

# THE CLINICAL EFFICACY OF SUBLINGUAL ALLERGEN-SPECIFIC IMMUNOTHERAPY IN CHILDREN AGED 3–5 YEARS

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## Abstract

The aim of this study was to determine the efficacy of sublingual allergen-specific immunotherapy (SLIT) in Ukrainian children younger than 5 years old with allergic rhinitis and bronchial asthma sensitized to house dust mite allergens.

**Material and methods:** Four hundred and fifty children aged 28 months up to 5 years with rhinitis or asthma were examined. One hundred and twenty five children sensitized to house dust mites *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* were included. *In vivo* and *in vitro* tests were made with a standard inhalant allergens panel.

**Results:** The high information value of molecular diagnostics methods applied prior to prescription of the given therapy in children is analyzed. It has been found that in children under 5 sensitized to allergens of house dust mites *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* the application of sublingual allergen-specific immunotherapy therapy allows gaining control over the symptoms of the disease during the first 6 months.

**Conclusion:** The high safety of SLIT in children has been proven. Comparative analysis in the group of patients not receiving SLIT shows a high frequency of symptoms of the disease after “free-of-symptoms interval” against full or partial baseline therapy denial.

**Keywords:** sublingual allergen-specific immunotherapy, children, Diater-Laboratories, bronchial asthma, allergic rhinitis, sensitization, allergens.

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## 1. Introduction

High frequency and advanced growth of the number of allergic diseases all over the world testifies to the need to further study of the problem that seems to have been well-studied. The search of new possibilities to diagnose and the related therapy methods constitutes a strategic task determined by WAO for the next decade. A feature of allergic diseases in children is the transformation of one form into the other. It is well-known that a special feature of the course of allergic diseases is age progression of allergy symptoms known in research literature as “atopic march”. Quite a number of papers are dedicated to the problem of “atopic march” diagnose, treatment and prevention in children [1–4]. However, today clinicians more and more frequently point out a parallel course of several allergic diseases connected with a common total pathogenesis chain. This process is characterized by relative instability of clinical allergy manifestations when some symptoms regularly prevail over the other ones in a child. For instance, there become fewer gastrointestinal allergy manifestations on the background of growth of respiratory disorders. In the pathogeny of allergic inflammation development the sensitization to allergenic molecules constitutes one of the main etiological factors. Therefore, to exercise control over the disease it is often insufficient to use

the means of baseline therapy (antileukotriene, antihistamine ones, iGCS, etc.) [5–7]. Thus, there arises the need to directly influence the degree of patient sensitization, which is already quite a complicated task. Since quite often patients are sensitized to several allergens at the same time. In addition the fact that with age not only the number of significant allergens, but the degree of sensitization to them can be increased is important.

The efficacy of ASIT in the treatment of allergic diseases of adults and children has been proven and it is represented by the results of numerous randomized double-blind placebo-controlled studies which have resulted in the issuance of the corresponding European and international non-binding Perhaps Immunotherapy that is recommended to the patients having allergic bronchial asthma, food allergy and manifestations of insect allergy [8–10]. The treatment of children with the use of immunotherapy methods is discussed in these articles [11, 12]. In addition to the method of sublingual allergen immunotherapy [11, 13–15]. First of all, that is connected to the issues of safety and administration convenience. A wide interest in the new forms of ASIT is also connected to the situation of “rejuvenation” of allergic pathology, i. e. appearance of symptoms characteristic of more advanced stages of disease in early-age children, as well as quick development of poly-sensitization. That is why the study of the issues related to timely prescription of SLIT (as a more comfortable and safe form for children) and the study of its effect on coming to control allergic symptoms and prevention of disease progression can be regarded as one of the units of the strategic direction suggested by WAO.

## 2. Aim

Study the efficacy of application of SLIT in children under 5 with allergic rhinitis (AR) and bronchial asthma (BA), sensitized to domestic house dust mite allergens.

## 3. Material and Methods

Studies with humans and human specimens were performed according to the Declaration of Helsinki and were approved by the local Bioethical Commission of the P. L. Shupyk National Medical Academy of Post-Graduate Education. The all patients' parents gave their informed consent to the study.

The research was carried out during 2013–2015 at the Department of Pediatrics No. 1 of the Shupyk National Medical Academy of Postg-Graduate Education at the premises of the pediatric unit of the National Specialized Hospital for Children “OKHMATDYT” and consultative polyclinic for children “OKHMATDYT”. Four hundred and fifty children aged 28 months up to 5 years were examined, out of whom for further study 125 children sensitized to house dust mites *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* were selected (according to skin prick tests data).

Inclusion criteria:

1. Age from 36 months to 5 years.
2. Clinical diagnosis AR and/or allergic BA in the intermitting or mild form/moderately severe form persisting – controlled, determined following ICONs criteria (2012).
3. Sensitization to domestic allergens of house dust mites D. and/or e.

Exclusion criteria:

1. Severe and/or uncontrolled BA.
2. Children who had undergone treatment with SLIT at the previous stages.
3. Children having counter-indications to SLIT.

SLIT was a viable alternative to the injection route, and its use in the clinical practice in children is justified. 20 patients underwent 2 year course of SLIT with standardized extract of sublingual allergens containing a mixture of house dust mites (*D. pteronyssinus* and *D. farinae*) in the correlation of 1(0,175 HEP):1(0,175 HEP) (Diater, Spain). SLIT was started with 47 children included into the first examination group. The part of 78 patients who refused to take SLIT (remoteness of allergologist and doubt as to the results) – 20 children made up the control group, as they got symptomatic baseline therapy under the corresponding protocols.

Children of the first group (47) underwent SLIT under the following treatment protocol: intake of the drug took place on a daily basis by way of 1 spraying into the sublingual area; and the initial phase made up 6 months (the overall dose for a patient was 1,325–1,425 HEP), the maintenance phase lasted for subsequent 18 months (overall allergen dose was on average 3,900 HEP). After the first drug dose patients stayed in the clinic under the supervision for 40 minutes, for possible adverse effects to be registered, and in further the drug was administered by the child's parents independently, control over possible adverse effects was exercised online by the allergologist.

Over the period of observation 4 visits a year were planned for the patients, and, if necessary – an additional control visit was possible.

Skin prick tests were made following the standard methodology in accordance with the recommendations of the EAACI [16]. Standard inhalant panel included spring arborescent pollen, grass pollen and weed pollen, mold fungi, house dust mites and pet allergens (cat, dog), diagnostic allergen extracts of Diater S. A. (Spain) were used. A solution of histamine hydrochloride in the concentration of 10 mg/ml and, 0.9 % saline solution were used as positive and a negative test controls respectively. Skin reaction was assessed after 15 minutes, a specimen where a 3-mm-papule was formed or where papule exceeded the size of the negative test control by more than 3 mm was considered positive.

Molecular diagnostics using ImmunoCAP (Phadia) to identify major (r Der p1, r Der p 2) and minor allergens (r Der p10) of house dust mites [17, 18] was performed.

The efficacy of SLIT was assessed by a combined visual analogue scale (VAS-all) including 6 indicators characterizing rhinitis and allergic asthma symptoms: nasal obstruction, rhinorrhea, nasal discharge, sneezing, nasal itch and itch of mucosa in the oral pharynx area and cough. A 5-point gradation of VAS-all was accepted: 0 points – “0” symptoms; 1 point – minimum symptoms; 2 points – light symptoms; 3 points – moderately severe symptoms; 4 points – severe symptoms. Taking into account the age of the examined patients, graphic images were suggested – different variants of “smiles” for them as a visualization scale, which were then controlled by their parents. Besides that, during the whole examination period the parents of the patients got recommendations on additional intake of symptomatic drugs, if necessary. Additional drug intake was recorded in a special diary. The need for a daily drug use was assessed in the following way: 2 points – 1 pill (5 mg)/day of anti-histamine drug, 3 points – 2 sprays (400 mkg)/day of nasal inhalant glucocorticosteroids, while 1 pill (4 mg/5 mg) of antileukotriene drug for children with allergic BA was assessed as 5 points. In the case of absence of the need for drug intake – 0 points.

Statistical processing of the results obtained was made using the standard statistical package Statistical for Windows 7.0.

The details of adverse events were collected during the study in a form that recorded all events, irrespective of suspected relationship to the study of medication of the mild, moderate or serious severity.

Such examination enabled to apply a predictive algorithm of the efficacy of SLIT in children (Table 1).

**Table 1**

The predictive algorithm of SLIT in children under 5 years old

Skin prick test +	Skin prick test +	Skin prick test +/-
r Der p1, r Der p 2 +	r Der p1, r Der p 2 +	r Der p1, r Der p 2 –
r Der p10 –	r Der p10 +	r Der p10 +/-
HIGH	MIDDLE	LOW

## 5. Results

Out of 125 children who showed positive results of skin prick test for identification of house dust mites *D. pteronyssinus* and/or *D. farinae* 38 (30.4 %) children were monosensitized and 87 (69.6 %) of the examined patients showed different variants of polyvalent sensitization.

In the group of monosensitized children 20 (52.6 %) children were traced, using molecular diagnostics methods, availability of sIgE specific for rDer p1, rDer p2 and absence of rDer p10, which enabled to prescribe SLIT with the possibility of predicting high efficacy, following the algorithm used.

In the group of polysensitized patients (87 children) molecular diagnostics was made for 21 patients (24.1 %). Eighteen children in the group of monosensitized and 66 children in the group of polysensitized patients refused to undergo because they had indeterminate results. The results of children examination are provided in the **Table 2**.

**Table 2**

The figures for skin prick test and the data of molecular diagnostics in children with allergic rhinitis and allergic bronchial asthma

Groups of patients	Skin prick tests, average papule diameter in mm	rDer p 1, kUA/L (M±m)	rDer p 2, kUA/L (M±m)	rDer p 10, kUA/L (M±m)	Coefficient of correlation of "positive" prick test and major allergens rDer p1/rDer p 2, R
Monosensitized children (n=20)	7,4±4,3	13,2±9,8	30,4±12,6	0,01±0,009	0,98/0,92
Polysensitized children (n=21)	6,1±3,8	8,7±6,3	12,7±8,5	0,02±0,01	0,83/0,72

Comparative analysis of the results of skin prick tests involving domestic allergens of house dust mites *D. pteronyssinus* and/or *D. farinae* (Diater, Spain) showed that in the group of monosensitized patients 19 (95 %) people out of the 20 examined ones have major allergens of house dust mite. Among polysensitized patients the percentage of result coincidence is lower, reaching 81 %, which can possibly be related to cross-responsiveness and individual skin sensitivity of children of that age category. Such results require further study and analysis.

Patients with confirmed sensitization to allergens of house dust mites (125 children, of which 41 children with high and middle efficacy prognosis for SLIT) were offered a therapy using sublingual allergens containing a mixture of house dust mites (*D. pteronyssinus* and *D. farinae*) in the correlation of 1(0,175 HEP):1(0,175 HEP) (Diater, Spain). SLIT was started with 47 children included into the first examination group. Out of 78 patients who refused to take SLIT (remoteness of allergologist and doubt as to the results) 20 children made up the control group, as they got symptomatic baseline therapy under the corresponding protocols.

The patients of both groups underwent the baseline therapy under the protocols. If necessary, anti-histamine drugs of the second generation, inhalation beta-agonists, inhalant glucocorticosteroids and antileukotriene drugs were prescribed to the control respiratory symptoms.

## 6. Discussion

The analysis of clinical characteristics of 67 children of the 1<sup>st</sup> and the 2<sup>nd</sup> groups participating in the examination testifies to availability of considerable sensitization to house dust mites in both groups of patients, as confirmed by the results of molecular diagnostics and the corresponding clinical symptoms manifested to a different extent. A high percent of allergic rhinitis and cough symptoms in the children under examination attracts attention, it coinciding with the data of literature [2]. Both groups show quite a high percent: 1<sup>st</sup> group – 44.6 %, and in the 2<sup>nd</sup> group – 45 % of poly-sensitized children. Anyway, taking into account the fact that the results were obtained by the skin prick test method, and the tasks of the examination did not include assessment of possible adverse effects of cross-reactions – the data is slightly inflated. All the patients underwent randomization in correspondence with the specificity of their clinical characteristics (**Table 3**).

The assessment of clinical efficacy of sublingual allergen-specific immunotherapy in the first group of children testifies to reliable differences in VAS-all figures prior to the therapy and 6 months after its application. Thus, the most clearly manifested symptom "nasal obstruction" prior to the beginning of the therapy was assessed as 2.3±1.6 points, and 6 months later the figure reduced almost twice (1.3±1.1); P<0,05; while 12 and 24 months later SLIT indicator made up 0.91±0.9 and 0.34±0.5;

$P < 0,01$ , correspondingly. The other indicators were also characterized by a considerable reduction, for example, that of cough before the therapy was  $2.2 \pm 1.5$  – which was clinically manifested in availability of moderately severe and severe cough symptoms in 60.8 % of children, in particular, in the night time and early in the morning, while in the observation dynamics there could be traced a reliable ( $P < 0.05$ ) symptom regression to  $1.3 \pm 1.1$  6 months later,  $0.7 \pm 0.3$  12 months later, and  $0.2 \pm 0.5$  – 24 months later. Thus, by the end of the first year of therapy 56 % had only minimum or light symptom manifestation in the form of infrequent cough in the morning hours, without night awakenings, and it almost disappeared by the end of the 2<sup>nd</sup> year of therapy. Of interest, in our opinion, is observation and the assessment of nasal itch and mouth cavity mucosa itch. Out of all the children under examination there were registered only 2 patients with severe manifestations – 4 points under VAS-all. The cases were described for two children. The first one was a female, 32 months old, with a high class of sensitization to major house dust mites allergens (r Der p 1 > 100 kU\l) and availability of covalent sensitization to weed allergens. The second child was a female, 36 months of age, with monosensitization to major and minor house dust mite allergens and anamnestic data on the development of acute reactions in the form of local angioneurotic oedema and urticaria fever, when fish and sea food were consumed. The remaining majority (95.7 %) of the children under examination was not characterized by such complaints. That could possibly be accounted for by age specificity and availability of more manifested system reactions characteristic of the given age category. A considerable role in the given study goes to comparative characteristics of the first-group patients as compared to the second-group patients who did not undergo sublingual allergen-specific immunotherapy. As of the date of the study, patients of both groups had similar indicators in VAS-all symptoms (Table 4). For example, the same as the symptoms of nasal obstruction and cough described above. Thus, as of the beginning of the therapy the indicator “cough” with the second-group children made up  $2.6 \pm 1.3$  points and did not differ significantly ( $P > 0.05$ ) from that of the first-group children –  $2.2 \pm 1.5$ . And as of the end of the second year of the therapy there was already a significant difference traced in the results of the 1<sup>st</sup> and the 2<sup>nd</sup> groups:  $0.2 \pm 0.1$  and  $2.3 \pm 0.8$  points ( $P < 0.01$ ). Return of some indicators with the 2<sup>nd</sup>-group children to almost initial condition requires further study. In the given study that was related to dedication of parents to the applied basic therapy which normally did not last more than 6–12 months (in that period reduction of VAS-all indicators “cough” to  $1.5 \pm 0.7$  and  $1.6 \pm 0.4$  points could be traced) as well as availability of a high class of sensitization to house dust mites in children of the group in parallel to complexities of controlling allergen exposition, which, on the background of therapy denial, led to re-occurrence of disease symptoms.

**Table 3**Clinical characteristics of patients of the 1<sup>st</sup> and 2<sup>nd</sup> study groups

Indicator	Children of the 1st study group	Children of the 2nd study group
Number of patients	47	20
Sex, n (%)		
Male	33 (70.2)	13 (65)
Female	14 (29.8)	7 (35)
Age (M±m), years	$4.11 \pm 0.83$	$3.8 \pm 1.2$
Age limits	3–5	3–5
Clinical symptoms, n (%)*		
Rhinitis	41 (87.2)	20 (100)
Rhinoconjunctivitis	4 (8.5)	3 (15)
Allergic asthma	16 (34.0)	7 (35)
Wheezing	5 (10.6)	–
Upper palate itching	2 (4.2)	–
Cough	41 (87.2)	17 (85)
The results of skin prick test with allergens of house dust mites (average diameter of papule, mm)	$8.4 \pm 4.1$	$7.9 \pm 3.27$
Number of patients with polyvalent sensitization, n (%) – according to the data of skin prick test	21 (44.6 %)	9 (45 %)

Note: \* – symptom combination possible

**Table 4**

Indicators of visual analogue scale in children in the background of sublingual allergen-specific immunotherapy and in control group

Symptom, points (0–4)	Before treatment	Ist group (n=47)			Before treatment	IInd group (n=20)		
		6 months	12 months	24 months		6 months	12 months	24 months
Nasal obstruction	2.3±1.6**	1.3±1.1*	0.91±0.9*	0.34±0.5*	2.4±1.4	2.4±1.2	2.2±0.9	2.2±0.8
Rhinorrhea	2.2±0.9**	0.5±0.5*	0.5±0.6*	0.2±0.4*	1.8±0.9	1.3±0.8	2.5±1.2	2.2±1.1
Sneezing	1.83±1.4**	0.5±0.5*	0.3±0.4*	0.34±0.5*	1.8±1.2	0.9±0.5	0.7±0.4	1.3±0.9
Nasal mucosa itch, mouth mucosa itch	0.2±0.9**	0.08±0.9**	0.04±0.2**	0.04±0.2**	0.04±0.2	0.04±0.2	0.04±0.2	0.04±0.2
Nasal discharge	1.8±1.3**	1.3±1.1**	0.6±0.5*	0.4±0.13*	2.2±1.1	1.5±0.7	1.6±0.5	2.2±0.9
Cough	2.2±1.5**	1.3±0.09**	0.7±0.3*	0.2±0.1*	2.6±1.3	1.5±0.7	1.6±0.4	2.3±0.8

Note: \* –  $P < 0.05$  – statistically significant differences between the first and second groups; \*\* –  $P > 0.05$  – statistically insignificant differences between the first and the second groups

One of the most important components of SLIT therapy is the possibility of its safe application with due account of the risks of development of possible anaphylactic reactions and its tolerance with children. SLIT tolerance was assessed for the first-group children using a linear scale described above. 57.4 % of patients (and their parents) assessed SLIT tolerance as “good” and 31.9 % as “very good”. Thus, the aggregate result of good and very good tolerance made up 89.3 %, which proves high safety of treatment and absence of serious adverse reactions. Over the whole period of observation not a single severe drug-related allergic/anaphylactic reaction was recorded.

## 7. Conclusions

The above study has shown that application of SLIT with standardized medical allergens in children under 5 sensitized to domestic allergens of house dust mites and having clinical manifestations of allergic rhinitis and/or allergic bronchial asthma constitutes an effective and safe treatment method and enables to quickly (over the first 6 months of SLIT) come to control of the disease symptoms. The necessary condition for effective therapy is compliance with the rules of diagnostics which should be made following international standards using the algorithms and also taking into account the results of molecular diagnostics. The data of comparative analysis in the group of patients not undergoing SLIT has pointed to high frequency of disease symptom occurrence after the “lucid space” against the background of full or partial baseline therapy denial. Quite a number of unsolved issues related to SLIT application in early-age children require further study of the given therapeutic direction.

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