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Research Article

Analysis of the Level of IgG to SARS-CoV-2 Virus and Molecular Markers of Activation of CD25, CD54 (ICAM-1) and CD95 Lymphocytes in the Patients Who were Not Ill with COVID-19, Recovered from COVID-19 and Who had Acute Respiratory Infections. The Results of the Correction of Impaired Immune Homeostasis Using the Multitarget Immunotherapy Drug Mercureid

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Abstract

Currently, the researchers have come across a paradox which consists in detecting protective IgG antibodies to SARS-CoV-2 virus only in a subset of patients who have recovered from COVID-19. The other patients, who were in contact with the infected people, have not contracted COVID-19 (there were no symptoms of this illness detected and PCR was negative). Nevertheless, these people have got IgG antibodies to SARS-CoV-2 virus too. It's also worth pointing out that the presence of IgG to SARS-CoV-2 virus correlates with an altered immune

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response when infected with seasonal viral diseases; in particular, the ability to produce protective antibodies decreases.

All these factors predetermine different clinical courses of the disease and the consequences of the patient's post-COVID condition (post-COVID conditions / PCC).

To examine the diverse immune responses of patients, including asymptomatic carriage, a study on 414 patients was conducted. The novelty of the research is the following. For the first time, not only the levels of protective IgG antibody titers to SARS-CoV-2 virus were determined, but also their correlations with lymphocyte activation markers CD25, CD54 (ICAM-1) and CD95 in three groups of patients, namely, people who did not have COVID-19, who recovered from COVID-19 and who had acute respiratory infections, were examined. The research is aimed at both scientific and practical purposes, including the search for new therapeutic options. The possibility of controlling the activation molecules of T-lymphocytes and editing their activity using the multitarget immunotherapy drug Mercureid was studied. The therapeutic efficacy of Mercureid usage was 75.6%.

Keywords

COVID-19; T-lymphocyte; Acute Respiratory Infections; Monoclonal Antibodies; Mercureid

Relevance

Coronavirus infection is a global health problem. The laboratory diagnostics of the infected patients and assessment of the immune status are considered to be a cornerstone in the fight against the pandemic. The study of SARS-CoV-2 virus, its structure and origin, carried out by many researchers, does not provide an unambiguous answer about a wide variety of reasons for various host responses, including absolutely asymptomatic carriage and formation of an immune response that can't always be predictable [1]. The attention is paid to: the diversity of variants of the course of the disease; complicated and uncomplicated course of the disease. However, the development of an adequate specific immune response may not occur [2]. Assessing the immunity of patients infected with coronavirus is the most important task of the world health care, as the formation of an immune response after interaction with SARS-CoV-2 virus is not always predictable.

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The Aim of the Study

The analysis of the level of IgG to SARS-CoV-2 virus, and molecular markers of activation of CD25, CD54 (ICAM-1) and CD95 lymphocytes in patients who were not ill with COVID-19, who recovered from COVID-19 and who had acute respiratory infections. Study of the possibility to correct the markers of lymphocyte activation by using the drug of multitarget immunotherapy - Mercureid.

Material and Methods

In this study 414 people took part. Among them there were 43.7% of men and 56.3% of women. All these respondents were divided into three groups:

1. Healthy individuals who did not fall ill either with COVID-19 or acute respiratory infections (a control group)
2. Patients who were ill with COVID-19 and had clinical symptoms of the disease, confirmed by a positive PCR test
3. Patients who were diagnosed with acute respiratory infections

The age of the female patients was 58.19±16.4 years. The age of the male patients was 46.43±10.2 years. The level of IgG to SARS-CoV-2 virus was detected by the standard method of enzyme immunoassay with the help of Awareness Technology STAT FAX equipment (USA) on the 18^{th}, 20^{th} day after testing.

The study of the expression of lymphocyte activation markers in the patients under examination was carried out by the immunocytochemical method using monoclonal antibodies (PAP detection method using the immune complex peroxidase-anti-peroxidase) [3].

Lymphocyte activation markers CD25, CD54 (ICAM-1) and CD95 were determined in 54 patients (age 53.2±8.1 years) and in 60 patients (age 51.4±11.3 years) who didn't fall ill with both COVID-19 and acute respiratory infections (control group). These patients took the drug of multitarget immunotherapy - Mercureid, according to the recommended scheme, 7 granules, sublingually, for 2 months. Sublingual administration has certain advantages over oral administration because, in this case, the active substance, before entering the bloodstream, will come into contact only with enzymes in saliva. Sublingual administration is particularly effective for immunoactive Mercureid molecules due to the presence of immune receptor cells near the sublingual space. In addition, in this part of the tongue there is a high density of blood vessels, that's why drug molecules quickly enter the blood circulation. For

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immunophenotyping, a panel of monoclonal Antibodies (mAb) which included antibodies reacting with antigens CD25, CD54 (ICAM-1), CD95 was used [4].

The examination of patients was carried out in the laboratories of microbiology and immunology of the State Institution, Filatov Institute of Eye Diseases and Tissue Therapy at the National Academy of Medical Sciences of Ukraine, Odessa, Ukraine. The study was approved by the ethical committee. The work presents measures to ensure the patient safety and health, respect for patient rights, human dignity and moral standards in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and the laws of Ukraine.

Statistics

Statistical processing was carried out using parametric and nonparametric statistical methods. Accumulation, systematization of initial information, visualization of the obtained results and statistical analysis were carried out in spreadsheets using STATISTICA software version 8.0 (StatSoft.Inc). When comparing mean values, Student's t-test was used for calculations. Nominal data were described with absolute values and percentages. Differences in values were considered statistically significant at the significance level of $p<0.05$. The strength of correlations was studied by the Spearman and Pearson coefficient.

Results

There were 414 patients involved in clinical trials. They were divided into three groups (the distribution of patients by groups is shown in Fig. 1).

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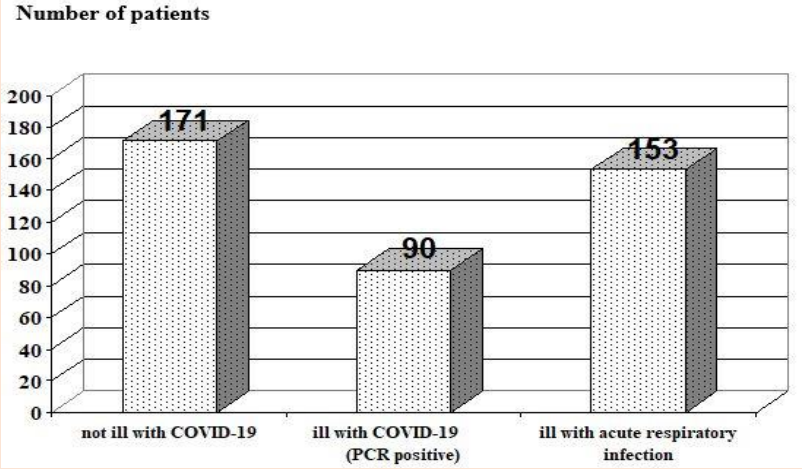

Figure 1: Distribution of patients by groups.

Our studies showed that in the group of patients with COVID-19, IgG to SARS-CoV-2 virus was detected in 90% of the patients (81 people) and amounted to 1.64±0.47 (Fig. 2). Nevertheless, it is worth stressing that in 10% of the patients (9 people), despite the clinical manifestations of the disease and the diagnosis confirmed by PCR test, the enzyme-linked immunosorbent assay did not detect IgG to SARS-COV-2 virus on the 18-20th day after PCR test (Table 1, Fig. 2).

Values Under Study	Statistic Values	Group I - control, people without COVID-19 (n=171)	Group II patients ill with COVID-19 (n=90)	Group III patients ill with acute respiratory infections (n=153)
Ig G Positive Test	n	52	81	101
	M±m	0,54±0,26*	1,64±0,47*	0,87±0,34
	%	30,4	90	66
	p	-	p = 0,044	p = 0,188
Ig G Negative Test	n	119	9	52
	%	69,6	10	34
* - p (groups I - II) differences are statistically significant, p<0.05				

Table 1: Number (n), percentage (%) and values of IgG SARS-CoV-2 in the patients who were examined.

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The control group of the study consisted of the employees of the institute who did not fall ill with COVID-19. In this group, IgG to SARS-CoV-2 virus was not detected in 69.6% of the individuals (119 people). However, IgG to SARS-CoV-2 virus was detected in 52 examined individuals who did not become clinically ill. It amounted to 30.4%. Such situation may take place because of a previous asymptomatic form of COVID-19. As a result of the statistical analysis performed using the parametric Student's t-test, statistically significant differences in IgG values were detected in the groups of the examined individuals who fell ill with COVID-19 and who didn't fall ill with COVID-19.

The titer of IgG antibodies to SARS-CoV-2 virus in the control group of healthy individuals was 0.54±0.26 and it significantly differed from that in the group of patients with COVID-19 and amounted to 1.64±0.47 (differences are statistically significant, $p<0.05$).

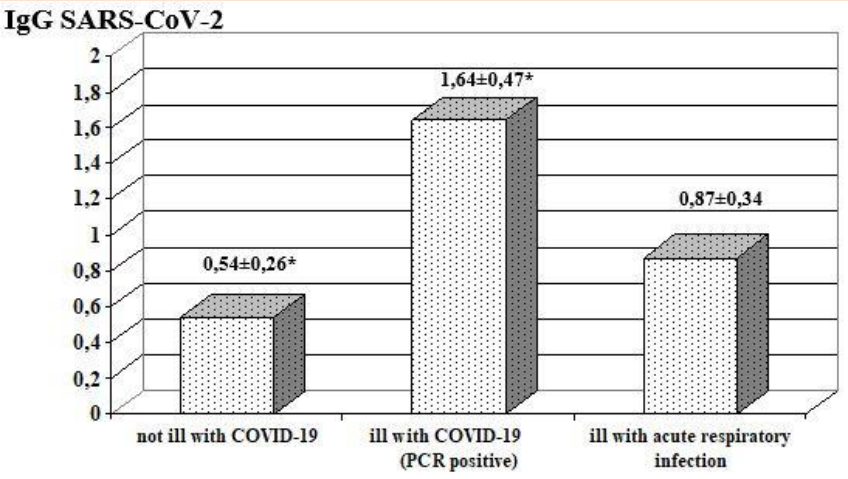

Figure 2: Quantitative ratio of IgG levels to SARS-COV-2 virus in the patients who did not fall ill with COVID-19, fell with COVID-19 and were ill with acute respiratory infections. (* - p (groups I - II) differences are statistically significant, $p<0.05$).

Study of IgG Level to SARS-CoV-2 Virus

A positive test result suggests that an individual has been potentially exposed to SARS-CoV-2. However, this is not always connected with the disease. Our studies showed the presence of a positive test for SARS-CoV-2 virus in 30.4% (52 people) of the examined individuals who did not fall ill with COVID-19 and who did not have any signs of the disease at all. This phenomenon can be explained in the following way. There is a possibility that a test for antibodies to coronavirus may erroneously give a positive result due to the so-called cross-

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reaction when antibodies to COVID-19 are taken for antibodies that are slightly similar in form, but they remained after a common acute respiratory infection [2-4]. Thus, predicting the degree of immune protection based only on one indicator of the level of IgG antibodies to SARS-COV-2 virus is a complicated task. Pradenas, et al., found that individuals with mild or asymptomatic infection had a slight decrease in neutralizing activity, antibodies, which persisted 6 months after the onset of symptoms or diagnosis [5]. Antibody levels decrease over some period of time, but the number of memory cells required to produce antibodies upon reinfection remains unchanged, even 6 months after infection with SARS-CoV-2 [6]. The researchers have found that IgM and IgG antibody titers against the Receptor-Binding Domain (RBD) of SARS-CoV-2 spike protein decrease significantly over this time period. In contrast, the number of RBD-specific memory cells remains unchanged even after 6 months when the infection takes place. Memory cells show clonal proliferation and differentiation after 6 months, and the antibodies they express have the ability to hypermutate, indicating the ongoing evolution of the immune response [7].

There is one group of particular interest in our experiment. These are patients ill with acute respiratory infections, among which 66% (101 people) had IgG to SARS-CoV-2 virus, the antibody titer was 0.87±0.34. In 34% of these patients (52 people), IgG to SARS-CoV-2 virus was not detected. Statistical comparison of IgG values to SARS-CoV-2 virus in this group and in the group of people, whose diagnosis of COVID-19 was confirmed (IgG=1.64±0.47), showed significant differences between them (differences are statistically significant, $p<0.05$).

Dynamics of Changes in Lymphocyte Activation Markers

In this research, a high expression level of the molecular marker of intercellular adhesion CD54 in the patients who were ill with COVID-19 - 34.3±5.6% was fixed. The patients who did not fall ill with COVID-19 had a significantly lower value - 25.2±2.4% ($p<0.05$ according to the Mann-Whitney test). The data are presented in Table 2.

The study of the expression level of the molecular marker of apoptosis CD95 showed the same trend: its values in the patients who recovered from COVID-19 were higher than in the patients who did not fall ill, respectively, 29.2±3.7% and 23.4±2.5% ($p>0.05$ according to the Mann-Whitney test).

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Groups of Patients	Ig G to SARS-COV-2 virus	Values of CD 25 (%)	Values of CD 54 (%)	Values of CD 95 (%)
Group I, patients, not ill with COVID-19 (n=60)	0,45±0,28	26,3±2,3*	25,2±2,4*	23,4±2,5
Group II, patients ill with COVID-19 (n=54)	1,71±0,54	16,7±1,8*	34,3±5,6*	29,2±3,7
* - p (groups I - II) differences are statistically significant, p<0.05				

Table 2: The values of expression of molecular markers of lymphocyte activation CD25, CD54 (ICAM-1) and CD95 in the patients who did not fall ill and who fell ill with COVID-19.

Results of Treatment with Mercureid (Table 3)

Groups of Patients	Ig G to SARS-COV-2 virus	Values of CD 25 (%)	Values of CD 54 (%)	Values of CD 95 (%)
Group I, patients, not ill with COVID-19 (n=60)	0,44±0,31	23,4±2,4*	21,8±2,1*	21,5±2,3
Group II, patients ill with COVID-19 (n=54)	1,92±0,47	20,4±2,3*	28,3±4,3*	25,3±4,2
* - p (groups I - II) differences are statistically significant, p<0.05				

Table 3: The dynamics of changes in the expression of lymphocyte activation markers CD25, CD54 (ICAM-1) and CD95 in the patients who did not fall ill and who fell ill with COVID-19 after taking Mercureid.

Dynamics of Changes in IgG to SARS-CoV-2

Based on the results of 2-month taking drug Mercureid, we can note that in group I, IgG level to SARS-CoV-2 virus slightly decreased from 0.45±0.28 to 0.44±0.31 that demonstrates Mercureid ability to prolong adequate production of long-lived protective antibodies to SARS-CoV-2 (Fig. 3).

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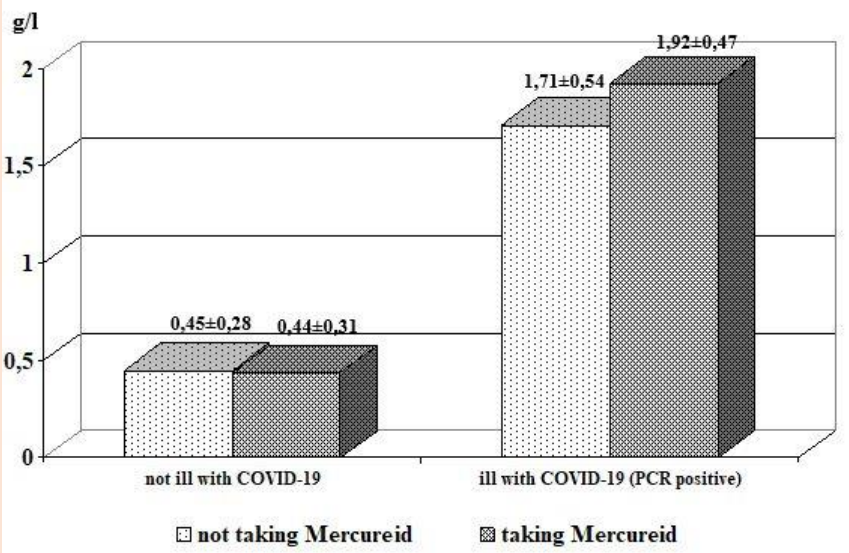

Figure 3: Indicators Ig G-SARS-COV-2 in the patients who did not fall ill and fell ill with COVID-19, who took and did not take drug Mercureid.

In group II, IgG level after taking drug Mercureid increased from 1.71±0.54 to 1.92±0.47. These patients had COVID-19 that was confirmed by PCR-test. In this group of patients, Mercureid normalized impaired immune homeostasis (CD25, CD54 / ICAM-1, CD95) and, as a result, there was an increase in immunological protection with the effective formation of protective memory cells to SARS-CoV-2.

Dynamics of CD25 Change

CD25 - IL-2 (interleukin-2) receptor, transmembrane glycoprotein, molecular weight 55 kDa. It is expressed on activated T and B-lymphocytes, monocytes, macrophages. As previously established, an increase in CD25 levels is often caused by an insufficient antiviral T-cell immune response, and as a result, the expansion of PD-1 + CD8 + T-cells, which are involved in the pro-inflammatory response and determine the severity of the disease [8].

The study of the expression level of the molecular marker of lymphocyte activation CD25 (IL-2 receptor) showed that its amount in the group of people with COVID-19 is 16.7±1.8%. It is significantly lower than in the patients who were not ill with COVID, 26.3±2.3% ($p<0.05$ according to the Mann-Whitney test). In these groups of patients, IgG enzyme immunoassay was analyzed.

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Notably, an increase in the molecular marker of CD25 activation to 26.3±2.3% was reliably established in the patients with low IgG values to SARS-CoV-2 virus (the group of people who did not fall ill with COVID-19). At the same time, the patients who were ill with COVID-19 and who had elevated IgG level to SARS-CoV-2 virus showed lower CD25 values - 16.7±1.8%. Thus, it seems likely that there is a compensatory mechanism of T-cell activation. Due to this mechanism, in individuals with low IgG antibodies to SARS-CoV-2 virus, or their absence, a possibility of protection against the virus exists.

In addition, this research finding suggests that CD25 has an important role in maintaining immune tolerance and immune balance in relation to the virus antigen after becoming infected [9].

After taking drug Mercureid, CD25 decreased in group I to 23.4±2.4, while in group II, it increased to 20.4±2.3 ($p<0.05$ according to the Mann-Whitney test). This may indicate the formation of a high level of immune response in the short term after recovery, due to overcoming the phenotype of exhausted T-lymphocytes (Fig. 4).

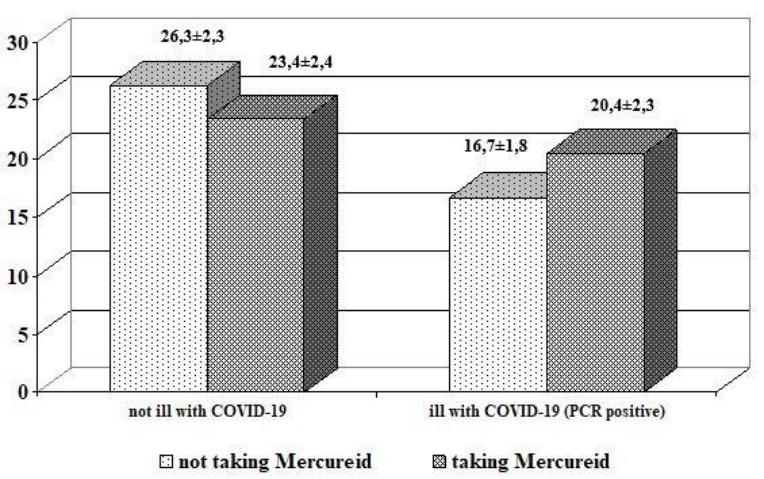

Figure 4: Indicators of the molecular marker of CD25 activation (IL-2 receptor) in the patients who did not fall ill and fell ill with COVID-19, who took and did not take drug Mercureid.

Dynamics of CD54 (ICAM-1) Change

CD54 (ICAM-1) - intercellular adhesion molecule-1 belongs to the superfamily of immunoglobulin proteins (IgSF, molecular weight 90 kDa). It has a high level of expression on the cell surface of leukocytes, on activated endothelial cells, regulates the migration of leukocytes to inflammation sites. Expression of CD54 (ICAM-1) is induced on the cell surface

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of leukocytes, macrophage neutrophils, epithelial, endothelial cells and fibroblasts and is increased under the action of cytokines (TNF-α, IL-1, INFγ).

Endothelial cell infection caused by SARS-CoV-2 induces vascular changes and increases ICAM-1 expression in the patients with COVID-19 and it can be used as a biomarker of disease severity or recovery [10].

In addition, it's worth mentioning that an increased expression of CD54 (ICAM-1) is connected not only with the severity of COVID-19 disease, but may also cause blood clotting dysfunction [11].

Intercellular adhesion molecule (ICAM-1, CD54) expression indicates the involvement of the endothelium of the vascular wall, as one of the mechanisms of the pathogenesis of post-COVID syndrome, in the inflammatory process [12].

According to the works of the other researchers, ICAM-1 can bind to alveolar macrophages and enhance the production of inflammatory cytokines [13].

CD54 indicator in group I was increased and amounted to 25.2±2.4. In group II, it was pathologically high 34.3±5.6. After taking drug Mercureid, CD54 decreased in group I to 21.8±2.1. In group II, it decreased to 28.3±4.3 ($p<0.05$ according to the Mann-Whitney test). Thus, a decrease in CD54 (ICAM-1) indicates a decrease in the production of pro-inflammatory cytokines, contributes to the protection of the endothelium and presents a favourable trend in the patients' recovery (Fig. 5).

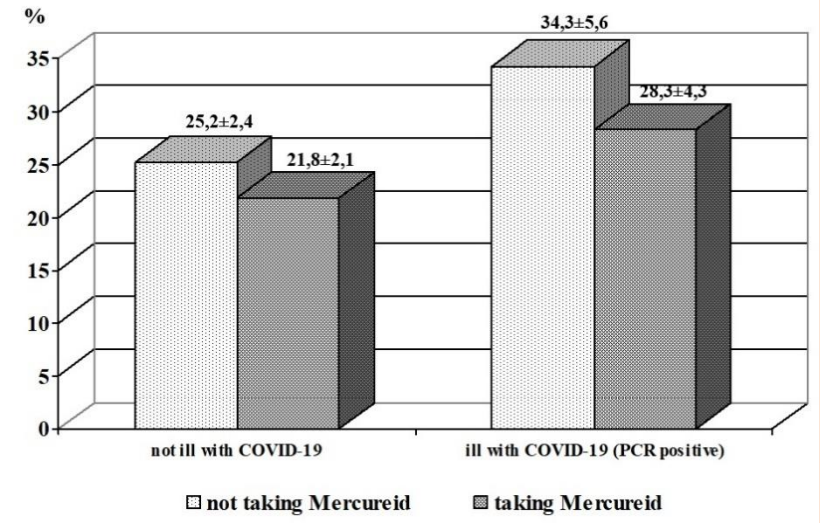

Figure 5: Indicators of the molecular marker of intercellular adhesion CD54 in the patients who did not fall ill and fell ill with COVID-19, who took and did not take drug Mercureid.

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Dynamics of CD95 Change

CD95 is an apoptosis antigen, or Fas antigen with a molecular weight of 45 kD. It mediates signals that induce apoptosis. It is a transmembrane molecule belonging to the TNF-α receptor superfamily. It has a high level of expression on activated T and B cells.

High expression of CD95 (Fas) is also connected with increased activation of PD-1 marker. PD-1 is a checkpoint protein on immune cells. It acts as a kind of "switch" that "prohibits" T-cells attacking other cells in the body, including those affected by a virus or tumor. Hyperactivation of CD95 increases the propensity of immune cells to apoptosis and leads to their functional depletion during COVID-19 infection. It, in its turn, impairs the elimination of the virus from the body [14]. CD95 indicator in group I was increased and amounted to 23.4±2.5. In group II, it was pathologically higher - 29.2±3.7. After a 2-month course of taking drug Mercureid, CD95 decreased in group I to 21.5±2.3. In group II, it decreased to 25.3±4.2 ($p<0.05$ according to the Mann-Whitney test).

On the one hand, an increase in the level of molecular markers expression of apoptosis CD95 and intercellular adhesion CD54 on blood lymphocytes in the patients with COVID-19 indicates a continuing high level of immune response in the short term after recovery [15].

On the other hand, prolonged hyperactivation of these markers may bring to the development of inflammation of the vascular endothelium, impaired blood clotting, development of thrombosis and depletion of the antiviral activity of lymphocytes, followed by lymphopenia. Therefore, the tactics of targeted immunotherapy aimed at normalizing these parameters is necessary to reduce the risk of developing adverse effects of Post-COVID Conditions (PCC) (Fig. 6).

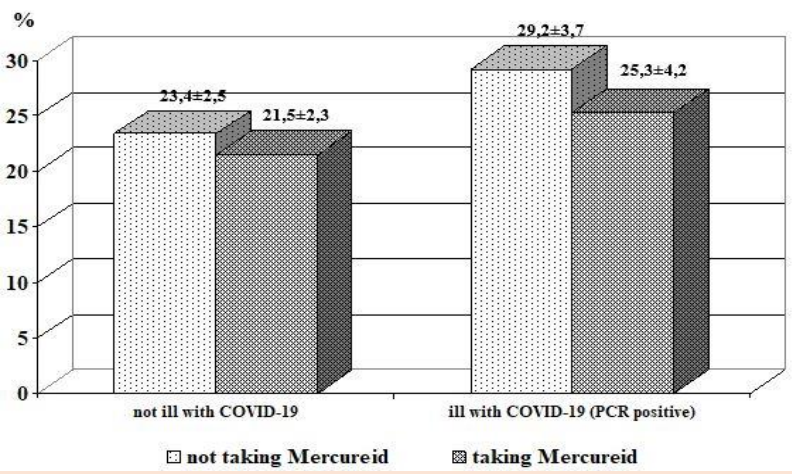

Figure 6: Indicators of the molecular marker CD95 (apoptosis) in the patients who did not fall ill and fell ill with COVID-19, who took and did not take drug Mercureid.

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Discussion

COVID-19 disease is an infection with a short incubation period and high contagiousness. It should be noted that this type of pathogens also includes various types of influenza, SARS, acute respiratory infections. The rapid development of the disease puts forward an urgent task for doctors to diagnose it quickly and accurately. Antibody tests detect antibodies or immunoglobulins that are produced as a result of a person's immune response to SARS-CoV-2 infection.

The presence of Immunoglobulin M (IgM) antibodies may indicate a current or recent infection, while antibodies to Immunoglobulin G (IgG) appear later during the infection process and can often indicate a past infection, however, they do not exclude cases with recently infected patients who may remain contagious, especially if IgM antibodies are detected at the same time. Generally, in viral infections, IgG antibodies persist longer than IgM antibodies and confer immunity from reinfection, but it is not still clear whether it's true for COVID-19 [16].

The study of IgG level to SARS-CoV-2 virus is a necessary primary test that is relevant for all groups of patients. The interpretation of test results is quite difficult and depends on many variables and factors, including sensitivity, specificity, and possible cross-reactivity [17]. Most often, the potential of immune protection can be determined by the level of production of neutralizing antibodies, but the usual serological test only indicates the fact that the immune system has encountered COVID-19 virus. However, it should be noted that in some cases, there is a very high titer of antibodies; in this case it is likely that the neutralizing activity will be higher. At the same time, a number of research studies have shown that the concentration of antibodies to coronavirus in the blood of the recovered patients has an indirect relationship to the level of protection against COVID-19. It is connected with the fact that having a low level of antibodies, a high level of protection against the virus may exist due to cellular immunity. In the publications on this subject some important facts were established. The researchers observed that after 6-7 months when the infection arose in patients, the number of CD4 and CD8 cells producing γ-interferon increased when stimulating with SARS-CoV-2 antigen. These results indicate that strong immunity against SARS-CoV-2 is common among convalescents [18].

Our studies showed that the quantitative indicators of IgG to SARS-CoV-2 virus were low. This fact confirms the possibility of an alternative cellular immune response.

A study of the long-term response and neutralizing activity of antibodies in response to SARS-CoV-2 infection demonstrated that in most patients, IgG titers stabilize at a relatively high level during the 6-month follow-up period. At a later date, the positivity rate for binding and

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neutralization of SARS-CoV-2-specific antibodies still exceeds 70%. These results indicate robust immunity in recovered patients with COVID-19 symptoms [19].

It should also be noted that patients who asymptomatically underwent COVID-19 and who were in the group of patients ill with COVID-19 (these are 10% of patients (9 people)) can also count on long-term immune protection due to specific memory T-lymphocytes programmed to produce antibodies.

SARS-Cov-2 virus has a tropism for the tissues of the upper and lower respiratory tract and vascular endothelium. It is attached to this tissue, which lines the inner surface of the blood, lymphatic vessels, and heart cavities. In an attempt to destroy the virus, the immune system attacks this endothelium, resulting in massive inflammation. The so-called cytokine storm is essentially a protective reaction of the body, however, it is able to destroy the body.

The problem of immune protection of the patients who have been seriously ill with COVID-19 is very important. In critically ill patients, the hypertrophied response to infection that has led to a cytokine storm can weaken the body and prevent from having a long-term immunity [20]. The possibility of COVID-19 relapse is connected with the long-term detection of SARS-CoV-2 RNA traces in the samples of the respiratory tracts of the recovered patients. The virus inability to replicate *in-vitro* suggests its inability to replicate *in-vivo* [21].

Antibodies are key immune effectors that provide protection against pathogenic threats. What is more, the severity of symptoms sometimes directly correlates with the magnitude of virus-specific antibodies. Patients with strong immune responses recovered faster from COVID-19 and had higher numbers of activated CD4 T-cells. Thus, there is an effective immune phenotype that connects the rate of symptoms elimination with the dynamics of antibody production [22].

Conclusion

The present study showed that in the group of patients ill with COVID-19, protective IgG antibodies to SARS-CoV-2 virus were detected in 90% of cases (81 people). In 10% of patients (9 people), despite the clinical manifestations of the disease and the diagnosis confirmed by PCR test, the ELISA analysis that was performed on the 18-20th day after having PCR test did not reveal IgG to the virus.

In the control group (patients not ill with COVID-19), IgG to SARS-CoV-2 virus was not detected in 69.6% of patients (119 people). At the same time, 30.4% (52 people) had a positive test result for IgG to SARS-CoV-2 virus. This may be due to a previous asymptomatic infection.

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Statistically significant differences were found between the values of IgG antibody titer to SARS-CoV-2 virus in the control group of individuals (not ill people) and those with a confirmed COVID-19 diagnosis. IgG values to SARS-CoV-2 virus in the control group were 0.54±0.26, this indicator significantly differed from that in the group of patients with COVID-19 - 1.64±0.47 (t=2.05, indicators significant p=0.044).

In the group of patients ill with acute respiratory infections, 66% had IgG to SARS-COV-2 virus, despite the absence of COVID-19 symptoms and a negative PCR test. It is possible that the test for antibodies to coronavirus erroneously gives a positive result due to a cross-reaction, when antibodies to COVID-19 are taken for antibodies that are similar in form, and which remained after a common acute respiratory infection.

It was found out that the expression level of molecular markers of intercellular adhesion CD54 on lymphocytes in patients ill with COVID-19 was significantly higher than in the group of those who did not fall ill, respectively, 34.3±5.6% and 25.2±2.4%, ($p< 0.05$ according to the Mann-Whitney test). For these patients it may be connected with the development of inflammation of the vascular endothelium and the risk of developing pathologies of blood clotting in the future.

The study of the expression level of the molecular marker of lymphocyte activation CD25 (IL-2 receptor) showed that its amount in the group of people who fell ill with COVID-19 was 16.7±1.8%; it is significantly lower than in the group of people who were not ill with COVID-19, namely, 26.3±2.3% ($p<0.05$ according to the Mann-Whitney test). In the future, these patients are likely to develop the phenotype of exhausted T-lymphocytes that is extremely unfavourably as to the risk of violation of antitumor and antiviral protection.

An increase in the molecular marker of CD25 activation up to 26.3±2.3% was observed in the patients with low IgG values to SARS-COV-2 virus (the group of those who did not fall ill with COVID-19). At the same time, patients who underwent COVID-19 and who had elevated IgG to SARS-COV-2 virus, showed lower CD25 values, namely, - 16.7±1.8%. This research finding suggests that CD25 is a T-cell activation mechanism thanks to which the individuals with low IgG antibodies to SARS-CoV-2 virus or with their complete absence may be protected from the virus by means of cellular immunity.

Concluding Remarks

Patients who underwent COVID-19 face a dysfunction of immune reactivity, a violation of immune homeostasis that can cause risks of developing life-threatening pathologies in the post-COVID period. These are such pathologies as: strokes, memory problems, depression, anxiety

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and migraines. Besides, there can be: movement disorders, from tremors and involuntary muscle contractions to epileptic seizures, impaired hearing and vision (according to the analysis of federal data conducted by the researchers from Washington University School of Medicine in St. Louis, USA, published on Sept. 22 in Nature Medicine, 2022). Therefore, the search for drugs capable of restoring the disturbed balance of T-lymphocyte activation markers to reduce the risk of developing these problems is a therapeutic necessity. When prescribing drug Mercureid, the SMART effect was noted. SMART is the method of action of "smart" drugs, which normalizes only the disturbed indicators of the immune response. This method improves the therapeutic effect of the drug and minimizes side effects. It allowed increasing the expression of CD25 in group II with a reduced indicator and decreasing to the norm in group I with an initially elevated level of CD25. At the same time, drug Mercureid reduced pathologically high levels of CD54 (ICAM-1), CD95 in both groups.

Such multidirectional effect of drug Mercureid is probably due to the fact that its molecules have mixed agonist-antagonist properties. This made it possible to increase the expression of lymphocyte activation markers, which were initially reduced, and to reduce those that were pathologically increased.

Selectivity and multidirectionality of the influence favorably distinguishes Mercureid from other immunotropic drugs and allows restoring the lost immune homeostasis with a high degree of efficiency and, most importantly, safety. This therapy is necessary both for the effective formation of long-lived memory cells capable of providing an effectively high protective titer of IgG to SARS-CoV-2 virus, and for risk reduction development of adverse consequences for the patient in the post-COVID condition (post-COVID conditions/PCC). To improve the results of treatment, it is advisable to use Mercureid in a preventive mode for the people with an increased risk of SARS-CoV-2 infection, especially during the COVID-19 pandemic, as well as for the patients with chronic somatic diseases capable of causing or intensifying immune dysfunction. The overall therapeutic efficacy of Mercureid was 75.6%. The drug was well tolerated; there are no data on its intolerance or development of significant side effects.

Conflict of Interest

The authors declare that they have no competing interests.

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