Changes in the immune system, inflammatory mediators of fibrosis and stone formation in the dynamics of treatment of patients with chronic pancreatitis

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Chronic pancreatitis (CP) — widespread disease that is characterized by a long course, the development of serious complications, significantly affects the quality of life of large segments of the population and therefore has great social significance and requires a fundamental study of pathogenetic mechanisms of the disease [2, 9, 10, 11].

In patients with CP pathological changes observed in many organs and systems, including the immune system, which plays an important role in the pathogenesis of the disease.

Objective. Examine the condition of the immune system, the level of inflammatory mediators, fibrosis, stone and their dynamics as a result of treatment in patients with various forms of chronic pancreatitis.

Material research. The observation was located 210 patients with CP. Research conducted in SI "Institute of Gastroenterology NAMS Ukraine" (Dnipro). Among the patients were 169 men and 41 women, age of the patients ranged from 26 to 72 years, the average age was 47,3±0,7 years. Value for Women and Men — 1: 4.1. According to the Marseille-Roman classification of 1998 patients were divided into 4 clinical groups: I group — 26 (12.4%) patients with obstructive form of CP, II — 56 (26.7%) patients with calcificating form, III — 78 (34.1%) patients with parenchymal fibrous form IV — 50 (23.8%) patients with CP, complicated pseudocyst.

Research methods. To study the immune system defined subpopulations composition lymphocytes using monoclonal antibody company "Sorbent TM" molecules CD3, CD19, CD4, CD8, CD16, CD25 using limfotsytotoksychnoho test (standard method NIH USA) using monoclonal antibodies [6, 8]. Humoral immunity (change in levels of IgA classes of immunoglobulins, IgM, IgG in serum) was determined by radial immunodiffusion for Mancini (1965) [13].Mononuclear cells isolated from peripheral venous blood of patients gradient density 1,077 g/cm. The functional activity of granulocytes NBT-evaluated to test the reaction of the restoration nitroblue tetrazol [4]. Circulating immune complexes (CIC) were determined by V. Haskova (1977) [12]. Study of pro-inflammatory interleukins profibrotychnyh and TNF-α, IL-10, REG-1α, TGF-β1 was performed by enzyme immunoassay (ELISA) kits using "Vector BEST" (c. Novosibirsk) according to the instructions to them. Determination of lactoferrin was conducted to test systems lactoferrin Strip Production Company "Vector-Best" according to the manufacturer's instructions. ELISA results recorded the OD Stat Fax 303+. Used the method of statistical analysis.

Research results. Violation found in the immune status of patients with CP. The number of leukocytes in patients with CP was significantly higher compared

with the control group ($p<0.01$), but did not exceed the conventional rate (Table. 1). Activation of inflammation, according to indicators of leukocytes in the blood, was in 18.9% of patients. Analysis of this indicator depending on the form CP showed that most increase of leukocytes determined in the first group of patients — more than a third (38.5%), which was significantly higher than in the third group (11,4%, $\chi 2 = 4\ 26$, $p = 0.039$), but no different from the second level (17.2%) and fourth (20.7%) (Table. 2).

All patients noted a significant increase in the total number of lymphocytes, as the absolute number and the percentage of them (see. Table. 1, $p<0.01$), regardless of the form of the disease. Patients of all groups showed a reduction in the content of T lymphocytes (CD3+), T-helper cells (CD4+) ($p<0.01$). It was noted increase in the absolute number of cytotoxic T lymphocytes (CD8+) patients, II and IV groups (P1, 2, 4<0.01). Established a significant increase in the absolute number of natural killer (SD16+) in CP, but their relative number had no significant deviations from that of the control group. All patients had reduced immunoregulation index (CD4+/CD8+), and much more — in patient groups III and IV ($p<0.01$).

NBT test characterizes the two main stages of phagocytosis — the absorption and digestion of foreign body particles — "oxygen burst." The research NBT test in patients with CP indicate the usefulness of functional neutrophils in this disease. In all patients the increased phagocytic activity of neutrophils — indicators of nonspecific resistance (NBT) were significantly higher than the control, the most significant of increase was determined in the second group of patients compared with III and IV ($p<0.002$), which may indicate the highest bacterial population of which leads to the increase in the number of activated granulocytes, able to absorb and recover NST (30-40%).

Concerning humoral immunity — also established significant changes in its performance (see. Table. 2). Thus, the activation of humoral immunity in all patients indicated a significant increase in CIC and markers of B cells (CD19+) ($p<0.01$), with significant differences in the values of these parameters groups is not installed. The level of antibodies measured to determine the adequacy of the response of the immune system. Established that the content of IgG and IgA was increased, and most significantly in patients with second and third groups ($p<0.01$) and IgM levels were not significantly different from control.

For more detailed specifications immune disorders expected rate of diagnostic value, which allows taking into account average values of the parameters in the group, their variances to select indicators that are different from the norm in greater degree and thereby obtain a formula disorders of the immune system (FDIS), which includes three of the most informative indicator. According to FDIS (tab. 3), and a group of the most significant deviations were observed in terms of total CD3+ T cells, the level of CD4+ T cells, CD8+ cytotoxic T cells. In the second group of the most important diagnostic indicator is the level of CD4+ T lymphocytes, then — the level of total CD3+ T cells and CD8+ cytotoxic T lymphocytes. In the third and fourth groups most diagnostically important indicator was the level of CD4+ T lymphocytes, then — the level of total CD3+ T cells, immunoregulation index CD4+/CD8+.

Table 3

Formula of disorders of the immune system in the examined groups of patients

Groups of patients	FDIS	
	cellular immunity	humoral immunity
I group	CD3 2-, CD4 2- CD8 1+	ЦИК2+, IgG2+, IgA1+
II group	CD4 2-, CD3 2-, CD8 1+	ЦИК2+, IgG3+, IgA2+
III group	CD4 2-, CD3 2-, CD4/CD8 2-	CD19 3+, ЦИК3+, IgG2+
IV group	CD4 2-, CD3 2-, CD4/CD8 2-	CD19 3+, ЦИК2+, IgG1+

Notes:

1. (+) — hyperfunction;
2. (-) — immune failure;
3. 1 (2, 3) — degree of immune disorders.

Analyzing the performance of humoral immunity, found that for all the studied groups of patients characterized by high levels of circulating immune complexes (in the third group higher, 3rd degree). FDIS in the third and fourth groups is to increase the level of B lymphocytes 3rd degree. All groups were observed hyperproduction IgG (in the second group a higher degree). In addition, the second group watched IgA hyperproduction 2nd degree. Thus, our findings suggest activation of humoral immunity and complete immune response in patients, II group. In the third group of immune disorders significantly expressed and complete immune response, we have not identified. FDIS By characterizing cellular immunity, the most significant rejection of established patients III and IV groups, and for humoral immunity — in the second and third groups.

It is known that a significant role in the development and progression of CP played interleukins (inflammatory and anti-inflammatory) mediators and fibrotic processes. Therefore, it was important to determine the level of interleukin — inflammatory TNF-α, anti-inflammatory — IL-10 marker fibrosis — TGF-β1. The study noted significant differences in serum cytokines in patients with CP relative to that of the control group (tab. 4). It was noted increasing the ability of cells to the main production of proinflammatory cytokines: TNF-α, which level was significantly elevated in all patients and in groups I and IV established it significantly more substantial increase than in II and III ($p<0.05$).

The level of production of anti-inflammatory cytokine IL-10 was increased in all patients, most significantly — in the fourth group of patients ($p<0.001$), indicating the stress immunity and cytokine imbalance in the immune system link. The level of TGF-β1 production was also significantly higher in all groups of patients compared with controls ($p<0.001$). In addition to anti-inflammatory activity of TGF-β1 is a potent factor profibrohennym. It can block the inflammatory response, while roztormozhuyuchy collagen and extracellular matrix remodeling providing.

Table 4

Characteristics of inflammatory mediators and markers of fibrogenesis in patients with CP

Group	TNF-α, pg/ml	IL-10, pg/ml	TGF-β1, ng/ml

I (n=9)	197,33±2,21*	31,32±0,32*	23,5±0,64*£
II (n=37)	174,34±12,16*+	30,41±0,41*	29,06±0,55*
III (n=32)	178,78±1,88*1	31,67±0,68*	27,62±0,56*
IV (n=17)	194,44±2,62*	42,08±0,94*#	21,16±0,67*£
total (n=95)	185,84±2,61*	33,01±0,54*	26,50±0,44*
control (n=20)	22,0±0,81	28,6±1,83	3,46±0,07

Notes:

1. * — statistically significant (p<0,001) difference between the rates in patients compared with healthy people;

2.+ — statistically significant (p<0,001) difference between the rates of patients II group compared with the I, IV;

3. 1 — statistically significant (p<0,05) difference between the rates of patients III group compared with the I, IV;

4. £ — statistically significant (p<0,001) difference between the rates of patients I and IV group compared with the II, III;

5. # — statistically significant (p<0,001) difference between the rates of patients IV group compared with the II.

It should be noted that the inter-group analysis determined that the level profibrohennoho cytokine TGF-β1 was significantly higher in the second and third groups of patients that demonstrates the highest activity fibrotic processes in the pancreatic parenchyma these groups of patients (p<0.001). TGF-β1 — plays a major role in pancreatic fibrogenesis, it stimulates growth of cells of mesenchymal origin and increases the synthesis of extracellular matrix proteins such as collagen, fibronectin and proteoglycans.

Violation of cytokine regulation of the immune system in patients with CP indicates the presence of secondary immune deficiency, which contributes to the persistence of the inflammatory process in the software. Improving the ability of immune cells tsytokinprodukuyuchoyi consistent with disease activity according to clinical, biochemical and instrumental examination of patients with CP. Attention is drawn to the fact that many patients change production of proinflammatory and anti-inflammatory cytokines are multidirectional nature.

The participation litostatyn (REG-1α and lactoferrin in the process of calcification and formation of concretions in the straits software illustrated by many researchers [1, 7, 14, 15]. The specific protein "pancreatic stones» — pancreatic stone protein (PSP, or litostatyn) is 5% of the total protein secreted acini and inhibits the growth of crystals of calcium carbonate. Lactoferrin, opposite is the basis "of pancreatic stones" formed by its absorption of protein precipitates.

We have studied the content of these indicators in blood of patients with various forms of CP. Results are presented in Table 5.

Table 5

Characteristics pancreatic lithiasis and markers of apoptosis receptor in patients with CP

Group	**Litostatyn (REG-**	**Lactoferrin, ng/ml**	**CD95+**

	1α), pg/ml		**abs.n.**	**%**
I (n=9)	1183,22±70,69*×	17669,44±841,39*	0,31±0,06	15,89±1,36
II (n=37)	983,86±8,83*	17461,892±261,18*	0,27±0,03	15,08±0,83*
III (n=32)	1779,91±109,86*!#	7305,72±40,74*#	0,24±0,02*	15,78±0,43*
IV (n=17)	2256,94±57,79*#	7218,88±51,45*#	0,27±0,03*	19,06±1,05
total (n=95)	1498,71±63,80*	12227,57±542,29*	0,26±0,02*	16,11±0,45
control (n=20)	185,0±23,0	653,57±11,89	0,24±0,02	17,24±0,57

Notes:

1. * — statistically significant (p<0,001) difference between the rates in patients compared with healthy people;

2. # — statistically significant (p<0,001) difference between the rates of patients III and IV group compared with I, II groups;

3. × — statistically significant (p<0,001) difference between the rates of patients I and II groups;

4. ! — statistically significant (p<0,001) difference between the rates of patients III and IV groups.

It is known that an important role in the pathogenesis of pancreatitis has apoptosis — programmed cell death and regulated. With increasing apoptosis develops necrosis, ie increases autoliz software. With the weakening of apoptosis genetically damaged cells the opportunity to proliferate, which leads to hiperplaziyi and then to malignant transformation. We found that the content receptor apoptotic CD95+ marked multi-directional changes. Thus, in patients IV group level it was a little high relative to the comparison group, the I, II and III groups — its content was reduced, and the last two — significantly (p<0.01).

As shown in the Table. 5 for all patients with CP characterized by a considerable increase of litostatyn (REG-1α to 8.7 times (p<0.001). Litostatyn is one of the stabilizers of calcium, which means it supports calcium in a soluble state. The main role litostatyn associated with inhibition of enucleation, aggregation and occurrence of calcium. Increased litostatyn in patients with CP, is probably a protective reaction obstacles to the formation of stones in the ducts in the parenchyma calcifications and software.

However, the inter-group analysis found that patients in Groups I and II of its level significantly lower compared with patients III and IV — 1.5 and 1.9 and 1.8 and 2.3 times, respectively (p<0.001). Most significantly reduced level of this index was in the second group of patients, indicating the protective effect its lowest calculus formation in the ducts and parenchyma calcifications in patients with CP kaltsyfikuyuchoyu form.

For another participant stone — lactoferrin — were the same characteristic changes: a significant increase in its content in the blood serum of patients in the 18.7-fold (p<0.001); more patients conceive and II groups compared with patients III and IV in the same proportion — 2.4 times (p<0.001).

For comparison, depending fibrosis markers and stone that are outstanding in different units of measurement, we calculated ratios relative values of these control parameters and their value (control value indicators studied by taking 1.0) (tab. 6).

Table 6

Odds ratios of indicators of stone fibrosis in patients with CP

Coefficient	I group (n=12)	II group (n=33)	III group (n=42)	IV group (n=33)	Control (n=20)
REG-1α	6,4	5,3	9,9	12,2	1,0
Lactoferrin	27,0	26,7	11,2	11,0	1,0
TGF-β1	6,8	8,4	8,0	6,1	1,0
REG-1α/lactoferrin	0,2	0,2	0,9	2	1,0
REG-1α/TGF-β1	0,9	0,6	1,2	2	1,0

As shown in the Table. 6, stone figures were most significantly altered in patients with the first and second groups. Thus, in these patients the level litostatyn (REG-1α was almost 2 times lower and lactoferrin — almost 2 times higher than in patients III and IV groups. Marker fibrosis and its activator (TGF-β1) was the most altered in patients with second and third groups, although significant differences with those patients I and IV groups not installed.

In determining the relationship between markers of stone REG-1α/lactoferrin (coefficient calcification) found that the lowest value of its characteristic and second group (0.2), which found calcinates in duct/calcifications of the parenchyma. In the third group of patients with calcification rate was 0.9, that is approaching 1.0, which can be an indicator of the likelihood of stone formation. A fourth group of patients mentioned ratio was 2.0, that is, the probability of stone formation in patients in this group is low.

In determining correlations between markers and stone fibrosis found that the coefficient REG-1α indicates the presence of stones mentioned it below 1.0. Moreover, the higher its value to patients and groups (0.6 to 1.0) may indicate the presence of calcinates in the main pancreatic Strait and below 0.6 are prescribed for patients II group — to calcifications of the parenchyma. For values of this ratio slightly higher than 1.0 (the third group — 1.2) and calcifications not set, but a high probability of their formation. In the fourth group of patients in which the ratio is 2.0, the likelihood of calcification and formation in the ducts of calcinates low.

Thus all patients with CP as a result of the study found violations of regulatory, proliferation and activation functions of the immune system that leads to frustration in cytokine link of immunity and, consequently, to deepen and fibrous inflammatory process, activation of stone.

Analysis of correlations confirmed the importance disorders of the immune system in the development and course of CP. The largest number of identified correlations between indicators of immune system and biochemical markers fibrosis (hydroxyproline protein-binding — r = 0,63; p = 0.002, hexosamine — r = 0,71; p =

0.007), endogenous intoxication (average molecular weight — r = 0,84; p = 0.001), POL-AOP (r = 068, p = 0.001), cholestasis (r = 0,76, p = 0.0001), metabolic disorders (Ca — r = 0,95 ; p = 0,0008), which confirmed the interplay of immune factors, indicators of oxidative stress in patients with cholestasis CP. In the second group of patients correlations confirmed the participation of anti-inflammatory cytokines (IL-10) and lactoferrin in the development of calcifications of the parenchyma of software by ultrasound (r = -0,82; p = 0,005 and r = 0,59; p = 0,044, respectively).

Results of treatment of patients with CP were studied in terms of 6 to 12 months. To study the effectiveness of the proposed treatment, the patients were divided into two groups: — 34 patients of group I and II — 25 patients of comparison. CP basic treatment was conducted in accordance with the standards [5]. In addition to the normalization of proinflammatory cytokines and profibrotychnyh and correction of the immune system as used autotsytokinoterapiyu 3 Dial-up autotsytokiniv subcutaneous administration established peripheral blood mononuclear cells of patients who received stimulation cascade. Course autotsytokinoterapiyi administered for 14-16 days stay of the patient in the clinic (in the subacute phase of disease) sessions conducted at intervals of 3-5 days, autotsytokiniv dose — 100 mg/ml. To limit oxidative stress and reduce lipid peroxidation products, improve the antioxidant defense system and normalize the metabolism of collagen patients administered CP GLUTARGIN 3 tablets (0.75 g) three times a day for 15-21 days. For kupiyuvannya chronic pain vyhrove applied pulsed magnetic field (WIMPs) with exposure to the projection software and acupressure points on course for 5-15 minutes 10-15. WIMPs activates defense mechanisms of the body by improving circulation, normalize blood rheology, biochemical parameters and disorders of the immune system, changes the speed of transmission of nerve impulses. WIMPs used after 8-10 days of treatment (during subsiding exacerbation). Duration of treatment 3-4 weeks to complete normalization of clinical data, the decline in indicators of inflammation, loss of neutral fat, starch and muscle fibers in feces [3].

The analysis of the changes in immune parameters studied groups of patients after treatment showed positive changes in cytokines, activation of corresponding software stellate cells, regulation and fibrozoutvorennya stone (tab. 7).

Table 7

Changes in performance of triggers pathology in CP in the examined patients after treatment

Indicator	**Before treatment (n=12)**	**After treatment (n=12)**	**Norm**
IL-10,pg/ml	30,57±1,47	29,36±0,87	28,6±1,83
TNF-α, pg/ml	302,43±117,64	177,89±110,51	2,20±0,81
Lactoferrin, ng/ml	17458,35±846,91	7167,68±1599,15**	653,57±11,89
Litostatyn (REG-1α, pg/ml)	2143,17±87,29	1179,83±99,51**	185,0±23,0
TGF-β1, ngml	39,34±8,05	22,12±3,37*	3,46±0,07
Fecal elastase mcg/g	156,5±12,73	198,6±11,39*	200

Notes: * — p<0,05, ** — p<0,001 — significant differences before and after treatment.

Thus, the analysis of these parameters in patients one year after treatment revealed that patients observed a significant reduction of lactoferrin in the serum of 17458,35±846,91 ng/ml to 7167,68±1599,15 ng/ml (P< 0.001); litostatyn (c REG-1α) — from 2143,17±87,29 pg/ml to 1179,83±99,51 pg/ml (p<0.001); activator fibrosis TGF-β1 — with 39,34±8,05 ng/ml to 22,12±3.37 ng/ml (p<0.05). Level stool elastase, index exocrine insufficiency software significantly increased (p<0.05) and 75% of patients were in the normal range.

These changes occurred against the background of improving all parts of immunity in patients of groups: humoral, cellular, regulatory (tab. 8). The analysis showed that after treatment, the absolute number of T cells in patients of 100.0% normalizuvalos group (p<0.05). Significantly increased the relative number of T-helper cells (p<0.05). Significant decrease in the relative number of T-suppressor (p<0.05) after treatment so that their level does not differ from the control group. The above changes have led to the restoration of immunoregulatory index CD4+/CD8+, which after treatment did not differ from the control group (p>0,05).

In 41.6% of cases, elevated levels of B cells after treatment in the intervention group decreased (P<0.05), which led to the normalization of this index in the whole group. In the study group patients after treatment observed normalization and CIC NBT (p<0.05), indicating a normalization of functional activity of neutrophils and phagocytic immunity.

In the comparison group were noted such positive changes all parts of immunity (humoral, cellular, regulatory) in patients of the main group.

Noted normalization relative number of β-cells (SD19+) and CIC levels (p<0.05). Other indicators significantly after treatment did not change, and most importantly — not noted positive changes in the restoration of immunoregulation.

Thus, in patients with CP after complex treatment using autotsytokiniv, glutargin and WIMPs were observed full recovery of the immune system, due to its importance in the chronicity and progression of CP. At the same time the rate of TGF-β1, which shows the development of fibrotic processes, software activates stellate cells that produce extracellular matrix and are responsible for fibrosis gland parenchyma was significantly reduced (p<0.05), and the level of cytokines, which indirectly related processes fibrosis — IL-10, TNF-α — had a downward trend (p>0.05). The positive effect of treatment on the calcification processes — significantly reduced the level of REG-1α (litostatyn), which is the main component of pancreatic stones (p<0.001).

Thus all patients with CP as a result of the study found violations of regulatory, proliferation and activation functions of the immune system that leads to frustration in cytokine link of immunity and, consequently, to deepen and fibrous inflammatory process, activation of stone. The treatment using autocytokines allowed to obtain a positive effect in most patients by improving the immune system, significant decrease in performance fibrosis and calcification.

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Indicators of immunity system, the level of interleukines (inflammatory TNF-α, anti — IL-10, a marker of fibrosis — TGF-β1), litostatin (REG-1α) and lactoferrin were studied in patients with different forms of chronic pancreatitis. Violation of regulatory, proliferative and activation functions of the immune system was found in all the patients, which leaded to an imbalance in cytokine mediated immunity and, as a result, aggravating inflammatory and fibrotic processes, activation of stone formation. There was a positive response in most patients for given treatment with autocytokines due to the improved immune system, significantly reduced level of indicators of fibrosis and calcification.

Table 1

Indicators of cellular immunity in patients with CP

Indicator	I group (n=13)	II group (n=29)	III group (n=35)	IV group (n=29)	Total (n=106)	Control (n=50)
Leukocytes, 10^9/L	7,42±0,82*#	6,35±0,44*	5,65±0,34	7,20±0,73*	6,49±0,28*	5,35±0,21
Lymphocytes, %	33,69±3,54	33,45±2,09*	34,77±1,67*	30,52±1,88	32,81±1,07*	28,71±0,81
Lymphocytes, 10^9/L	2,43±0,33*	2,01±0,15*	1,89±0,12*	2,01±0,17*	2,02±0,08*	1,61±0,07
CD3+, %	42,31±1,69*	44,93±2,21*	44,38±1,70*	44,07±1,64*	44,19±0,96*	50,88±0,68
CD3+, 10^9/L	1,06±0,13*	0,96±0,11	0,82±0,06	0,89±0,08	0,91±0,05*	0,76±0,04
CD4+, %	27,23±1,13*	27,97±1,72*	28,68±1,49*	26,11±1,13*	27,62±0,76*	38,71±0,52
CD4+, 10^9/L	0,66±0,08	0,59±0,08	0,54±0,05	0,51±0,03	0,56±0,03	0,53±0,03
CD8+, %	19,15±1,64	17,21±1,22	17,91±1,31	19,30±1,13	18,23±0,66	18,39±0,57
CD8+, 10^9/L	0,50±0,07*	0,37±0,02*	0,33±0,03	0,39±0,04*	0,38±0,02*	0,30±0,02
CD16+, %	20,85±2,77	19,83±2,38	19,74±1,44	18,78±1,74	19,55±1,04	19,07±0,90
CD16+, 10^9/L	0,48±0,09	0,46±0,10	0,37±0,04	0,37±0,04	0,41±0,03*	0,31±0,02
CD4+/CD8+	1,92±0,25	1,82±0,13	1,79±0,13*	1,47±0,08*	1,73±0,07*	1,97±0,07
HCT	19,92±1,81*	25,32±1,20*	14,00±0,83*1	23,18±5,22*1	18,43±1,96*	12,03±0,74

Notes: 1. * — statistically significant ($p<0,01$) difference between the indices patients compared with healthy people;
2. + — statistically significant ($p<0,02$) difference between the rates of patients II and III groups;
3. # — statistically significant ($p<0,02$) difference between the indexes of patients and III groups;

4. 1 — statistically significant (p<0,002) difference between the rates of patients II compared with III and IV.

Table 2

Humoral immune indicators and expression of activation receptors on lymphocytes of HLA-DR in patients with CP

Indicator	**I group (n=13)**	**II group (n=29)**	**III group (n=35)**	**IV group (n=29)**	**Total (n=106)**	**Control (n=50)**
CD19+, %	18,85±2,69	17,35±1,42	20,74±1,29*	19,52±2,04*	19,22±0,86	14,78±0,48
CD19+, 10^9/L	0,51±0,12*	0,38±0,06*	0,40±0,04*	0,38±0,04*	0,40±0,03*	0,25±0,01
T/B	2,83±0,35	2,87±0,19	2,47±0,19	2,75±0,24	2,70±0,11	2,78±0,15
HLA-DR, %	20,6±2,26	17,89±0,67*	18,16±0,99*	26,06±1,25*	19,69±0,6*	21,49±0,59
HLA-DR, 10^9/L	0,27±0,03	0,19±0,02*	0,21±0,01*	0,34±0,05	0,23±0,01*	0,33±0,02
ЦИК, UOD	5,17±0,56*	4,97±0,54*+	7,38±0,56*	5,66±0,57*	5,98±0,33*	3,42±0,23
IgA, g/L	3,63±0,70	3,12±0,26*	3,02±0,28*	2,46±0,16	3,02±0,16*	2,25±0,26
IgM, g/L	1,82±0,24	1,65±0,13	1,71±0,14	1,88±0,19	0,73±0,08	1,53±0,1
IgG, g/L	14,60±0,85*	15,05±0,66*	14,68±0,69*	13,78±0,90	14,65±0,39*	12,72±0,42

Notes:

1. * — statistically significant (p<0,01) difference between the indices patients compared with healthy people;
2. + — statistically significant (p<0,02) difference between the rates of patients II and III groups;
3. # — statistically significant (p<0,02) difference between the indexes of patients and III groups;
4. 1 — statistically significant (p<0,002) difference between the rates of patients II compared with III and IV.

Table 8

Indicators of immune status in patients after treatment

Indicator	**Control group (n=20)**	**I group (n=34)**		**II group (n=25)**	
		before treatment	**after treatment**	**before treatment**	**after treatment**
1	2	3	4	5	6
Leukocytes, 10^9/L	5,35±0,21	6,98±0,68*	5,89±0,39	6,87±0,72*	6,63±0,81
Lymphocytes, %	28,71±0,81	33,73±1,73*	29,58±2,65	34,2±1,76*	34,7±2,03*
Lymphocytes, 10^9/L	1,61±0,07	2,32±0,29*	2,17±0,22*	2,34±0,31*	2,19±0,27*
CD3+, %	50,88±0,68	41,07±1,46**	49,25±1,51+	40,84±1,51**	39,87±1,74**
CD3+, 10^9/L	0,76±0,04	0,95±0,08*	0,84±0,09	0,96±0,09*	0,87±0,08
CD19+, %	14,78±0,48	21,34±1,64*	15,67±1,70+	21,09±1,72*	16,3±1,49+
CD19+, 10^9/L	0,25±0,01	0,36±0,04*	0,33±0,05	0,39±0,03**	0,34±0,06
CD4+, %	38,71±0,52	28,38±1,73**	36,08±0,87+	29,14±1,81**	27,3±1,07#
CD4+, 10^9/л	0,53±0,03	0,53±0,09	0,52±0,05	0,54±0,09	0,56±0,08
CD8+, %	18,39±0,57	26,46±1,75**	18,05±1,32+	27,07±1,64**	24,94±1,72**
CD8+, 10^9/L	0,30±0,02	0,42±0,06	0,32±0,08	0,43±0,07	0,39±0,08
CD16+, %	19,07±0,90	19,08±1,81	18,83±1,33	19,11±1,76	21,42±1,36

CD16+, 10^9/L	0,31±0,02	0,43±0,07	0,35±0,08	0,44±0,07	0,41±0,08
CD95+, %	17,24±0,57	15,08±0,83*	16,94±0,67	14,97±0,93*	15,01±0,97
CD95+, 10^9/L	0,24±0,02	0,27±0,03	0,24±0,04	0,28±0,04	0,27±0,03
T/B	2,78±0,15	2,75±0,18	2,77±0,28	2,67±0,23	2,48±0,94
CD4+/CD8+	1,97±0,07	1,56±0,12*	1,89±0,23	1,54±0,21	1,52±0,87
ЦІК, UOD	3,42±0,23	6,94±0,28#	2,99±0,31+	6,76±0,3#1	4,02±1,08+
НСТ	12,03±0,74	19,82±3,26*	12,56±2,35	20,01±2,94*	16,27±1,56*
ЦПА	0,20±0,01	0,34±0,08	0,18±0,05	0,36±0,09	0,29±0,09

Примітки:

1. * — $p<0,05$, ** — $p<0,01$, # — $p<0,001$ — significant differences comparatively with control;
+ — $p<0,05$ — significant differences before and after treatment.