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Comparative Effectiveness and Safety of Different Allergen-Specific Immunotherapy Types in Pollinosis.

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ABSTRACT

The results of comparative research of sublingual (SLIT) and subcutaneous (SCIT) allergen-specific immunotherapy (ASIT) in pollinosis are presented in this article. 228 patients with diagnosed pollen sensitization to wormwood and without previous immunotherapy were enrolled in our study during 2014-2016 years, 28 were excluded. In order to separate intrinsic sensitization and cross-reactions in patients with multiple sensitizations molecular allegro-diagnostic testing with recombinant allergens was used. In order to evaluate the severity of allergic process, the concentration of eosinophilic cationic protein (ECP) in the blood serum and nasal secret was determined. Symptoms of rhino-conjunctivitis were estimated using total nasal symptom score (TNSS), quality of life was assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Total serum IgE and allergen specific IgE, IgG_4 antibodies to the pollen of wormwood were determined for the ASIT effectiveness evaluation. ASIT safety was estimated according to the frequency of local and systemic reactions. Our results showed that prominent part of sensitization pattern belong to wormwood, thus Artv1 in 39,13%, Artv3 in 21,74%. ECP level positively correlated with the intensity of nasal inflammation ($p<0,001$). As a result of SLIT rhinoconjunctival manifestations significantly decreased. Reliable decrease of the RQLQ general score ($p<0,001$) was revealed after SLIT treatment, compared to SCIT. Likewise, the level of serum specific IgE to wormwood decreased at the end of treatment course, IgG4 level increased and coefficient of IgE/IgG4 decreased. Undesirable events were noted more frequently during the SCIT application compared to SLIT. Complex comparison of the effectiveness and safety of two different types of hay fever treatment revealed that SLIT is effective and safe method and could be recommended in patients with multiple sensitization type

Keywords: pollinosis, allergen-specific immunotherapy, molecular allergodiagnostics, recombinant allergens, eosinophilic cationic protein, definitive medicine.

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INTRODUCTION

According to the statistic data of World Health Organization, about 40% of population of our world suffer from allergy. Respiratory allergoses are on the first place and almost 12-45% of them are pollinosis [1, 2].

The leading cause of pollinosis disease growth and its prevalence of medium-severe and severe forms is the leadership of symptomatic pharmacotherapy over the pathogenetic specific immunotherapy. More effective method of treatment for allergic diseases is ASIT, affecting on all pathogenetic links of allergic process and having a long prophylactic effect after the completion of curative courses [3-5].

If parenteral methods, developed in 1908, had already received a common recognition throughout the world, the peroral methods were discredited by the use of uncleansed vaccines during the long decade, which weren't undergone depolymerization and depigmentation [6, 7].

Only in the last two decades, these methods have been widely used firstly in European countries, then in North and Central America, and in recent years they are used in Kazakhstan. A comparative study of the effectiveness of sublingual and subcutaneous ASIT investigated insignificantly, mostly in European countries [8 -10]. This kind of research hasn't been performed in our republic.

The feature of allergic diseases in the Republic of Kazakhstan is that the major allergenic plants are wormwood and other weeds, the intensity of sensibilization approximately in million times greater than in the Central Europe and European part of the Russian Federation [11- 14].

The aim of the research: clinical study of the effectiveness and safety of sublingual ASIT in comparison with subcutaneous ASIT at patients with pollinosis.

MATERIALS AND METHODS

The research was carried out in the design of clinical, experimental, controlled, randomized, open, prospective study in parallel groups. We examined 200 patients, there were children 5-18 years and adults with pollinosis among them (male patients - 108, females - 93). The middle age of the examined patients was 24,0±3,5 years old, the minimum age - 5 years, maximum - 60 years. Diagnosis was established on the basis of data comparison of allergological anamnesis, clinics and results of skin scarificative tests, determination of general IgE and allergen-specific IgE, IgG_4 antibodies to the pollen of wormwood. To separate intrinsic sensibilization and cross-reactions at polysensitized patients methods of molecular allergodiagnostics were used and levels of some recombinant allergens were investigated. Thus, the level of recombinant allergens of wormwood - Artv1 in examined patients was 39,13%, Artv3 - 21,74%; birch - Betv1 composed 18,84%; meadow grasses - Phlp1 composed 13,05%, Phlp5 5,80%; ambrosia - Amba1 1,44%.

The concentration of ECP in blood serum and nasal secretion was determined in order to estimate the degree of course severity of the allergic inflammation and exacerbation of allergic process. To determine the effectiveness of ASIT symptoms of rhinoconjunctivitis were evaluated on a scale T5SS, life quality by questionnaire RQLQ. Scale TNSS included following symptoms: rhinorrhea, sneezing, nasal stuffiness, itch in the area of nose and eyes. The intensity of each symptom was estimated in scores - from 0 to 15 and calculated the average number. During the analysis of TNSS scale we assumed that 0 point - the symptoms do not afflict, 1 point - slightly afflict, 2 points - moderately afflict, 3 points - significantly afflict. The maximum total score was 15 points. The evaluation of therapy effectiveness was performed before and after treatment. Also we determined general IgE and allergen-specific IgE, IgG_4 antibodies to the pollen of wormwood. ASIT safety was estimated by the frequency and intensity of undesirable local and systemic reactions. Patients who participated in a clinical study had a comprehensive medical examination and survey both during the disease remission and during the exacerbation. Repeated examinations were made in dynamics after 3, 6, 9, 12 months. At the time of inclusion into the research none of the patients received ASIT. Patients of the 1 group received the sublingual type of immunotherapy, therapeutic autumn pollen mixture, 2 group - subcutaneous type of immunotherapy, the mixed allergen from weeds' pollen. Patients had 2 courses of ASIT with allergens' pollen with subsequent dynamic observation. The treatment of patients with pollinosis was carried out

according to the national standard, based on the European declaration of immunotherapy from 2011, published by the European academy of allergology and clinical immunology [15 - 17].

Before the research performing, criteria of inclusion and exclusion in the research were defined in accordance with the realization of aim and objectives.

Inclusion criteria for ASIT performing: established diagnosis of pollinosis with sensibilization to allergens of wormwood pollen, age from 5 to 18 years and adult population from 19 to 60 years;

- control absence of disease symptoms in the right degree after elimination of pollen allergens or if complete elimination is not possible, proven IgE-dependent nature of the disease (positive skin scarificative test with pollen allergens, increased level of general and/or specific IgE in blood serum), positive results of major recombinant pollen Artv1, Artv3 at cross-reactions in polysensitized patients, wormwood allergens, receiving written informed compliance for the participation in the research.

Exclusion criteria: children younger than 5 years, psychical diseases, complicating contact with a patient, severe immunological conditions and immunodeficiencies, oncological diseases at any stage, any clinically significant chronic diseases in the stage of exacerbation, the presence of hypersensitivity to the components of studied preparations, impossibility to follow scheme and regimen of recommended treatment by patients and parents.

Statistical analyses were performed using SPSS for Windows 20.0 (StatSoft Inc., version 10.0.228.8, Oklahoma, USA). All of the measured parameters had nonparametric distribution (according to Shapiro-Wilk's criteria), so statistical analysis was performed using nonparametric Mann-Whitney test for independent samples Wilcoxon's signed-rank test was used to compare baseline and follow-up data. Results are expressed as means ± SD. Correlation was calculated using Pearson statistics. A value of p< 0, 05 was considered statistically significant.

RESULTS OF THE RESEARCH AND DISCUSSION

The recombinant major allergens of the wormwood Artv1, Artv3 composed a significant part (69, 87%), during the determination of cross-reactivity among the polysensitized respondents. Average level of Artv1-30,62 ku/l, Artv3-11,92 ku/l. On the background of the performed therapy in all studied groups the improvement of clinical parameters is marked. But the most expressive it was in the first group, who received SLIT. Score estimation of disease symptoms was carried out on the basis of clinical symptoms analysis of pollen allergy at the control visits during the flowering period after each course of treatment and patients' diaries. On T5SS scale, after the performed pre-seasonal course of SLIT, the total index of rhinoconjunctivitis symptoms comparatively with SKIT statistically decreased significantly from 10,5 (8,0; 13,0) points till 6,5 (5,5, 7,5) points (p<0.001).

Clinical effectiveness of SLIT on dynamics of rhinoconjunctivitis symptoms according to the TNSS scale

	Rhinorrhea before and after ASIT	Sneezing before and after ASIT	Itch in the nose before and after ASIT	Itch of the eyes before and after ASIT	Nasal stuffiness before and after ASIT
Z	-8,553[b]	-8,553[b]	-8,417[b]	-8,346[b]	-8,553[b]
Asymptomatic value (two sides)	,000*	,000*	,000*	,000*	,000*

Notes: * - p <0.001 in comparison with the initial amount according to the criteria of Wilcoxon
b. Positive ranks are used.

Score analysis of intensity estimation of each pollinosis symptom showed statistically significant decrease after the SLIT (p<0.001).

Also, by the completion of the second course of SLIT, statistically significant (p<0.001) reduction of the total score RQLQ was revealed from 39,5 (31,4; 47,5) till 24,2 (17,5; 30,9) points. Sleep and emotional condition improved at the treated patients, expressivity of rhinoconjunctivitis manifestations decreased.

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Received data confirms high effectiveness of SLIT and its positive impact on the life quality of patients in comparison with SCIT.

Dynamics of criteria of patients life quality with pollinosis before and after the SLIT by questionnaire RQLQ							
	Limitation of activity before and after ASIT	Sleep before and after ASIT	General symptoms before and after ASIT	Practical problems before and after ASIT	Nasal symptoms before and after ASIT	Eye symptoms before and after ASIT	Emotional condition before and after ASIT
Z	-7,693[b]	-7,648[b]	-8,806[b]	-8,330[b]	-8,650[b]	-8,618[b]	-8,701[b]
Asymptomatic value (two sides)	,000*	,000*	,000*	,000*	,000*	,000*	,000*
Notes: * - p <0.001 in comparison with the initial amount according to the criteria of Wilcoxon b. Positive ranks are used.							

During the correlation analysis between the intensity decrease of rhinoconjunctivitis manifestations and improvement of patients life quality a statistically significant (p<0.001) interconnection of these two symptoms (r = 0,79) was revealed.

Undesirable local and systemic reactions were manifested in 2,8 times more frequent during the SCIT (51.68%) in comparison with sublingual (18.50%) type of therapy. During the use of SLIT the majority of undesirable reactions resolved singly and did not require discontinuance of treatment or correlation of dose regimen. 18,10% of patients had undesirable effects, such as: itch of throat 6,94%, itch of tongue 11,10%, itch of nose and nasal excretion 5,6%, itch of eyes 4,20%, tiredness 2,80% and 1,4% of patients had edema of the lips. Intensity of all local and systemic reactions was evaluated as mild. Following undesirable local and systemic reactions were revealed at patients with pollinosis on the background of SCIT therapy: hyperemia 36,70%, local itch 31,20%, blister and itch of the eyes 15,6%, infiltration 11,70%, itch of the nose and nasal excretion 10.40%, tiredness 6.50%, bronchospasm 5.20%. More frequent occurrence of local side reactions was found authentically during the carrying out of SCIT in comparison with the SLIT.

Laboratory data showed that the level of general IgE significantly decreased in this group in 1.4 times - 239,45 ± 51,14 in comparison with patients, receiving SCIT (p <0.01). Also, the content of serous specific IgE antibodies of wormwood statistically reduced significantly, the level of IgG4 increased and coefficient of IgE/IgG4 decreased.

Correlational interconnection of allergen-specific IgE level of wormwood with coefficient IgE/IgG4 after SLIT			
Allergen-specific immunoglobulins		IgE	IgG4
IgE	Pearson correlation (r)	1	,629***
	P (2- sides)		,000
	N	100	100
IgE/IgG4	Pearson correlation (r)	,629***	1
	P (2 - sides)	,000	
	N	100	100
Notes: ***. Correlation is significant at the level of 0.001 (2-sides.).			

During the correlation analysis between the exponents of IgE concentration and coefficient of IgE/IgG4 at patients, received SLIT statistically significant (p<0.001) interconnection (r = 0,629) was established. Also, the content dynamics of allergen - specific IgE antibodies of wormwood in the serum of patients with pollinosis after ASIT significantly decreased in 1,2 times - 8,48 ± 0,24 IU/ml in comparison with patients, received SCIT (p<0.01).

Dynamics of ECP levels in the blood serum and eosinophils in nasal secretion on the background of sublingual ASIT

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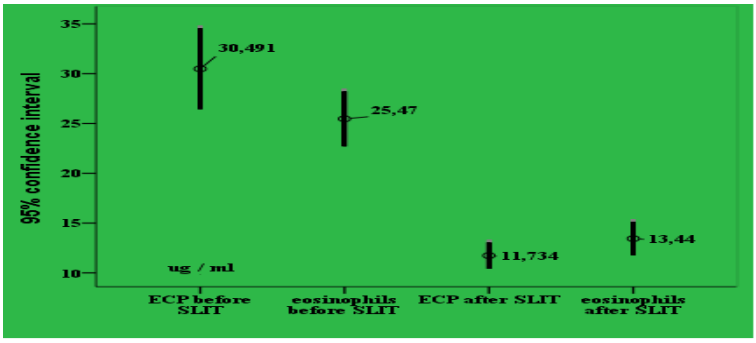
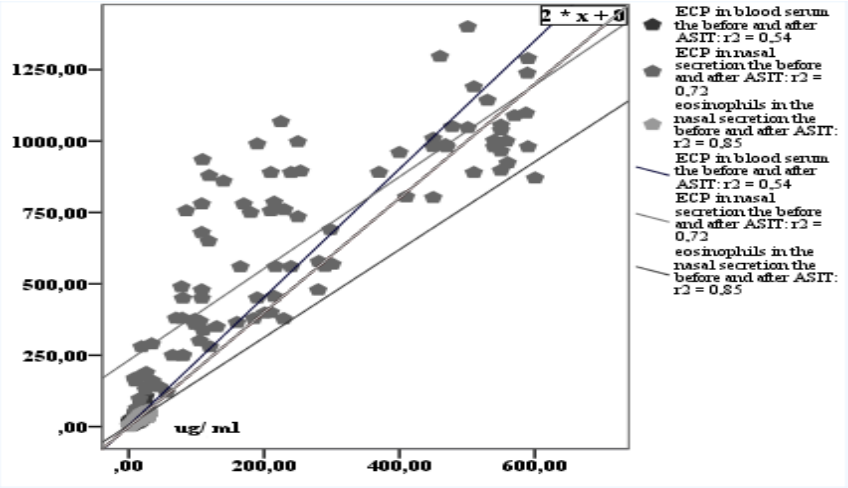


Authentic decrease of ECP was revealed almost in 2,5 times after the second course of ASIT in both investigated groups. The average level of ECP in the 1st group decreased in 2,6 times (from 30,5±21 till 11,7±18 mcg/l), in the 2nd group in 2,4 times (from 34,6±24 to 14,41±11 mcg/l).

Interconnection between ECP concentration in blood serum, nasal secretion and number of eosinophils after sublingual ASIT



The best results were obtained in the first group, that indicated about the interconnection of ECP concentration decrease in blood serum with the degree reduction of allergic inflammation intensity of mucous membrane of the nose, determined by the ECP level and eosinophils of nasal secretion ($p<0.001$).

Correlational analysis on the background of SLIT				
		The content of ECP in blood serum	The content of ECP in nasal secretion	The content of eosinophils in the nasal secretion
The content of ECP in blood serum	Pearson correlation (r)	1	,529***	,573***
	P (2-sides)		,000	,000
	N	100	100	100
The content of ECP in nasal secretion	Pearson correlation (r)	,529**	1	,698***
	P (2-sides)	,000		,000
	N	100	100	100
The content of eosinophils in the nasal secretion	Pearson correlation (r)	,573**	,698***	1
	P (2-sides)	,000	,000	
	N	100	100	100
Notes: ***. Correlation is significant at the level of 0.001 (2-sides.).				

Received results indicate about the presence of linear dependence and significant correlational connection between mentioned above allergic markers, confirming the effectiveness of SLIT at patients with pollinosis, especially of child age.

CONCLUSION

Thus, according to this research results, the achievement of positive clinical effect using subcutaneous and sublingual methods of ASIT demonstrates the expedience of its performing and allows to consider them as perspective treatment methods of pollinosis, especially at patients of child age.

Our carried out research of methods of allergen-specific immunotherapy performing showed that sublingual ASIT during the pollen sensibilization is more effective and safe method of pollinosis treatment nowadays.

Today, the molecular allergodiagnostics with the study of recombinant allergens levels is more useful and acceptable method at the selection of patients for ASIT, determining the cross-reactivity and reaction severity, associated with various allergens.

Patients were determined as priority groups for the administration of sublingual ASIT, having less experience of sickness rate, child age, patients with monosensibilization.

REFERENGES

[1] Papadopoulos NG, Hatzler L, Hofmaier S. Allergic airway diseases in childhood - marching from epidemiology to novel concepts of prevention.*Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology,2012,* 23(7):616-22.

[2] Maslova L. Efficacy and mechanisms of sublingual immunotherapy in patients with allergic diseases of the respiratory tract, Cand ... Doctor. Honey. Sciences: 14.03.09 - Belarus 2014.

[3] Ado A.D. Total allergist. M.: Medicine, 1978, 463 p.

[4] Papadopoulos NG, Schmid-Grendelmeier P, Carlsen KH. How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA (2) LEN statement. // Allergy. 2011, Jun;66(6):765-74.

[5] E. Valovirta, L. Jacobsen, C. Ljørring. Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children // Allergy October 2009Volume 61, Issue 10, pages 1177–1183.

[6] Valovirta E, Calderon MA, Eichler I, Matricardi PM. Perspectives on allergen-specific immunotherapy in childhood: an EAACI position statement // Pediatric Allergy and Immunology 2012 Volume 23, Issue 4, pages 300–306.

[7] Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M. Sublingual immunotherapy: World Allergy Organization position paper 2013 update // World Allergy Organization Journal 2014.

[8] Moises A Calderon, Pascal Demoly, Roy Gerth van Wijk, Jean Bousquet et al. EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy // Clinical and Translational Allergy 2012, 2:20 (30 October 2012).

[9] Cheryl S. Hankin, Linda Cox, Amy Bronstoneet al. Allergy immunotherapy: Reduced health care costs in adults and children with allergic rhinitis // Journal of Allergy and Clinical Immunology February 01, 2013

[10] Rudolf Valenta, Clarissa Cabauatan, RaffaelaCampana, Garib Victoria et al.Induction of allergen-specific blocking IgG using patch delivered recombinant Bet v 1 in guinea pigs // Clinical and Translational Allergy 2014, 4(Suppl 2):O18 (17 March 2014)

[11] Morenko M.A.Clinico - pharmacological rationale for inclusion of preparations of glycyrrhizic acid in the pharmacotherapy of bronchial asthma in children Author. ... Doctor. Honey. Sciences: 14.00.25 - Astana, 2010. – 28

[12] Skuchalina L.N.Starosvetova E.N., Gavrish L.N. The prevalence of symptoms of asthma, allergic rhinitis and allergic children of Northern Kazakhstan according to the criteria ISAAC // Allergology. - 2001. - №1. - S.10-13

[13] Ispaeva J.B. Allergic diseases in children of the Republic of Kazakhstan // Abstracts of the second International Conference «Allergic diseases in children." - Almaty, 2000. - C.5.

[14] Rozenson R.I., Saparova L.T., Garkalov K.A. Peak expiratory flow rate in schoolchildren in Northern Kazakhstan // Astana Meditsinalyқ Journals. - 2000. - №4. - S.128-129.

[15] Moises A Calderon, Pascal Demoly, Roy Gerth van Wijk, Jean Bousquet et al. EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy **//** Clinical and Translational Allergy 2012, 2:20 (30 October 2012).

[16] Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ; Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy ClinImmunol. 2010 Sep; 126(3):466-76. doi: 10.1016/j.jaci.2010.06.047.

[17] Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M. Sublingual immunotherapy: World Allergy Organization position paper 2013 update // World Allergy Organization Journal 2014.