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Immunotherapy with Leukocyte Immunomodulator Dialysate in Patients with Multidrug-Resistant Tuberculosis

Key words: *multidrug-resistant tuberculosis, leukocyte immunomodulator.*

Leukocyte immunomodulators are high-purity homogenous low molecular weight proteins (< 5 kDa) from immune cells which take part in reactions of inhibited type and are able to transfer reactions of cell-mediated immunity from sensitized donor to non-immune recipients [10]. They include high level of tyrosine and glycine with high similarity to N-terminal sites of some neuropeptides of enkephalin family and are antigen-specific [10]. From the moment of their discovery by Sherwood Lawrence, almost 50 years ago, the interest to these peptides is connected with their therapeutic and prophylactic action in case of diseases where cell-mediated immunity plays the key role – intracellular bacterial diseases (tuberculosis, leprosy), viral infections (herpes simplex virus, chickenpox), parasitic infections (leishmaniasis, toxoplasmosis), as well as primary immunodeficiency (chronic granulomatosis, Wiskott-Aldrich syndrome) of certain types of cancer [3, 4, 7, 8, 12].

Tuberculous infection is controlled mainly by cellular component of immune system. Th1-type proinflammatory cytokines – such as interferon gamma and tumor necrosis factor alpha (TNF-α) – play the central part in this process inducing macrophage activation and expression of nitric oxide synthetase which bacterially acts on the intracellulary located mycobacteria. This protective potency is significantly decreased or lost if Th2-type cytokines dominate in inflammatory process [6]. Using cellular models of pulmonary tuberculosis of mice it was found out that at the initial phase of the disease the active production of TNF-α and nitric oxide takes place, and the tuberculous granuloma is developed. A month after infection, their concentration in supernatant of immune cell culture is significantly decreased, and the inflammation becomes chronic with decrease in reactions of inhibited type versus mycobacteria antigens. There begins the pneumonia with apparent humoral reactions, which dominates over granulomatous inflammation [5, 9]. Using this cellular model, F. A. Fahre and co-authors injected leukocyte immunomodulator to mice infected with tuberculosis, from which, after the course of treatment, they received bronchoalveolar lavage for cultivation of cell culture. Leukocyte immunomodulator was produced out of immune cells of donors sensitized by tuberculosis mycobacteria (positive tuberculin test). It was proved that concentration of TNF-α and nitric oxide in supernatant of macrophage culture received out of brochoalveolar lavage of treated mice increased as compared to initial level, and the survival rate of infected animals also grew up [11].

As of today, there have been determined the universal indications for use of leukocyte immunomodulators – inhibition of T-cell component of the immune system with disturbance of balance between Th1 and Th2 lymphocytes for its optimization. Disseminated pulmonary tuberculosis in patients with multidrug-resistant tuberculosis mycobacteria (TMB) is accompanied by lower indices of proliferative activity of T-lymphocytes, levels of $CD4^+$, $CD8^+$, $CD20^+$, $CD25^+$ cells, and concentration of TNF-α, interleukin 2 (IL-2) in blood serum than in patients with TMB resistant to not more than one drug [1]. In patients with multidrug-resistant tuberculosis (MRTB) the immune response is developed mainly by humoral type [2].

All mentioned above has become the grounds for application of leukocyte immunomodulator in patients with MRTB and determined the objective of study – to determine the effect of leukocyte immunomodulator on the immunological reactivity and efficiency of chemotherapy for patients with MRTB.

Materials and methods of study

Clinical and immunological controlled study included 36 patients with MRTB and extended-resistance tuberculosis (XDTB). Main criteria for inclusion into the study were: absence of positive roentgenological dynamics during

2–4 months of intensive antituberculous chemotherapy. The distribution of patients between study and control groups was performed by matching pairs according the character of tuberculous process and the profile of tuberculosis mycobacteria susceptibility to drugs. In the study group during the intensive phase of chemotherapy the leukocyte transfer factor was used (18 patients), while 17 patients from control group received chemotherapy alone.

The study group included 15 women (83,3 %) and 3 men (17,7 %), while in control group their number was 12 and 6, respectively, which did not presented any intergroup, $p > 0,05$. The age of patients was (32,0 ± 2,2) years and (30,8 ± 3,1) years, $p > 0,05$. Both groups had the equal number of patients with the same type of disease and profile of drug resistance: MRTB was in 11 (61,1 %) patients, and extended-resistance tuberculosis – in 7 (38,9) patients. Chemotherapy was carried out according to the results of drugs resistance test using 5–6 antituberculous drugs.

In course of study the leukocyte immunomodulator Immodin of Sevafarma: production (Czech Republic) was used. The drug is produced in ampules in the form of frozen-dried powder for preparation of injection solution (1 dose contains the quantity of active substance which is equal to that contained in 200 million donor leukocytes; this dose is solved in 4 ml of water for injections and is injected subcutaneously). The drug contains over 200 immunomodulating components: cytokines (interleukins, interferons, colony-stimulating factor, etc.), specific components of antigens, receptors (epitopes), with the help of which immunocompetent cells interact forming the adequate immunological response («sum of immunological experience» of donors, according to G. Pizza, 2004). The treatment regimen included taking of 4 doses: three main doses (1 dose once a week), and the fourth dose is taken month later.

The results of treatment were evaluated in two months after the beginning of therapy with leukocyte immunomodulator and at the end of such treatment on the background of intensive phase of chemotherapy on the basis of clinical and laboratory indices, roentgenological data and immunological indices.

The content of leukocytes and their distinct populations in blood was determined with the help of hemanalyzer ABX-mscros 60 (France). With the help of two-color continuous-flow laser cytometry (continuous-flow cytofluorometer FACSCalibur, Canada), using monoclonal antibodies (Beckman Coulter, USA) we performed lymphocyte phenotyping and determined relative and absolute content of pan-T-cells ($CD3^+19^-$), T-helpers/inducers ($CD4^+8^-$), cytotoxic T-cells ($CD4^-8^+$), balance of CD4 and CD8 lymphocytes (immunoregulatory index for detection of immunoregulatory subpopulations imbalance), mature B-lymphocytes ($CD3^-19^+$), natural killers ($CD3^-16^+$). Proliferative response of lymphocytes to phytohemagglutinin was studied within the reaction of blast formation (BFR with PHA), and the calculations were made with the help of microscoping of colored smears.

Activity of B-cells (CD19) was evaluated according to the levels of serum immunoglobulins of A, M, G types, using the method of solid-phase immune-enzyme analysis, with the help of commercial test systems «Hema-Medica» (Russia).

The condition of phagocytic component of the immune system was evaluated using the method of continuous-flow cytometry according to the ability of neutrophylic granulocytes and monocytes to absorb the test objects labeled with fluorochromes (FITC). Oxygen-dependent metabolism of these cells was evaluated according to indices of oxygen active forms (OAF-test – spontaneous and zymosan-induced), which were also determined by the method of continuous-flow cytofluorometry using DCFH DA and calculating the coefficient of phagocyte stimulation (induced OAF-test results to spontaneous OAF-test results ratio).

Cytokine content in blood serum was determined by the method of solid-phase immune-enzyme analysis using commercial test-systems: TNF-α, IL-4, IL-6, IL-2 («Vector-Best», Russia) in immune-enzyme analyzer pi LX80 (USA).

All the results were presented as n — number of examined patients in the group, arithmetical mean value (M), error of arithmetical mean value (m), and as proportions and percentage with indication of confidence interval (CI). Confidence intervals were calculated at the set significance level of $\alpha < 0.05$. In order to evaluate the statistically significant difference between mean values of indices in samples the Wilcoxon-Mann-Whitney criterion was used. The probability level was regarded as the values of the index of probability of the difference between the groups (p) which were equal to/less than 0,05. The presence of relation between samples with qualitative parameters was verified using contingency table with the help of Pearson criterion c2. If the analyzed values were equal to or less than 5, the accurate Fisher's test was used.

The works were performed at the expense of the state budget.

Results and discussion

Table 1 contains the treatment results after the end of leukocyte immunomodulator course (in 2 months).

In the result of complex therapy using leukocyte immunomodulator, the significantly larger number of patients with MRTB showed significant improvement within 2 months, which was manifested by the disappearance of clinical symptoms, severe resorption of infiltrative changes in lungs, healing and regression of cavities (fig. 1, 2).

Leukocyte transfer factor was well-tolerated and did not cause any side reactions during the course of application.

In a study of cellular immunity in patients with MRTB from both groups before the appointment of immunomodulator during chemotherapy, we found a significant decrease in the total number of CD3 lymphocytes (relative and absolute indices), number of CD4 lymphocytes, an increase in number of CD8 lymphocytes, and the reduction in the rates of immunoregulatory index as compared to the healthy, $p < 0,05$ (table 2).

After the course of leukocyte immunomodulator therapy the patients from study group, as opposed to the control group, demonstrated probable positive changes in T-mediated immunity, which showed themselves in the form of increase in absolute number of CD3 lymphocytes, mainly due to absolute and relative amount of their T-helper fraction – CD4

Table 1

Effect of leukocyte immunomodulator on the efficiency of treatment of patients with multidrug-resistant tuberculosis

Clinical-laboratory and roentgenological dynamics	Groups of patients					
	Study (n = 18)			Control (n = 18)		
	Abs. number	%	CI	Abs. number	%	CI
Significant improvement (disappearance of symptoms, significant/complete resorption of infiltrative changes, healing and regression of cavities)	10	55.6*	30.8-78.5	4	22.2	6,4–46,7
Moderate improvement (symptom relief, moderate resorption of infiltrative changes, regression of cavities)	6	33.3*	13,3–59,0	5	27.8	9,7–53,5
No positive dynamics	2	11,1	1,4–34,7	9	50.0	26,0–74,0
Deterioration	0	0.0		0	0.0	

Note: * – intergroup difference in index values is statistically reliable, $p < 0.05$.

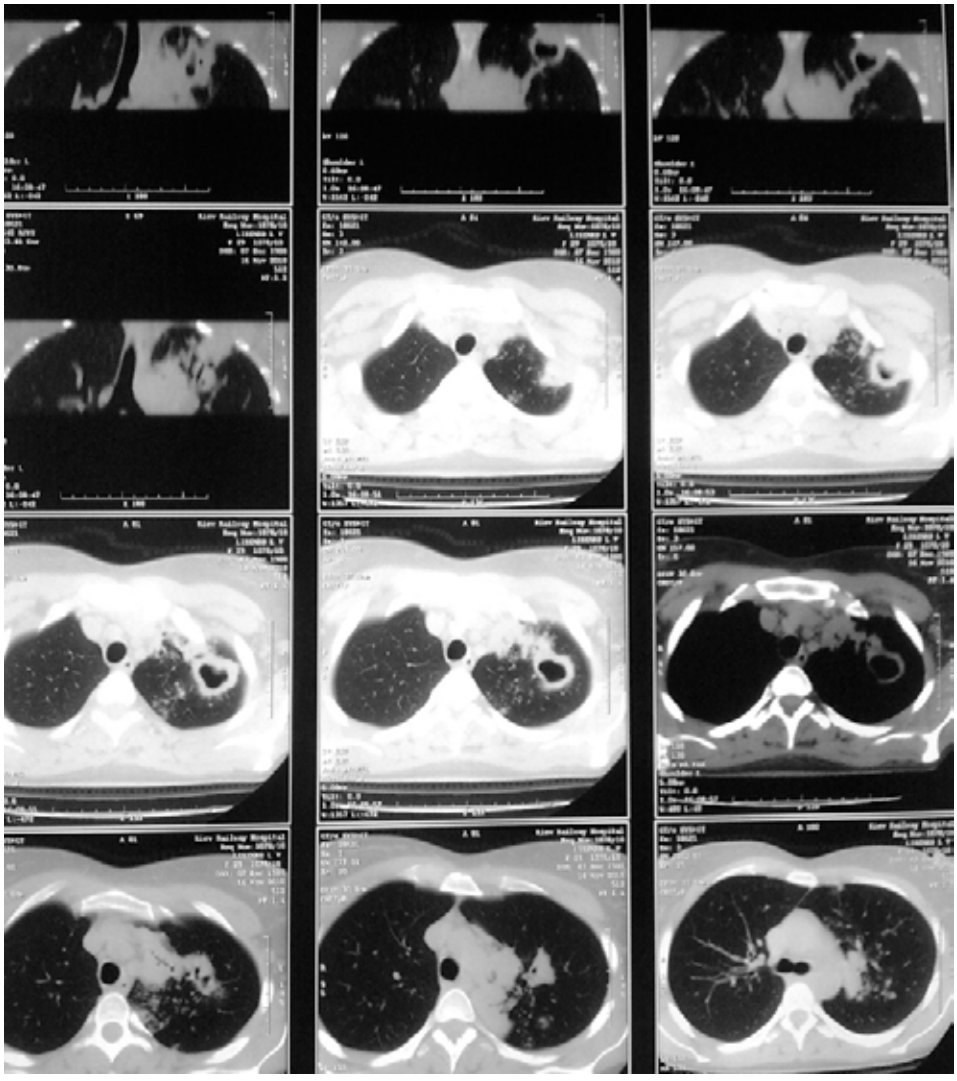

Fig. 1. **Axial section on CT-scans of the patient at the moment of appointment of leukocyte immunomodulator: showing the cavity with thick walls surrounded by infiltrative and focal lesions of pulmonary tissue**

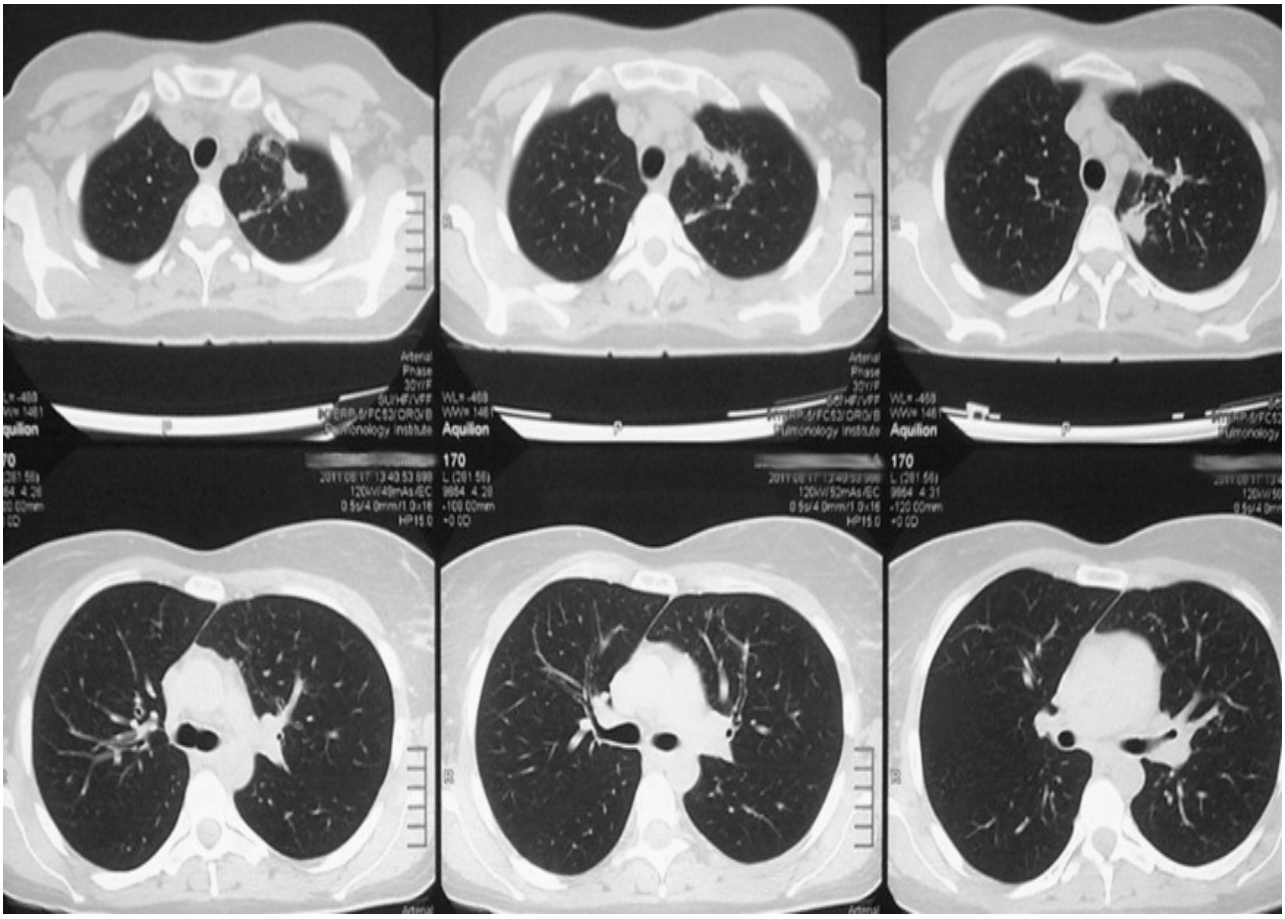

Fig. 2. **Axial sections on CT-scans of the patient after the course of leukocyte immunomodulator therapy: showing apparent resorption of infiltrative and focal changes in lungs, healing of the cavity**

Table 2

Effect of leukocyte immunomodulator on indices of T-mediated immunity in patients with multidrug-resistant tuberculosis (M ± m)

Indices of T-mediated immunity	Groups of patients				
	Study (n = 18)		Control (n = 18)		Healthy (n = 25)
	Before treatment	After treatment	Before treatment	After treatment	
CD3 (%)	62,2 ± 3,0 *	63,5 ± 2,4*	63,1 ± 2,8 *	64,6 ± 2,2*	71,5 ± 0,8
CD3 (10^9/l)	1,2 ± 0,07*	1,5 ± 0,1#	1,2 ± 0,02*	1,2 ± 0,01*	1,4 ± 0,04
CD4 (%)	35, 0± 2,1*	39,6 ± 1,9#	36,3 ± 1,9*	36,6 ± 2,1*	41,2 ± 0,9
CD4 (10^9/l)	0,7 ± 0,04*	0,94 ± 0,07#	0,7 ± 0,02*	0,7 ± 0,06*	0,88 ± 0,02
CD8 (%)	33,5 ± 3,4*	24,6 ± 1,8	36,7 ± 2,7*	34,5 it 2,2*	25,5±0,6
CD8 (10^9/l)	0,78 ± 0,1*	0,6 ± 0,06	0,7 ± 0,06*	0,7 ± 0,04	0,51± 0,04
CD16 (%)	9,5 ± 1,8	11,4 ± 1,8	10,4 ± 2,1	10,4 ± 2,2	12,5 ± 0,7
CD16 (10^9/l)	0,2 ± 0,05	0,3 ± 0,05	0,2 ± 0,04	0,2 ± 0,04	0,3 ± 0,03
CD4/CD8 (s.u.)	1,4 ± 0,1*	1,8 ± 0,09#	1,4 ± 0,05*	1,5 ± 0,02*	2,0 ± 0,06
BFR with FHA (%)	60,3 ± 2,2	62,8 ± 1,8	62,8 ± 2,6	63,2 ± 2,5	63,5 ± 0,7

Notes: * – difference in index values as compared to such in healthy is statistically reliable, $p < 0.05$;
– difference in index values is statistically reliable as compared to initial level, $p < 0.05$.

Table 3
Effect of leukocyte immunomodulator on B-cell immunity system in patients with multidrug-resistant tuberculosis (M ± m)

Indices of B-cell immunity	Groups of examined patients				
	Study (n = 18)		Control (n = 18)		Healthy (n = 25)
	Before treatment	After treatment	Before treatment	After treatment	
CD19 (%)	11,7 ± 1,3	9,0 ± 1,0*#	12,3 ± 2,1	11,5 ± 2,2	14,0 ± 0,6
CD19 (109/l)	0,25 ± 0,04	0,21 ± 0,03	0,22 ± 0,02	0,22 ± 0,06	0,22 ± 0,02
Ig G (g/l)	15,8 ± 2,0	14,0 ± 1,6	14,5 ± 2,4	14,2 ± 2,6	14,5 ± 0,6
Ig M (g/l)	3,27 ± 0,7*	2,4 ± 0,2#	3,5 ± 0,4*	3,6 ± 0,3*	2,2 ± 0,2
Ig A (g/l)	2,3 ± 0,3	2,8 ± 0,2	2,5 ± 0,4	2,6 ± 0,2	2,9 ± 0,2

Notes: Ig – immunoglobulin; * – difference in index values as compared to such in healthy is statistically reliable, $p < 0.05$;
– difference in index values is statistically reliable as compared to the initial level, $p < 0.05$.

Table 4
Effect of leukocyte immunomodulator on phagocytosis indices in patients with multidrug-resistant tuberculosis (M ± m)

Indices of phagocytic component of the immune system	Groups of examined patients				
	Study (n = 18)		Control (n = 18)		Healthy (n = 25)
	Before treatment	After treatment	Before treatment	After treatment	
neutrophilocytes (Nc)					
Nc (%)	65,7 ± 2,6*	61,5 ± 2,3#	67,3± 3,0*	66,2 ± 1,9*	60,0± 1,1
Nc (10^9/l)	6,8 ± 0,9*	5,2 ± 0,6#	6,6 ± 0,5*	6,9± 1,0*	4,5± 0,2
OAF-test (spontaneous) (s.u.)	36,6 ±7,3*	40,8 ± 2,7*	39,3±6,9*	42,2±6,5*	18,7 ± 0,9
OAF-test (induced) (s.u.)	280,0 ±32,2	319,5±21,7	340,7±19,6	390,4±32,7	338,7 ± 10,2
Stimulation factor (%)	3,5±0,7	3,1 ±0,9	3,3±0,5	3,1 ±0,9	3,8 ±0,1
Monocytes (Mc)					
Monocytes (%)	3,7 ± 0,2*	4,5 ± 0,4#	3,5 ± 0,4*	3,3 ± 0,4*	5,0 ± 0,4
Monocytes (10^9/l)	0,29 ± 0,02*	0,4± 0,04#	0,26 ± 0,05*	0,2± 0,05*	0,5 ± 0,03
OAF-test (spontaneous) (s.u.)	29,4 ± 4,8	24,6 ± 2,1	36,1 ± 4,6*	34,6 ± 6,1	25,8 ± 1,4
OAF-test (induced (s.u.)	144,1 ± 18,0	152,6 ± 10,1	154,6 ± 12,7	162,6 ± 15,5	159,7 ± 2,7
Stimulation factor (s.u.)	4,3 ± 1,3	3,4 ± 0,6	3,2 ± 1,1	3,3 ± 1,2	2,7 ± 0,1

Notes: * – difference in index values as compared to such in healthy is statistically significant, $p < 0,05$;
– difference in index values is statistically significant as compared to the initial level, $p < 0,05$.

lymphocytes, with some tendency to a decrease in number of CD8 lymphocytes, which caused statistically significant increase in the immunoregulatory index and approximation of its level to the level of healthy group (table 2).

At the same time, in the control group the above-mentioned indices of T-mediated immunity did not undergo any significant changes in course of 2-month chemotherapy: continued showing inhibition of T-cells, especially helpers – CD4 lymphocytes, and activation of cytotoxic T-cells ($CD8^+$ lymphocytes), which indicated on the continuous inflammatory process. Hence, application of leukocyte immunomodulator therapy in patients with MRTB favored activation of mycobacterium-inhibited cell reactions of the immune system, namely – activation of T-helper component (CD4 lymphocytes), which probably caused significant clinical decrease in activity of specific inflammation in lungs, and, therefore, - decrease in the amount of cytotoxic cells (CD8 lymphocytes).

Patients from study and control groups simultaneously demonstrated certain signs of activation of B-cell immunity, which were represented by probable increase in immunoglobulin M concentration as compared to the healthy (table 3). Taking into account the fact that the patients were ineffectively treated for a long time, the discovered changes in the condition of humoral-cell regulation system may be regarded as the manifestations of excessive functional

Table 5

Cytokine content in peripheral blood in patients with multidrug-resistant tuberculosis, pg/ml

Index	Groups of the examined patients				
	Study (n = 18)		Control(n = 18)		Healthy
	Before treatment	After treatment	Before treatment	After treatment	
TNFα	3,3 ± 0,09*	3,5 ± 0,1*	3,6 ± 0,06*	3,6 ± 0,07*	0,5 ± 0,1
IL-6	3,7 ± 0,7*	2,3 ± 0,06#	3,5 ± 0,4*	3,2± 0,03*	2,1 ± 0,1
IL-4	1,3 ± 0,08*	1,2 ± 0,2*	1,2 ± 0,05*	1,1 ± 0,09*	0,24 ± 0,02
IL-2	0,9 ± 0,1*	1,2 ± 0,2*	0,7 ± 0,08*	0,7 ± 0,02*	0,1 ± 0,02

Notes: * – difference in index values as compared to such in healthy is statistically significant, $p < 0,05$; # – difference in index values is statistically significant as compared to the initial level, $p < 0,05$.

activation of B-cells (in the result of domination of T-helper reactions of 2nd type). After the course of leukocyte immunomodulator therapy the intensity of reactions of humoral component of the immune system decreased, which manifested in the form of probable decrease in relative amounts of B-lymphocytes and decrease in concentration of immunoglobulin M which is an antigen-recognizing receptor of B-lymphocytes. In the control group the analyzed figures have not changed significantly.

Analysis of the condition of phagocytic component of the immune system showed a statistically significant increase in absolute and relative neutrophilocytes content in blood and decrease in monocytes (table 4), which is connected with severe course of tuberculous process with high level of specific inflammation. Functional changes of neutrophilocytes and monocytes were the same and showed the signs of intensive functional stress with increase in oxygen active forms (OAF-test) with satisfactory ability to additional stimulation (without change of stimulation factor)

After the course of leukocyte immunomodulator therapy, , as opposed to the control group, the number of neutrophilocytes and monocytes in blood of the patients from study group was normalized ($p < 0,05$), with normalization of oxygen-dependent activity of monocytes in OAF-test, which indicated on apparent positive effect of the drug on phagocytes and reflected the inhibition of inflammatory process.

According to data presented in table 5, all the patients with MRTB showed,in average, the elevated level of both pro- and anti-inflammatory cytokines during the observation period (except for IL-6 in patients of the study group after the course of immunomodulator therapy). Increase in levels of IL-2 and IL-4 in patients with tuberculosis indicates on participation of both cell and humoral components of the immune system in the process of immunogenesis [5]. In course of process development the differentiation of immunological response takes place, which causes significant dispersion of indices. The level of IL-6 in blood of patients from the study group significantly decreased. The main action of IL-6 is aimed at differentiation of B-lymphocytes, their maturing and transformation into plasma cells which decree immunoglobulin. Thus, decrease in level of this cytokine favored the decrease in activity of humoral reactions in patients with MRTB and indicated on the decrease of activity of T-helper response of 2nd type.

Conclusions

The conducted study gives us possibility to make the following conclusions.

1. The patients with MRTB with slow clinical-roentgenological dynamics that undergo intensive chemotherapy demonstrated apparent immunological disturbances with decrease in the amount of T-helper lymphocytes and monocytes in blood, increase in the content of cytotoxic T-lymphocytes, activation of humoral component of the immune system and phagocytes, which reflects the high activity of specific inflammation.

2. Leukocyte transfer factor positively influences the immunological parameters, helping to reduce the immunological changes and to normalize the balance of Th1/Th2-cell response (increases the amount of T-helper lymphocytes and monocytes while decreasing their excessive activity, decreases the content of cytotoxic T-lymphocytes, B-lymphocytes, immunoglobulin M, IL-6 in peripheral blood), and increases the treatment efficiency in 89% of patients with MRTB.

3. Leukocyte transfer factor is well-tolerated and does not cause any adverse reactions during the course of treatment.

4. The absence of positive effect of leukocyte transfer factor on the course of tuberculous process in 11.1% patients may be caused by the insufficient period of its application, which requires further study in order to develop the optimal scheme of drug application in patients with tuberculosis.

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ПРИМЕНЕНИЕ ЛЕЙКОЦИТАРНЫХ ИММУНОМОДУЛЯТОРОВ ПРИ МУЛЬТИРЕЗИСТЕНТНЫХ ФОРМАХ ТУБЕРКУЛЕЗА ЛЕГКИХ

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Резюме

Цель исследования – *установить влияние лейкоцитарного иммуномодулятора на показатели иммунологической реактивности и эффективность химиотерапии больных мультирезистентным туберкулезом.*

Материалы и методы исследования. *Клинико-иммунологическое контролируемое исследование включало 36 больных мультирезистентным туберкулезом и туберкулезом с расширенной резистентностью. Распределение больных основной и контрольной групп проводили методом подбора пар по характеру туберкулезного процесса, профилю лекарственной чувствительности микобактерий туберкулеза. У больных основной группы на фоне интенсивной фазы химиотерапии применяли лейкоцитарный фактор переноса (18 человек), у 18 больных контрольной группы проводили только химиотерапию. В исследовании применяли лейкоцитарный иммуномодулятор «Immodin», производства Севафарма (Чешская Республика).*

Результаты и их обсуждение. *В результате комплексного лечения с применением лейкоцитарного иммуномодулятора достоверно у большего числа больных с мультирезистентным туберкулезом достигли значительного улучшения за 2 месяца, что проявлялось исчезновением клинических симптомов, выраженным рассасыванием инфильтративных изменений в легких, заживлением и регрессией каверн – у 55,5 % больных против 22,2 % в контрольной группе ($p < 0,05$). У 11,1 % больных не отмечено положительной клинической динамики. Лейкоцитарный фактор переноса имел хорошую переносимость и не вызывал каких-либо побочных реакций в течение курса применения.*

При обследовании клеточного звена иммунитета у больных с мультирезистентным туберкулезом обеих групп до назначения иммуномодулятора на фоне химиотерапии установлено достоверное уменьшение общего количества CD3 лимфоцитов, количества CD4, увеличение количества CD8 лимфоцитов, уменьшение показателя иммунорегуляторного индекса. Обнаружены некоторые признаки активации В-системы иммунитета, что проявлялось достоверным повышением концентрации иммуноглобулина М по сравнению со здоровыми. После курса лечения лейкоцитарным иммуномодулятором у больных основной группы, в отличие от контрольной, отмечали достоверные положительные изменения со стороны Т-звена иммунитета, которые проявлялись увеличением абсолютного количества CD3 лимфоцитов, в основном, за счет абсолютного и относительного количества их Т-хелперной фракции – CD4 лимфоцитов с некоторой тенденцией к уменьшению количества CD8 лимфоцитов, что привело к статистически значимому росту иммунорегуляторного индекса и приближению его уровня к группе здоровых, снижению концентрации иммуноглобулина М, который является антиген-распознающим рецептором В-лимфоцитов. В контрольной группе анализируемые показатели не претерпели существенных изменений. У всех больных с мультирезистентным туберкулезом наблюдали повышенный уровень как провоспалительных, так и противовоспалительных цитокинов в течение периода наблюдения (кроме ИЛ-6 у больных основной группы после курса лечения иммуномодулятором).

Выводы. *Лейкоцитарный фактор переноса положительно влияет на иммунологические показатели, способствуя уменьшению иммунологических изменений и нормализации баланса Th1/Th2-клеточного ответа, и повышает эффективность лечения у 88,9 % больных мультирезистентным туберкулезом, имеет хорошую переносимость и не вызывает никаких побочных реакций в течение 2-месячного курса применения на фоне интенсивной фазы химиотерапии.*

Ключевые слова: *мультирезистентный туберкулез легких, лейкоцитарный иммуномодулятор.*

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IMMUNOTHERAPY WITH LEUCOCYTE IMMUNOMODULATOR DIALYSATE OF PATIENTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

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Summary

Objective: *To determine the effect of leukocyte immunomodulator on the immunological reactivity and efficiency of chemotherapy for MRTB.*

Materials and methods. *Clinical and immunological controlled study included 36 patients with MRTB and XDR TB. The distribution of patients and control group was performed by matching with the nature of tuberculosis, drug susceptibility patterns. In the study group during the intensive phase of chemotherapy was used leukocyte transfer factor (18 patients), and 18 patients in the control group received chemotherapy alone. The study used the leukocyte immunomodulator «Immodin», production Sevafarma (Czech Republic).*

Results. *Found that the leukocyte immunomodulator had positive effect on effectiveness of treatment in 2 months, which manifested the disappearance of clinical symptoms, severe resorption of infiltrative changes in the lungs, healing and regression of cavities – in 55.5% of patients versus 22.2 % in the control group ($p < 0,05$). In 11.1% of patients were not observed positive clinical dynamics. Leukocyte transfer factor was well tolerated and did not cause any side-reactions during the course of application.*

In a study of cellular immunity in patients MRTB both groups until the appointment of an immunomodulator during chemotherapy found a significant decrease in the total number of CD3 lymphocytes, the number of CD4, an increase in the number of CD8 lymphocytes, reduction

in the rates of immunoregulatory index. Found some evidence of activation of B-cell immunity, manifested significant increase in the concentration of immunoglobulin M compared to healthy. After treatment leukocyte immune modulator in the study group, in contrast to the control group, there was a significant positive changes in the T-mediated immunity, which were shown an increase in the absolute number of CD3 lymphocytes, mainly due to the absolute and relative number of T-helper faction – CD4 lymphocytes with a tendency to a decrease of CD8 lymphocytes, which resulted in a statistically significant increase in the immunoregulatory index, and its level in the approximation of a group of healthy, reduced concentration of IgM, which is an antigen-recognizing receptors of B-lymphocytes. In the control group shifted figures have not changed significantly. All patients MRTB observed elevated levels of both proinflammatory and anti-inflammatory cytokines during the observation period (except for IL-6 in the study group after treatment immunomodulator).

Conclusion. *Leukocyte transfer factor positively influences immunologic parameters, helping to reduce and normalize immunological changes balance Th1/ Th2-cell response and increases the efficiency of treatment in 88,9 % of patients with MDR tuberculosis is well tolerated and does not cause any adverse reactions within 2 months applying on the background of the intensive phase of chemotherapy.*

Keywords: *Multidrug resistant tuberculosis, leukocyte immunomodulator.*

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