0,4 ± 0,1
Rhinorrhea	4,11 ± 0,07	0,58 ± 0,2	0,25 ± 0,01	4,18 ± 0,05	0,56 ± 0,4	0,39 ± 0,23
Sneeze	2,67 ± 0,23	0,31 ± 0,2	0,26 ± 0,2	2,74 ± 0,30	0,21 ± 0,2	0,2 ± 0,05
Itching of the nasal mucosa (upper palate)	1,92 ± 0,2	0,8 ± 0,3	0,51 ± 0,25	1,5 ± 0,24	0,67 ± 0,05	0,45 ± 0,24
Discharge from the nose	2,9 ± 0,25	0,3 ± 0,2	0,22 ± 0,1	2,56 ± 0,27	0,32 ± 0,05	0,31 ± 0,2

of SLIT scoring blockade nose improved 19 times, rhinorrhea – 16 times, sneezing – 10.3 times, itching of the nose – in 3,8 times, and rhinorrhea – at 13.2 times. In patients with a combination of the severity of asthma and AR blockade in the nose dropped 10.4 times, rhinorrhea – in 10.7 times, sneezing – at 13.7 times, itching in the nose – in 3,3 times and rhinorrhea – 8 times. In the background of one year SLIT positive effect was observed in 91.2 % of children. Positive effect was noted in 98.2 % of monosensitization patients, polysensitization – in 72.7 % of cases. In 48.3 % of children decreased incidence of acute respiratory disease, decreased number of admissions due to illness in preschool institutions significantly improved quality of life.

Conclusions. The use of molecular diagnostics in practice significantly improves the accuracy of diagnosis and thus providing an optimum result of SLIT and avoids the development of complications.

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