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Impact of immunotherapy with autologous activated T-lymphocytes on clinical parameters and quality of life in patients with allergic bronchial asthma

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ABSTRACT

Aim. To assess the impact of autologous activated T-lymphocyte immunotherapy on clinical parameters and quality of life in patients with allergic bronchial asthma (BA) in comparison with patients with allergic BA who received standard therapy.

Materials and methods. A non-randomized, pilot study included 19 patients with allergic BA of moderate severity (7 men and 12 women aged 23–61 years, average age – 38.5 ± 4.3 years) who received the T-cell vaccine (n = 12) and standard therapy with inhaled glucocorticoids, short- and long-acting β2-adrenergic agonists (n = 7). After signing an informed consent, the patients were subcutaneously injected with autologous activated T-lymphocytes with a frequency of 4 injections 1 time / week, and then 6 injections 1 time / month. The research methods included asthma control measurement according to the ACQ-5 questionnaire and quality of life assessment according to the AQLQ(S) questionnaire. Clinical data were collected during lung function tests and by measuring the total immunoglobulin E (IgE) level.

Results. In the course of the study, the immunotherapy was well tolerated, no systemic adverse reactions were noted. The treatment approach in the patients who received the T-cell vaccine resulted in significant improvement of asthma control parameters (according to the ACQ-5 questionnaire) and parameters of the patients' quality of life (according to the AQLQ(S) questionnaire) within all 4 categories. Besides, their lung function improved by the end of treatment, and the total IgE level decreased. No significant changes in these parameters were observed during the follow-up in patients who received standard therapy. The study was conducted before immunotherapy, after 2 months (after 5 injections), and after 7 months (after 10 injections).

Conclusion. Evaluation of the impact of immunotherapy with autologous activated T-lymphocytes on the clinical parameters and quality of life in patients with BA indicates effectiveness of treatment in patients with allergic BA.

Keywords: bronchial asthma, T-cell therapy, activated T-cells, patients' quality of life, lung function, immunoglobulin E

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Влияние иммунотерапии активированными аутологичными Т-лимфоцитами на клинические параметры и качество жизни пациентов с аллергической формой бронхиальной астмы

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РЕЗЮМЕ

Цель. Оценить влияние иммунотерапии активированными аутологичными Т-лимфоцитами на клинические параметры и качество жизни пациентов с аллергической формой бронхиальной астмы (БА) и сравнить с пациентами с аллергической формой БА, получавшими стандартную терапию.

Материалы и методы. В нерандомизированное пилотное исследование включены 19 пациентов с аллергической формой БА (7 мужчин и 12 женщин в возрасте от 23 лет до 61 года, средний возраст – 38,5 ± 4,3 лет) со средней степенью тяжести, получавших Т-клеточную вакцину (n = 12) и стандартную терапию ингаляционными глюкокортикостероидами, β2-адреномиметиками короткого и длительного действия (n = 7). Пациентам после получения информированного согласия вводились аутологичные активированные Т-лимфоциты подкожно с кратностью 4 инъекции 1 раз/нед, а затем 6 инъекций 1 раз/мес. Методы исследования включали оценку степени контроля над астмой по опроснику ACQ(5), оценку качества жизни больных БА по опроснику AQLQ(S). Определение клинических параметров оценивалось путем измерения функции внешнего дыхания и уровня общего иммуноглобулина Е (IgE).

Результаты. В ходе исследования была отмечена хорошая переносимость иммунотерапии, системные побочные реакции отсутствовали. При использовании данного метода показано достоверное улучшение показателей контроля над астмой (по опроснику ACQ5) и качества жизни пациентов (по опроснику AQLQ(S)) по всем четырем сферам влияния, а также увеличение уровня функции внешнего дыхания к окончанию лечения, снижение уровня общего IgE у пациентов, получавших Т-клеточную вакцинацию. У пациентов со стандартной терапией достоверных изменений данных показателей за период наблюдения не отмечено. Исследование проводилось до иммунотерапии, через 2 мес (после 5 инъекций) и через 7 мес (после 10 инъекций).

Заключение. Проведенная оценка влияния иммунотерапии активированными аутологичными Т-лимфоцитами на клинические параметры и качество жизни пациентов с БА свидетельствует об эффективности проведенного лечения у пациентов с аллергической формой заболевания.

Ключевые слова: бронхиальная астма, Т-клеточная терапия, активированные Т-клетки, качество жизни пациентов, функция внешнего дыхания, иммуноглобулин Е

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INTRODUCTION

Bronchial asthma (BA) is a chronic inflammatory disease of the respiratory tract, the pathogenesis of which involves a number of immunocompetent cells and inflammatory mediators, leading to specific pathophysiological changes [1]. Currently, statistics show that about 235 million people worldwide suffer from BA [2]. According to the latest estimates of the World Health Organization, released in December 2016, there were 383,000 asthma-related deaths around the world [2]. The majority of BA patients respond well to conventional therapy, achieving disease control. However, a significant proportion of patients (20–30%) are refractory to standard therapy [3].

It is necessary to search for new approaches to treatment that provide patients with the optimal quality of BA therapy. Regulatory T cells, which play a suppressive role in the immune response, are of great importance in the pathogenesis of BA. In addition to genetic predisposition to IgE hyperproduction and imbalance of Th2 / Th1 cells, a functional decline of regulatory T cells contributes to the development of allergic reactions. Regulatory cells exert a suppressive effect by inhibiting T-lymphocytes and B-lymphocytes, suppressing the production of proinflammatory cytokines and secreting transforming growth factor (TGF)-β and interleukin (IL)-10 [4]. Direct and indirect targets of regulatory T cells include dendritic cells, T-helpers, B-lymphocytes, IgE-producing cells, mast cells, basophils, and neutrophils. One of the innovative treatment approaches is cellular immunotherapy, based, in particular, on injection of autologous activated T cells [5]. The mechanism of action of immunotherapy is based on recognition and killing of T cells carrying activation marker determinants, which enhances the natural regulatory mechanisms in relation to regulatory T cells [6]. This approach has been shown to be effective in regulating allergic inflammation [5].

The aim of the study was to assess the effect of immunotherapy with autologous activated T-lymphocytes on the clinical parameters and quality of life in patients with allergic BA in comparison with patients in the control group receiving standard therapy.

MATERIALS AND METHODS

The study included 19 patients (7 men and 12 women aged 23–61 years, average age – 38.5 ± 4.3 years) with allergic BA of moderate severity, who were treated at the Immunopathology Clinic of the Research Institute of Fundamental and Clinical Immunology. The patients were receiving standard therapy during 12 weeks prior to enrollment in the study. Inhaled glucocorticoids (IGCs) in combination with long-acting β2-adrenergic agonists and antileukotriene drugs were used as backbone therapy. Inclusion criteria were the age range from 18 to 65 years inclusive; the diagnosis of BA verified at least 12 months prior to inclusion in the study; the presence of backbone IGC therapy for at least 12 weeks; a lack of complete control of BA; forced expiratory volume in one second (FEV1) of 50–90%; the absence of chronic infectious and autoimmune diseases and cancer.

The method for obtaining autologous activated T-lymphocytes from peripheral blood was described earlier [7]. In addition to standard backbone BA therapy, patients were administered autologous activated T-lymphocytes subcutaneously 1 time per week (4 injections), followed by 1 time per month (6 injections).

Evaluation methods to identify the clinical efficacy of immunotherapy included assessment of asthma control parameters (according to the ACQ-5 questionnaire) and quality of life parameters (according to the AQLQ(S) questionnaire), lung function tests and determination of the total IgE level. The study was conducted before the immunotherapy, after 2 months (5 injections), and after 7 months (10 injections). The volume and rate of respiration were measured to analyze the external respiration function. The survey data were recorded on a personal computer using the Spida_5 diagnostic software program. Serum IgE levels were assessed by enzyme-linked immunosorbent assay (ELISA). Statistical processing of quantitative data was carried out using Statistica software, version 6.0. The sample was tested for normal distribution using the Shapiro – Wilk test (for small samples). The data were presented as the median and interquartile range $Me\ (Q_{25};\ Q_{75})$, as well as the mean and its error $M \pm m$. To evaluate the research results, the nonparametric Mann – Whitney and Wilcoxon tests were used. The differences were considered statistically significant at $p < 0.05$.

RESULTS

During treatment with autologous activated T-lymphocytes, 2 out of 12 patients experienced single local adverse reactions, such as hyperemia, swelling, and pain at the injection site, which disappeared without a trace within a few hours.

The changes in the clinical parameters resulted in significant improvement of asthma control parameters according to the ACQ-5 questionnaire (Table 1). The mean score before treatment was 2.02; which, according to the ACQ-5 and ACT scores and the level of asthma control according to the Global Initiative for Asthma (GINA), corresponds to uncontrolled BA [8]. The mean score after treatment was 1.27, which corresponds to partially controlled BA [8]. The difference of 0.5 points is clinically significant during treatment [8].

Table 1

Assessment of asthma control parameters according to the ACQ-5 questionnaire during therapy with autologous activated T-lymphocytes, *M* ± *m*

Parameter	Comparison groups of patients with allergic BA					
	T cell therapy, *n* = 12			Standard treatment, *n* = 7		
	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)
ACQ-5	2.02 ± 0.46	1.53 ± 0.35	1.27 ± 0.39*	2.23 ± 0.48	2.26 ± 0.47	2.00 ± 0.65

* significant differences compared with the parameter before the therapy, $p = 0.02$.

The results of quality of life assessment in patients with allergic BA during immunotherapy according to the AQLQ(S) questionnaire are presented in Table 2. Friedman's test of variance showed that in the group of patients receiving immunotherapy, a significant change in parameters was noted by the end of treatment in all categories of the questionnaire, such as "Symptoms", "Activity limitation", "Emotional sphere", and "Environmental influence". In addition, in the course of therapy, the score in the "Activity limitation" category significantly increased compared with the parameter 2 months after the start of therapy.

The level of serum IgE in patients with allergic BA receiving immunotherapy significantly decreased after 2 months of such treatment and continued to significantly decrease after 7 months (Table 3). In the control group receiving standard therapy, no significant changes by the end of treatment were revealed.

Table 2

Assessment of the quality of life in patients with BA according to the AQLQ(S) questionnaire during therapy with autologous activated T-lymphocytes, *Me* (Q_{25}; Q_{75})

Parameter	Comparison groups of patients with allergic BA					
	T cell therapy, *n* = 12			Standard treatment, *n* = 7		
	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)
Symptoms	5.45 (3.2; 6.1)	5.25 (4.9; 6.2)	5.8 (5.08; 6.7)* $p_{3-1} = 0.045$	4.4 (3.8; 5.5)	4.5 (3.6; 5.8)	5 (4.04; 5.9)
Activity limitation	5.6 (4.9; 6.1)	6.3 (5.3; 6.7)	6.6 (5.4; 6.7)*# $p_{3-2} = 0.043$ $p_{3-1} = 0.005$	5.3 (5.1; 5.6)	5.4 (5.1; 6.5)	5.7 (4.9; 6.05)
Emotional sphere	5.3 (3.8; 6.6)	5.4 (5.0; 5.6)	6.4 (5.2; 6.4)* $p_{3-1} = 0.021$	4.8 (3.8; 6.0)	4.8 (3.8; 6.4)	6.5 (5.2; 6.7)
Environmental influence	4.9 (4.0; 5.75)	5.75 (4.0; 6.0)	6.25 (4.0; 7.0)* $p_{3-1} = 0.009$	5 (4.5; 6.5)	4.75 (4.25; 6.25)	6.9 (5.5; 8.0)

* significant differences compared with the parameters before the therapy ($p < 0.05$).
# significant differences compared with the parameters 2 months after the start of the therapy.

Table 3

The level of total serum IgE in the course of therapy with autologous activated T-lymphocytes, *Me* (Q_{25}; Q_{75})

Parameter	Comparison groups of patients with allergic BA					
	T cell therapy, *n* = 12			Standard treatment, *n* = 7		
	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)
lgE (IU / ml)	231 (58; 3,000)	163 (65; 1,721)*	145.5 (72; 1,357)* $p_{2-1} = 0.017$ $p_{3-1} = 0.033$	84 (32; 125)	90 (13; 326)	75 (11; 184)

* significant differences compared with the parameters before the treatment ($p < 0.05$)

According to spirometry data, in the group of patients with allergic BA receiving immunotherapy, there was significant improvement in forced expiratory volume in one second (FEV1), vital capacity (VC), and forced vital capacity (FVC) and a trend toward an increase in the Tiffeneau index ($p = 0.059$) by the end of the treatment. The results are presented in Table 4. In the control group receiving standard treatment, a significant increase in VC after 2 months was observed; no significant changes by the end of the follow-up were noted.

Table 4

Characteristics of the external respiration function in the course of therapy with autologous activated T-lymphocytes, *Me* (Q_{25}; Q_{75})

Parameter	Comparison groups of patients with allergic BA					
	T cell therapy, $n = 12$			Standard treatment, $n = 7$		
	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)	Point 1 (before the treatment)	Point 2 (after 2 months – 5 injections)	Point 3 (after 7 months – 10 injections)
VC	105 (99; 116)	110 (10; 113)	115 (103; 121)* $p_{3-1} = 0.033$	103 (93; 109)	111 (103; 117)* $p_{2-1} = 0.018$	112 (95; 114)
FVC	109.5 (103; 121)	112 (108; 117)	118 (109; 122)* $p_{3-1} = 0.014$	103 (100; 112)	110 (97; 120)	103 (95; 115)
FEV1	94 (88.5; 102.5)	99 (88; 114)	99.5 (93.5; 112.5)* $p_{3-1} = 0.028$	96 (93; 100)	99 (92; 109)	96 (95; 114)
Tiffeneau index	91 (78; 98)	93 (86; 102)	97 (84; 102)	97 (93; 99)	96 (89; 98)	103 (89; 106)

* significant differences compared with the parameters before the treatment, $p < 0.05$.

Based on the data obtained, we can speak of good tolerability and clinical efficacy of immunotherapy with autologous activated T-lymphocytes in patients with allergic BA.

DISCUSSION

The main advantages of cell therapy include safety and the absence of systemic side effects, since the patient is injected with their own cells with a slight modification. The study showed safety and good tolerability of immunotherapy with T-lymphocytes in BA; previously, safety of this was shown in atopic dermatitis [9].

An important criterion of therapy effectiveness is parameters of asthma control according to the ACQ-5 questionnaire. According to the comparative characteristics of the GINA, Goal, and ACQ-5 rating scales, there is reason to believe that the use of the ordinal ACQ-5 scale is a more appropriate and preferred tool for assessing changes in asthma control in clinical trials [10]. An increase in the asthma control level from uncontrolled to partially controlled BA according to GINA is clinically significant during treatment. The quality of life assessment in patients with BA is also a criterion of therapy effectiveness; an improvement in the parameters in all 4 categories is usually observed by the end of treatment, the changes are significant.

Immunoglobulin E is the main participant of type I hypersensitivity, according to which allergic reactions occur, including BA. The severity of clinical manifestations of allergy may depend on the quantitative parameter of allergen-specific IgE. Upon repeated contact with the allergen, which binds to allergen-specific IgE already produced during sensitization, degranulation of mast cells with release of preexisting early mediators of allergic inflammation occurs along with *de novo* synthesis of lipid mediators – products of arachidonic acid metabolism. A decrease in the IgE level indicates a positive effect of immunotherapy in patients with allergic BA.

Regular monitoring of lung function is especially important for patients with BA, as symptoms of the disease are difficult to detect until airflow obstruction becomes severe. The main parameters of spirometry, reflecting the degree of pulmonary obstruction, are FVC and FEV1. The use of immunotherapy with T-lymphocytes had a positive effect on the lung function in patients with allergic BA. Autologous activated T-lymphocytes are non-toxic and have practically no side effects, which makes immunotherapy a promising approach to BA treatment.

CONCLUSION

In our study, safety and good tolerability of immunotherapy with activated T-lymphocytes in patients with BA has been shown. The therapy was effective in relation to the allergic form of the disease. This was manifested through significant improvements in the degree of asthma control according to the ACQ-5 questionnaire and the quality of life parameters according to the AQLQ(S)

questionnaire, a significant decrease in the total IgE level, and significant improvement in the lung function by the end of the treatment.

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