

N.V. Shakhova<sup>1</sup>, Yu.F. Lobanov<sup>1</sup>, V.V. Gordeev<sup>1</sup>, V.P. Tokarev<sup>2</sup>, M.V. Surkova<sup>2</sup>

<sup>1</sup> Altai State Medical University of the Ministry of Health, Barnaul, Russian Federation

<sup>2</sup> Pediatric clinical hospital No. 7, Barnaul, Russian Federation

## **Effectiveness of subcutaneous allergen-specific immunotherapy with tree pollen allergen extract adsorbed on calcium phosphate in children with allergic rhinoconjunctivitis: results of a 2-year-long observation**

### **Author affiliation:**

*Shakhova Natal'ya Viktorovna*, MD, allergist-immunologist, assistant professor at the department of pediatrics No. 2 at the Altai State Medical University of the Ministry of Health (Territorial Budgetary Educational Institution of Higher Professional Education)

**Address:** 40, Lenina Ave., Barnaul; **tel.:** +7 (960) 959-81-98; **e-mail:** [natalia.shakhova@mail.ru](mailto:natalia.shakhova@mail.ru)

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*The study was aimed at evaluating effectiveness and safety of subcutaneous allergen-specific immunotherapy (scASIT) with tree pollen allergen extract adsorbed on calcium phosphate at allergic rhinoconjunctivitis in children. **Patients and methods:** open-label prospective study of 50 children and adolescents (5-17 years of age) with allergic rhinoconjunctivitis caused by high sensitivity to tree pollen allergens. The first group involved the patients undergoing scASIT for 2 years 6 months ( $n = 23$ ), the control group – the patients ( $n = 27$ ) not undergoing any specific immunotherapy. **Results:** scASIT was accompanied by a statistically significant (in comparison with the control group) reduction in intensity of rhinoconjunctivitis symptoms ( $6.1 \pm 3.1$ ;  $11.8 \pm 4.5$ ;  $p = 0.00002$ ), reduction in the use of symptomatic drugs ( $1.0 \pm 0.4$ ;  $1.8 \pm 0.3$ ;  $p = 0.000004$ ) and improvement of quality of all spheres of children's life – physical ( $p = 0.001$ ), social ( $p = 0.04$ ), emotional ( $p = 0.001$ ) and role functioning ( $p = 0.03$ ). Systemic side reactions were not observed in the patients. Local reactions were observed in 23% of all allergen injections. **Conclusions:** the authors established high effectiveness and safety of scASIT with tree pollen allergen extract adsorbed on calcium phosphate suspension at allergic rhinoconjunctivitis in children.*

**Keywords:** subcutaneous allergen-specific immunotherapy, children, allergic rhinoconjunctivitis, tree pollen allergen.

Ca. 600 mn patients of all ages, ethnic groups and countries suffer from allergic rhinitis/rhinoconjunctivitis. The studies demonstrate that the prevalence of allergic rhinitis varies across regions of Russia from 10 to 20%. Prevalence of allergic rhinitis and bronchial asthma among the adults residing in Western European countries varies from 12 to 34% [1], in Eastern European countries – 23% [2].

Results of the performed studies demonstrate that bothersome symptoms of allergic rhinitis negatively affect quality of life of both adults and children. Allergic rhinitis affects the ability to perform daily activities, degrades quality of sleep and cognitive function and negatively affects school studies [3-7].

Therapy of allergic rhinitis involves avoidance of contact with allergens, symptomatic therapy (antihistamine drugs, glucocorticoids, leukotriene receptor antagonists) and allergen-specific immunotherapy (ASIT). Currently, ASIT is seen as a highly effective method of treating IgE-mediated respiratory allergic diseases, including allergic rhinitis [8-11]. Successful ASIT course develops immunological tolerance towards the significant allergen, which helps to improve quality of life of patients by alleviating clinical symptoms and the need in drugs and attain complete remission of the disease preserving for several years after therapy withdrawal

[12-14]. ASIT is an effective method of interrupting atopic march, including bronchial asthma, in children; this makes use of this method of treatment in children especially relevant [15].

Phostal "Tree pollen allergen" (Stallergenes, S.A., France) – standardized mixture of Betulaceae (alder, birch, common hazel, hornbeam) tree pollen allergen extracts – was registered in Russia in 2010. This drug is an adjuvant standardized allergy vaccine adsorbed on calcium phosphate suspension for subcutaneous ASIT (scASIT). Allergen standardization, presence of an adjuvant, high extent of purification and convenient presentation (ready-for-use solutions) decrease risk of development of side allergic reactions at scASIT and provide convenient treatment patterns for the patient and the doctor.

There have been foreign publications dedicated to evaluation of effectiveness and safety of scASIT with a tree pollen allergen extract adsorbed on calcium phosphate suspension [16, 17]. However, there are only few Russian publications on this topic [18-23]. We analyzed effectiveness and safety of scASIT with a tree pollen allergen extract adsorbed on calcium phosphate suspension in children with seasonal allergic rhinoconjunctivitis with tree pollen allergen sensitization, results whereof we provide in this article.

**The study was aimed at** evaluating effectiveness and safety of scASIT with a tree pollen allergen extract adsorbed on calcium phosphate in children with allergic rhinoconjunctivitis.

## **PATIENTS AND METHODS**

The study was conducted at the allergy unit of the Pediatric clinical hospital No. 7, Barnaul (Territorial State Budgetary Healthcare Establishment). Study environment conformed to the "Regulations for clinical practice in the Russian Federation" ratified by Decree No. 266 of the Ministry of Health of the Russian Federation on 19.06.2003. Study protocol and other materials were approved by an independent Ethics Committee at the Altai State Medical University of the Ministry of Health of the Russian Federation (State Budgetary Educational Establishment of Higher Professional Education). We obtained written informed consent to children's participation in the examination from all the parents.

This open-label, prospective, randomized, single-center study involved 50 children and adolescents (5-17 years of age) with allergic rhinoconjunctivitis caused by increases sensitivity to tree pollen allergens (birch, alder, hazel). Duration of the study – 3 years (launch – November 2010, estimated finish – June 2014). In this article, we quote intermediate results of the study of effectiveness and safety of tree pollen allergen extract scASIT after 2 years 6 months of observation.

All the patients were divided into 2 groups – study group (n = 23) and control group (n = 27). The study group involved the patients, who were prescribed scASIT with the tree pollen allergen extract adsorbed on calcium phosphate (n = 23; mean age –  $8.5 \pm 3.3$  years); the control group – the patients (n = 27; mean age –  $8.2 \pm 2.0$  years), who had never undergone any specific immunotherapy.

The following criteria of including patients into the study were employed: confirmed diagnosis of allergic rhinoconjunctivitis caused by increased sensitivity to tree pollen allergens; age over 5 years; disease duration over 2 years; positive skin tests with tree pollen allergens (birch, alder, common hazel); level of specific immunoglobulins (Ig) E  $\geq$  class II; absence of contraindications against scASIT.

Criteria of exclusion from the study were as follows: age under 5 years; disease duration under 2 years; previously undergone tree pollen allergen ASIT courses; symptoms of rhinoconjunctivitis induced by a different allergen in the flowering period; severe course of bronchial asthma (FEV1 < 70% despite optimal therapy); chronic concurrent pathology; severe immunological disorders; neoplasms; chronic infectious diseases; severe mental disorders.

The main demographic and clinical data of the patients are given in the tb.

## **scASIT study design**

The treatment consisted of 2 stages. At the initial therapy stage (dose increase), the allergen dose is gradually increased from the minimal (0.01 RI/ml) to the maximal concentration (10 RI/ml) (RI – reactivity index – biological standard unit). Deep subcutaneous injection is administered into the middle third of the arm along the lateral line OW. The initial therapy stage lasts until the maximal tolerated dose is attained, the administration whereof does not lead to pronounced repeated topical or systemic reactions.

At the primary treatment stage (dose maintenance), the maximal tolerated dose is used (selected on an individual basis; up to 0.8 ml at concentration 10 RI/ml). The primary treatment stage starts 15 days after the end of the initial stage. The first two injections are administered 2 weeks apart; after that, the drug is administered once monthly or more rarely; however, the injections ought not to be administered more than 6 weeks apart. scASIT duration – 2 years.

In order to confirm sensitization, all the patients underwent specific allergological diagnosis by means of skin prick testing with 0.01% histamine solution, test control, water-salt pollen allergen extracts manufactured by Stavropol scientific production association “Allergen” (Russia); we also employed enzyme-linked immunoassay using test system ALLERgen System For specific IgE (Radim, Italy) in order to determine the level of specific IgE to Betulaceae pollen allergens in blood serum.

All the patients and their parents were polled twice. The first survey was conducted prior to the study launch and appraised initial parameters of intensity of rhinoconjunctivitis symptoms, of quality of life and drug load in the tree flowering period preceding the therapy launch. The second survey was conducted 2 years 6 months after the therapy launch (2 weeks after the tree flowering period).

### ***Rhinoconjunctivitis Total Symptom Score (RTSS)***

We used the standard system – RTSS scale – in order to register intensity of rhinoconjunctivitis symptoms [24, 25]; it includes intensity appraisal of the most frequent allergic rhinoconjunctivitis symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and lacrimation).

Each symptom is given a score of 0-3 points: 0 – no symptoms; 1 – mild symptoms; 2 – moderate symptoms; 3 – severe symptoms.

### ***Appraisal of quality of life of the patients***

In order to analyze effect of Phostal on the quality of life of the children with allergic rhinoconjunctivitis, the patients of both groups and their parents were polled using a Russian version of questionnaire PedsQL™4.0 (J. Varni, 1999). The questionnaire consists of forms for 3 age groups (5-7; 8-12; 13-18 years) and parents. Each form consists of 23 questions united under the following headings: physical functioning – 8 questions, emotional functioning – 5 questions, social functioning – 5 questions, role functioning (social life at school, kindergarten) – 3 or 5 questions (depending on the age). After code conversion, the total score was calculated on the basis of 100-point scale: the higher the resulting value, the better the quality of life of the child.

### ***Rescue Medication Score (RMS)***

We used the standard system – RMS scale – in order to register drug use in the tree flowering period [24, 25].

The 3-point scale is aimed at appraisal of drug use: 0 – not required; 1 – antihistamines; 2 – nasal corticosteroids; 3 – oral corticosteroids.

### ***Patient's subjective treatment effectiveness appraisal***

Patients appraised treatment effectiveness on the basis of subjective comparison of intensity of allergic rhinoconjunctivitis symptoms in the flowering period under consideration and the previous one (no changes, moderate improvement, pronounced improvement).

### ***Side effects***

All systemic and topical side reactions were being registered throughout the study. Topical reactions were divided into mild (development of edema and hyperemia  $\leq 3$  cm in the allergen injection site) and pronounced (edema and hyperemia  $> 3$  cm) reactions. Systemic reactions included urticaria, angioneurotic edema, exacerbation of bronchial asthma and allergic rhinitis and anaphylactic shock.

### **Statistical analysis**

The data were statistically manipulated using the commonly accepted methods of variation statistics – statistical software package Statistica 6.1 for Windows. The nature of data distribution was appraised using Shapiro-Wilk test. Results were reported in terms of  $M \pm m$ , where  $M$  is the arithmetic mean and  $m$  is the standard error of the mean. If distribution of the attribute was adopted as close to normal, we used non-parametric test for analysis (Student's t-test). If the distribution of results was abnormal, we used non-parametric statistics methods for analysis (Mann-Whitney U test). Qualitative variables were represented with absolute and relative (%) rates. Fisher's exact test was used for appraising statistical significance of differences between qualitative variables. Wilcoxon test (W) was used to compare dependent quantitative variables. Differences were considered statistically significant at  $p < 0.05$ .

## **STUDY RESULTS AND DISCUSSION**

No statistically significant differences between the compared groups in terms of initial parameters of intensity of rhinoconjunctivitis symptoms and quality of life were observed in the beginning of the study (pics. 1, 2).

### ***Rhinoconjunctivitis Total Symptom Score (RTSS)***

scASIT was accompanied by statistically significant (in comparison with group 2) decrease in the RTSS intensity of rhinoconjunctivitis symptoms ( $6.1 \pm 3.1$  and  $11.8 \pm 4.5$  in the study group and the control group, respectively;  $p = 0.00002$ ; pic. 3). Moreover, decrease in the intensity of five out of six rhinoconjunctivitis symptoms was statistically significant (sneezing:  $1.3 \pm 0.6$  and  $2.1 \pm 0.8$ ,  $p = 0.001$ ; rhinorrhea:  $0.8 \pm 0.6$  and  $2.3 \pm 0.6$ ,  $p = 0.00003$ ; nasal pruritus:  $0.9 \pm 0.7$  and  $1.7 \pm 0.8$ ,  $p = 0.03$ ; nasal congestion:  $1.3 \pm 0.8$  and  $2.3 \pm 0.6$ ,  $p = 0.00003$ ; ocular pruritus:  $1.0 \pm 0.9$  and  $2.1 \pm 0.9$ ,  $p = 0.00002$ ; lacrimation:  $0.9 \pm 0.7$  and  $1.7 \pm 0.8$ ,  $p = 0.00005$  [in the study group and the control group, respectively]).

### ***Quality of life***

We observed a statistically significant increase in parameters of quality of life in the group of patients undergoing scASIT in comparison with the control group in terms of physical ( $95.3 \pm 6.9$  and  $87.7 \pm 9.6$ ;  $p = 0.001$ ), emotional ( $86.3 \pm 11.6$  and  $69.2 \pm 19.5$ ;  $p = 0.001$ ), social ( $97.3 \pm 5.1$

and  $91.1 \pm 10.7$ ;  $p = 0.04$ ), and school social functioning ( $86.3 \pm 15.0$  and  $77.4 \pm 16.4$ ;  $p = 0.03$ ) (in the study group and the control group, respectively; pic. 4). Moreover, we observed a statistically significant increase in the total quality of life in the control group ( $91.3 \pm 6.1$  and  $81.4 \pm 11.4$ , respectively;  $p = 0.00061$ ). The children felt sad, worry about their disease and skip school or kindergarten (due to the need in visiting the doctor) less often. Analysis of the parental forms yielded similar results.

### ***Rescue Medication Score (RMS)***

We observed statistically significant decrease in the use of symptomatic drugs in the flowering period in the group of children undergoing ASIT in comparison with the control group ( $1.0 \pm 0.4$  and  $1.8 \pm 0.3$ , respectively;  $p = 0.000004$ ; pic. 5).

### ***Patient's subjective treatment effectiveness appraisal***

We analyzed subjective scASIT effectiveness appraisal and revealed high therapy success rate: 14 (60%) of the patients confirmed pronounced therapy effect, 10 (36%) – moderate effect; only 1 (4%) patient observed no therapy effect (pic. 6).

### ***Birch pollen extract prick test***

We observed a statistically significant decrease in the blister-hyperemic reaction to water-salt birch pollen extract prick test in the patients undergoing scASIT: from severe (4+ or 3+ in the beginning of the study) to moderate (2+ or 1+ by the end of the study) ( $W = 24$ ;  $p = 0.04$ ).

### ***Safety***

Topical reactions were registered in 19 out of the 23 patients throughout the study. Altogether, we performed 990 allergen injections and registered 227 topical reactions (23% of all the allergen injections). 148 out of the 227 topical reactions were mild (15% of all the allergen injections), 79 – pronounced (8% of all the allergen injections). Calculation of the Fisher's exact test revealed a statistically significant prevalence of mild reactions ( $p = 0.0006$ ).

Mild topical reactions were short-term, self-limited and did not require treatment. Antihistamines were prescribed in the event of pronounced topical reactions. We did not observe any systemic allergic reactions throughout the whole observation period.

It ought to be mentioned that pronounced topical reactions were more often observed in children with rhinoconjunctivitis concurrent with bronchial asthma ( $p = 0.032$ ) than in children with isolated rhinoconjunctivitis. The level of specific IgE to birch was statistically significantly higher in children pronounced topical reactions ( $2.3 \pm 0.2$  U/ml) than in children with mild reactions ( $1.26 \pm 0.26$  U/ml;  $p = 0.006$ ).

Thus, our study demonstrated that scASIT with Phostal considerably alleviates the course of allergic rhinoconjunctivitis in children by decreasing intensity of clinical symptoms of the disease and drug load and improving all parameters of quality of life: physical, social, emotional and role functioning. It ought to be mentioned that the birch pollen concentration was comparable in 2010 and 2013 (the maximum birch pollen concentration in 2010 was 114 units of pollen grains per  $m^3$ , in 2013 – 121 units of pollen grains per  $m^3$ ).

This study demonstrated high level of safety of tree pollen allergen extract scASIT. No patients developed systemic side reactions. Topical reactions (primarily mild) were registered in 23% of all the allergen injections. No patients abandoned the therapy due to side reactions.

## **CONCLUSIONS**

Our study indicates high effectiveness and safety of tree pollen allergen extract scASIT in patients with allergic rhinoconjunctivitis caused by increased sensitivity to tree pollen allergens.

## REFERENCES

1. Dahi R., Andersen P. S., Chivato T. National prevalence of respiratory allergic disorders. *Respir Med.* 2004; 98: 398–403.
2. Bauchau V., Durham S. R. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J.* 2004; 24: 758–764.
3. Bousquet J., Bullinger M., Fayol C. et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol.* 1994; 94: 182–188.
4. Leynaert B., Neukirch C., Liard R. et al. Quality of life in allergic rhinitis and asthma: A population-based study of young adults. *J Respir Crit Care Med.* 2000; 162: 1391–1396.
5. Storms W. W. Pharmacologic approaches to daytime and nighttime symptoms of allergic rhinitis. *J Allergy Clin Immunol.* 2004; 114 (Suppl.): 146–S153.
6. Stuck B. A., Czaikowski J., Hagner A. E. et al. Changes in daytime sleepiness, quality of life and objective sleep patterns in seasonal allergic rhinitis: A controlled clinical trial. *J Allergy Clin Immunol.* 2004; 113: 663–668.
7. Marshall P. S., Colon E. A. Effect of allergy season on mood and cognitive function. *Ann Allergy.* 1993; 71: 251–258.
8. Gushchin I. S., Kurbacheva O. M. *Allergiya i allergenspetsificheskaya immunoterapiya* [Allergy and Allergen-specific Immunotherapy]. Moscow, 2010. 227 p.
9. *Allergiya u detei: ot teorii — k praktike. Pod red. L.S. Namazovoi-Baranovoi. Seriya «Sovremennaya pediatriya: ot teorii — k praktike»* [Allergy in Children: from Theory to Practice. Edited by L.S. Namazova-Baranova. Edition “Current Pediatrics: from Theory to Practice”]. Moscow, 2011. 668 p.
10. Malling H.-J. Allergen immunotherapy efficacy in rhinitis and asthma. *Allergy Clin Immunol Int J World Allergy Org.* 2004; 16 (3): 92–95.
11. Kurbacheva O. M. *Rossiiskii allergologicheskii zhurnal – Russian allergological journal.* 2004; 2: 32–54.
12. Moller C., Dreborg S., Ferdousi H. A. et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol.* 2002; 109: 251–256.
13. Kumar P., Kamboj S., Rao P. et al. The cost of care and quality of life in patients with allergic rhinitis on allergen immunotherapy. *J Allergy Clin Immun Intern.* 1997; 9 (5): 133–135.
14. Yilmaz M., Bingol G., Altindas D. et al. Effect of SIT on quality of life. *Allergy.* 2000; 55: 302–309.
15. Standards for practical allergen-specific immunotherapy. *Allergy.* 2006; 61 (Suppl. 82): 1–20.
16. Botey J., Cadahia A., Cobo R. et al. Tolerancia de la inmunoterapia especifica con extractos alergenicos adsorbidos sobre fostato de calico. *Rev Esp Alergolo Immunol Clin.* 1997; 12: 45–50.
17. Fadel R., Andre C., Bellanger M. et al. Tolerans, compliance et efficacite de immunotherapie specifique par des extraits allergeniques aqueus ou adsorbes sur phosphate de calcium. Etude retrospective. *Rev Fr Allergol.* 1998; 38: 41–49.
18. Kurbacheva O. M., Pavlova K. S., Il'ina N. I. et al. *Rossiiskii allergologicheskii zhurnal – Russian allergological journal.* 2009; 3: 27–31.
19. Mokronosova M. A., Korovkina E. S. *Rossiiskii allergologicheskii zhurnal – Russian allergological journal.* 2010; 4: 79–84.
20. Shakhova N. V., Gordeev V. V., Kharchenko S. S. et al. *Rossiiskii allergologicheskii zhurnal – Russian allergological journal.* 2011; 6: 79–84.

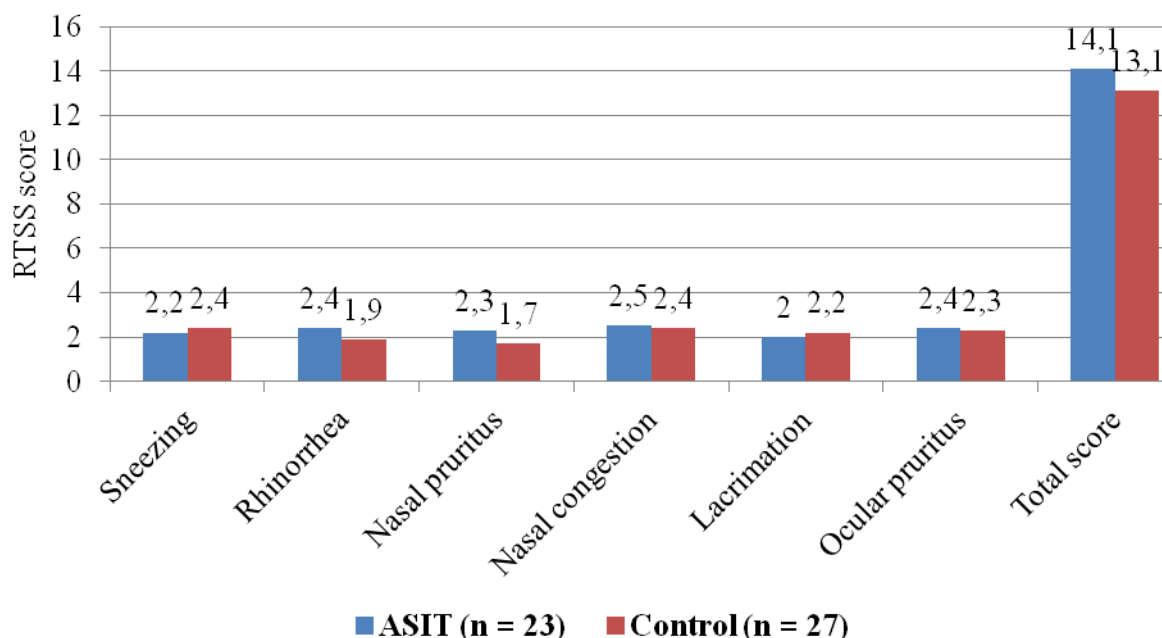
21. Shakhova N. V., Gordeev V. V., Tokarev V. P. et al. *Mat' i ditya v Kuzbasse – Mother and child in Kuzbass*. 2012; 3 (50): 37–41.
22. Shakhova N. V., Gordeev V. V., Tokarev V. P. et al. *Rossiiskii allergologicheskii zhurnal – Russian allergological journal*. 2012; 6: 44–48.
23. Shakhova N. V., Gordeev V. V., Lobanov Yu. F. et al. *Mat' i ditya v Kuzbasse – Mother and child in Kuzbass*. 2013; 1 (52): 50–54.
24. Wallner M., Briza P., Thalhamer J. Specific in pollen allergy. *Curr Opin Mol Ther*. 2007; 9 (2): 160–167.
25. Calderon M., Mosges R., Helmich M. et al. Towards evidence — based in specific grass pollen immunotherapy. *Allergy*. 2010; 65: 420–434.

**Table 1.** Demographic and clinical description of the patients

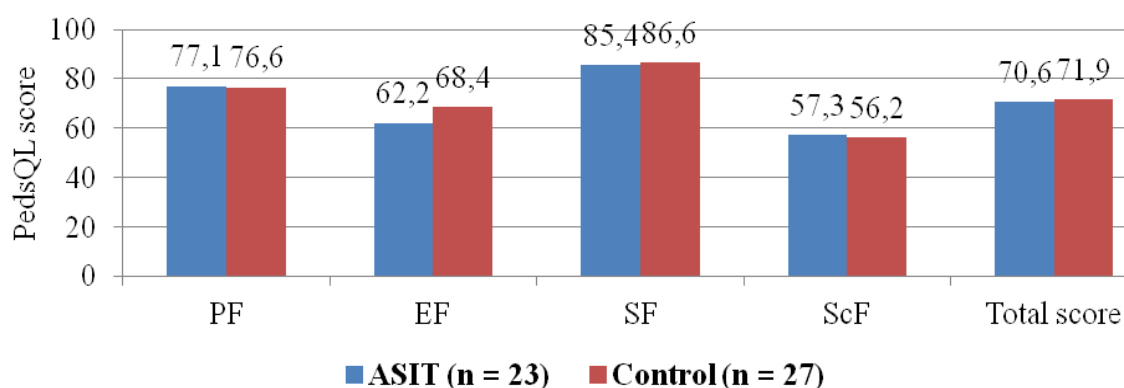
Parameter	Study group, n = 23 (%)	Control group, n = 27 (%)
Mean age (years)	8.5±3.3	8.2±2.0
Sex (F/M; %)	7/16	9/18
Amount of seasonal asthma cases	9 (40)	10 (42)
Sensitization (mono-/poly-; %)	28/72	30/70
Disease duration (years)	4.9±2.5	3.8±3.3
Disease severity (Abs./%)*:		
- mild persistent	2 (9)	2 (7)
- moderate persistent	5 (22)	7 (26)
- severe persistent	17 (69)	18 (67)
Allergen-specific IgE to birch (U/ml)	3.6±4.1	3.4±4.8

*Note.* \* - severity of rhinitis according to the ARIA (Allergic Rhinitis and Impact on Asthma) classification.

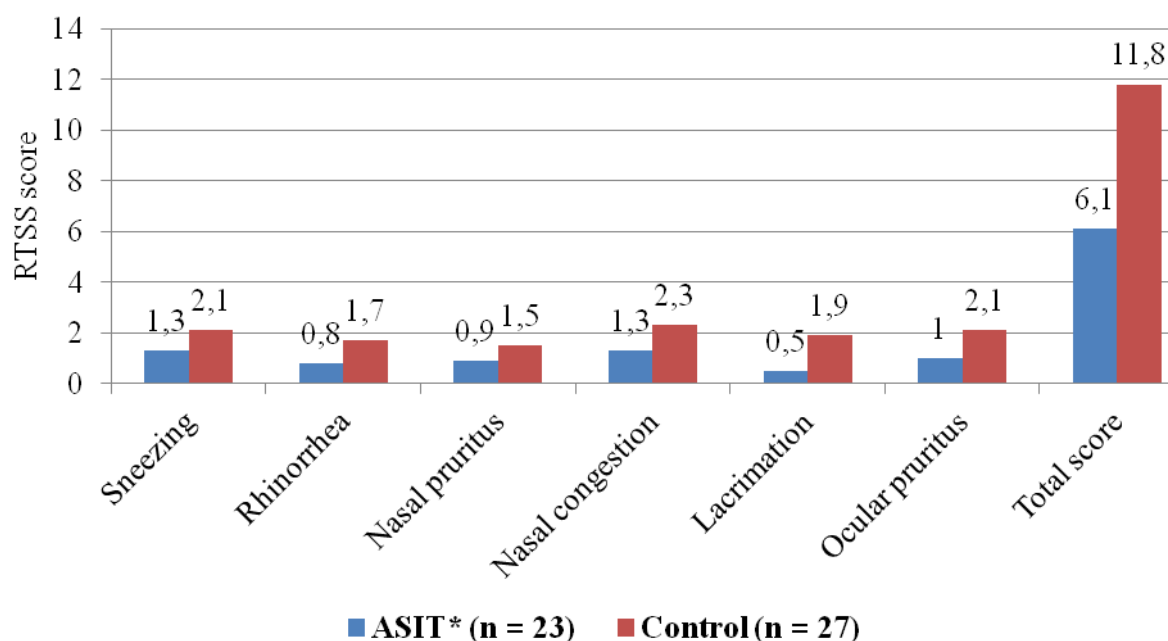
**Pic. 1.** Rhinoconjunctivitis symptoms in the group of children undergoing ASIT and in the control group before the therapy



**Pic. 2. Parameters of quality of life of the children undergoing ASIT and in the control group before the therapy**



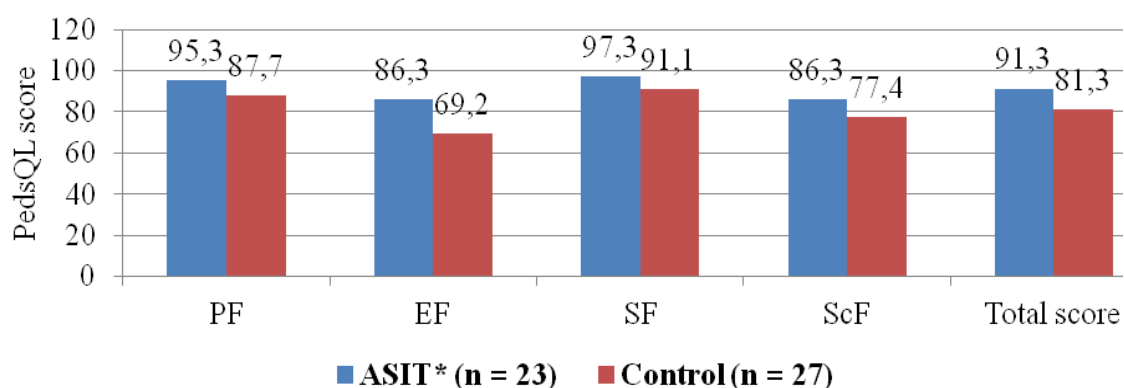
**Pic. 3. Rhinoconjunctivitis symptoms in the group of children undergoing ASIT and in the control group after the therapy**



*Note.* \* - decrease by 38% in sneezing, by 53% - in rhinorrhea, by 40% in nasal pruritus, by 43% - in nasal congestion, by 73% - in lacrimation, by 52% - in ocular pruritus, by 48% - in the total score.

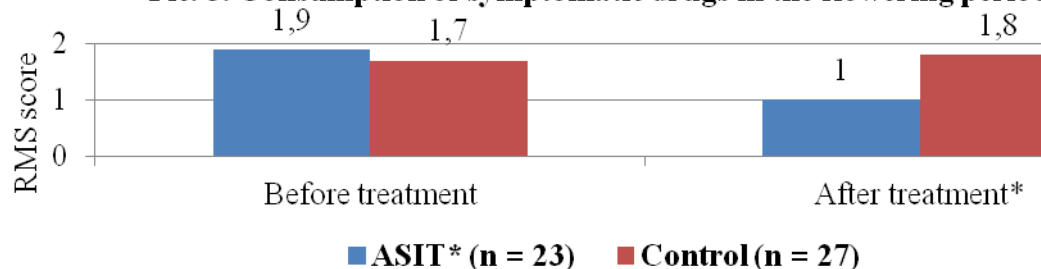


**Pic. 4. Parameters of quality of life of the children undergoing ASIT and in the control group after the therapy**



*Note.* \* - PF improved by 8.6%, EF – by 24.7%, SF – by 6.8%, ScF – by 11.4%, total score – by 12.3%.

**Pic. 5. Consumption of symptomatic drugs in the flowering period**



*Note.* \* - 44.5% decrease.

**Pic. 6. Patients' scASIT effectiveness appraisal**



*Note.* \* - 96% of the patients observed therapy effect.