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Dependence of changes in hematological and integrative parameters in patients with chronic viral hepatitis C on the received antiviral therapy

A. H. Lishnevskaya, M. D. Chemych

Sumy State University,

2, Rymkowskiego-Korsakowa st., 40007 Sumy, Ukraine

Abstract

A total of 287 patients were treated with various antiviral therapy options: group I – basic (pathogenetic and symptomatic) therapy, group II – pegylated interferon in combination with ribavirin, group III – pegylated interferon with ribavirin and sofosbuvir, group IV – direct-acting antivirals. Patients with chronic viral hepatitis C (CVHC) before the start of treatment showed a decrease in platelet counts, segmented neutrophils and an increase in level of lymphocytes, bilirubin content, alanine aminotransferase activity, aspartate, transferrinase (practice), with a comparison group (practically virus-free patients) <0.05 . After 4 weeks of receiving interferon-containing therapy, a further decrease was observed: leukocyte count, erythrocyte count, platelet count; ALT, AST and gamma-glutamyltranspeptidase (GGTP) activity; increased erythrocyte sedimentation rate (ESR), bilirubin content, and bilirubin activity $p < 0.05$. Patients who received direct-acting antivirals (DAAs) had a decrease in: erythrocyte count, total bilirubin content, ALT activity, AST, GGTP; increase in sed rate and the AST/ALT ratio, $p < 0.05$. After 12 weeks of treatment, patients treated with pegylated interferon were diagnosed with a decrease in platelet count, erythrocyte count, and leukocyte count (with the exception of patients with dual therapy that experienced the slight increase of the leukocytes) with hemoglobin content, $p < 0.05$. Also, in the group II subjects compared

with week 4 decreased: the content of bilirubin and creatinine, the activity of ALT, AST, GGTP, while the De Ritis ratio increased ($p < 0.05$). Patients in group III had lower GGTP activity than at 4 weeks and lower ALT and AST values compared with the onset of antiviral therapy ($p < 0.05$). Patients receiving DAAs experienced a decrease in hemoglobin content; no changes in biochemical parameters at this stage compared with the previous one were established.

The investigated integrative indicators suggest changes in the immune system of patients, in particular the prevalence of cellular immunity over the humoral link and the predominance of the autoimmune component. Patients with dual and triple PVT regimens had more pronounced changes compared to patients receiving DAAs.

Keywords: chronic viral hepatitis C; clinical blood test; biochemical blood test; integrative parameters; immunity.

Introduction. Around the world, about 71 million people are infected with the hepatitis C virus. However, the use of antiviral drugs can cure this infection, which reduces the risk of death from cirrhosis and hepatocellular carcinoma (HCC) [1].

Prior to synthesizing DAAs by standards of care for patients with chronic HCV infection, pegylated interferon (PEG-IFN) preparations in combination with ribavirin were used during 24 or 48 weeks depending on the genotype. This treatment was not only costly but also had significant side effects. These factors led to a decrease in the number of patients fully completing the treatment [2]. Currently, the need to administer antiviral therapy to all patients who have not received treatment and had no contraindication to therapy has been demonstrated [3]. The use of DAAs can reduce CVD prevalence and liver disease-related mortality by 94% and 75% in countries such as Egypt with high infection rates, so it can be treated as cost-effective for health care [4, 5]. The primary goal of HCV therapy is treatment until a stable virological response is defined, which is defined as HCV negative RNA within 12 or 24 weeks after completion of treatment, with a very low likelihood of late relapse. Treatment response is usually associated with normalization of enzyme levels, improvement or disappearance of inflammation and liver fibrosis (in patients without cirrhosis). Positive dynamics are observed after treatment and in patients with severe fibrosis (F3) or cirrhosis (F4), which reduces the risk of life-threatening complications (portal hypertension and liver failure). According to recent data, in patients with liver cirrhosis, which does not show viral RNA, the risk of HCC morbidity and mortality associated with liver function is significantly reduced, but not completely eliminated, compared with untreated patients [3, 6-8].

The aim of the study. To determine the dependence of changes in hematological, biochemical and integrative parameters in patients with chronic viral hepatitis C on the received antiviral therapy.

Patients and methods.

For the study, 287 patients were diagnosed with CVHC who were undergoing treatment at the Z. Y. Krasovytskyi Sumy Regional Infectious Clinical Hospital in the period from 2015 to 2019. Their medical records of inpatients and outpatients were also analyzed. The comparison group included 55 practically virus-free individuals who underwent a preventive medical examination at SSU University Clinic in 2018-2019. Patients were divided into 4 groups. 46.64% (131 individuals) of CVHC patients received basic (pathogenetic and symptomatic) therapy (group I), 54.36% (156) received antiviral therapy, including those treated with: a double regimen (PEG-IFN + ribavirin; group II) - 53.84% (84); triple (PEG-IFN + ribavirin + sofosbuvir; group III) 16.03% (25); bezinterferon (DAAs; group IV) 30.13% (47).

The patients were subjected to a clinical blood test (Elite 3, CobasMicros), a biochemical blood test (ChemWell, COBASEMira) before starting at the 4th and at the 12th week of antiviral therapy. PCR to confirm the diagnosis and to establish the genotype of the virus and to determine the fibrosis using FIBROTEST (METAVIR) was performed in the commercial laboratory "SINEVO". Integrative indices (integral severity index - ISI, entropy of leukocyte formula), indices of nonspecific reactivity (resistance coefficient - RC, immunoreactivity index - IR, neutrophil-lymphocyte ratio -NLR, lymphocyte-monocyte ratio - LMR , lymphocyte index - Ilymph, eosinophils-lymphocytes ratio - ELR, index of allergization - IA, nuclear index - NI); indexes of activity of inflammation (total index of inflammation - TII, Krebs index - KI, lymphocytic-granulocytic index - ILG, index of leukocyte and ESR ratio - ILESR), indexes of intoxication (leucocyte intoxication index - LII, aggression index – Iagr, hematological index of intoxication - HII, leukocyte shift index - LSI, index of intoxication severity - IIS, reactive response of neutrophils- NRR) were calculated.

The study materials were subjected to statistical analysis using nonparametric analysis methods. Accumulation, correction, systematization of the source information and visualization of the obtained results were performed in Microsoft Office Excel spreadsheets 2016. Statistical analysis was performed using IBM SPSS Statistics v.23 (IBM Corporation). Quantitative indicators were evaluated for compliance with the normal distribution with the use of the Shapiro-Wilk test (with fewer than 50 tested) or the Kolmogorov-Smirnov test (with more than 50 tested). The sets of quantitative indicators were described using the values

of the median (Me) and the lower and upper quartiles (Q1-Q3). To compare independent sets in the absence of signs of normal data distribution, the Mann-Whitney U-test was used. We used the Wilcoxon W-test to compare the differences between two dependent paired samples.

Results. Among the CVHC survey, the number of men was 1.96 times higher (66.20%) than women (33.80%). The age of patients in the general group comprised 46 (36-55) years.

In each group with different antiviral therapy schemes, the majority were also men (respectively group I - 60.31%, II - 66.67%, III - 84.00%, IV - 63.83%). Patients in all study groups were young and middle-aged: group I- 47,00 (37,00 - 58,00), II – 41,00 (32,25 - 51,00), III – 41,00 (34,00 - 47,00), IV - 50,00 (40,00 - 60,00).

Body mass index in all groups corresponded to the value of normal or excess body weight (respectively group I – 26,00 (24,00 – 29,00), II – 26,00 (23,25-29,00), III - 24,00 (23-28,00), IV – 26,00 (24,00-29,00)). Disease duration after diagnosis in most patients was less than 10 years: basic therapy - 2,00 (1,00-6,00), double - 6,00 (5,00 – 8,75), triple – 5,00 (3,00-7,00), non-interferon – 2,00 (2,00 – 6,00).

In all groups individuals with 1st and 3rd genotype prevailed (respectively, group I - 38.90% and 44.30%, II - 64.30% and 31.00%, III - 72.00% and 24.00%, IV - 57.40 and 27.70%). Most patients in each group had minimal activity (respectively, I - 73.3%, II - 75.00%, III - 68.00% and IV - 72.30%).

In patients from the groups who were prescribed antiviral therapy, the greatest number were patients with moderate liver fibrosis (double - 35.70%, triple - 40.00%, DAAs - 31.9%). Among patients receiving basic therapy, severe liver fibrosis (37.40%) prevailed, moderate fibrosis occupied the second position (27.50%).

In terms of epidemiological features, the distribution in the groups was homogeneous. The most widespread probable ways of infection were treatment at the dentist (accordingly group I - 76,34%, II - 54,76%, III - 64,00%, IV - 29,79%), surgical interventions and manipulations (accordingly basic therapy - 74,81%, double - 55,95%, triple - 44,00%, non-interferon - 44,68%). Less likely cases were manipulations in beauty salons (respectively group I - 26.72%, II - 30.95%, III - 28.00%, IV - 8.51%), transfusions of blood components (respectively basic therapy - 29 , 77%, double - 27.38%, triple - 16.00%, non-interferon - 17.02%).

The total number of leukocytes and erythrocytes in all surveyed, regardless of the group, was normal before the start of treatment and did not differ from the values of practically virus-free patients. The hemoglobin level was also within the physiological

fluctuations, but had a slight difference in patients in different groups: compared to patients who did not receive antiviral therapy, the hemoglobin level was 1.1 times higher in the group I and II patients. The average platelet count in patients with CVHC was lower than in the comparison group (1.2-1.3 times). The ratio of rod-core and segment-nucleotrophils differed 1.1-2.0 times in groups with a tendency to decrease the content of segment-nucleotrophils in patients. The lymphocyte content of the subjects was higher than in the comparison group.

In different groups of patients before antiviral therapy, laboratory parameters did not differ from patients not receiving antiviral therapy, but erythrocyte and hemoglobin levels were slightly higher (1.1-1.2 and 1.1 times, respectively) in the double, triple and non-interferon-treated groups. Also, the content of rod-neutrophils was 1.6-2.5 times lower. The number of segmented nuclear neutrophils and monocytes was only slightly lower in patients with dual therapy (1.1 and 1.3, respectively), and ESR in patients in group III (2.3) (Table 1).

In patients undergoing dual antiviral therapy after 4 weeks of treatment, the number of leukocytes and segmented nuclei decreased by 1.5 and 1.2 times, respectively; ESR, the number of rod, lymphocytes, monocytes, and neutrophils increased 1.3, 1.7, 2.2 and 1.7 times, respectively. Indicators of red blood changed as follows: the content of hemoglobin and erythrocytes decreased 1.1 times, platelets - 1.2 times); however, it remained lower (1.2 times) than before treatment. When compared with the results at 4 weeks, the leukocyte formula changed: segmental nucleotrophils increased (by 1.1 times), and lymphocytes decreased by 1.1 times, but compared with the beginning of therapy, rod-nuclear neutrophils increased (by 1.3 times) and lymphocytes (by 1.2 times), and eosinophils were halved. The level of hemoglobin and erythrocytes was 1.2 times lower than before antiviral therapy and 1.1 times compared to week 4, platelets - 1.3 times relative to baseline and 1.1 at comparison with week 4. The ESR has decreased (1.2 times) from the previous level, but was higher (1.9 times) compared to the initial value. The same dynamics of change during the passage of patients antiviral therapy has been presented by other researchers [10].

In patients with triple antiviral therapy, the results of the clinical blood test did not differ from the group with basic therapy, except for erythrocytes (in group III more than 1.1 times), hemoglobin (more than 1.2), rod-nuclear neutrophils (more than 2.5) and ESR (over 1.8).

After 4 weeks of treatment in patients from group II there was a decrease in the total number of leukocytes by 1.6 times, erythrocytes and hemoglobin by 1.1 times, ESR increased by 2.8 times. In leukocyte formula, the level of rod-neutrophils increased 2.5 times, lymphocytes 1.3 times, and the number of segmented nuclear neutrophils decreased 1.1 times.

In patients receiving triple therapy, after 12 weeks of therapy compared to 4 weeks, the total number of leukocytes, erythrocytes, hemoglobin decreased by 1.1 times, platelets - by 1.2 times. 8 times, erythrocytes, platelets and the content of hemoglobin - in 1,2, the number of segmented nuclear neutrophils in 1,1 times, increase in the number of rod-nuclear neutrophils 2.5 times, lymphocytes - 1.3 times, acceleration of ESR - 3.2 times. Other studies show that widespread side effects of dual interferon-containing therapy are reduced erythrocytes, leukocytes, and platelets [11-13].

Patients did not show any differences from those who did not receive specific therapy, except for more erythrocytes and smaller - rod-shaped neutrophils, before initiating DAAs.

After administration of DAAs for a month, the number of erythrocytes decreased and ESR increased in patients, after three months compared to 4 weeks and with the start of antiviral therapy, the hemoglobin content decreased.

In the biochemical analysis of blood in the course of treatment, patients were diagnosed with some features in groups. In group I, compared with healthy, the amount of total bilirubin increased (by 1.2 times), ALT activity (by 2.4), AST (by 2.1), GGTP (by 1.8), and decreased ALP (by 1.1), which is explained by the predominant severity of cytolytic syndrome compared with cholestatic. The changes were similar in patients from different groups before starting treatment, except for higher level of protein in the groups with triple and non-interferon treatment regimens (Table 2).

In patients undergoing double therapy after 4 weeks of treatment compared to the beginning of therapy, the amount of total bilirubin increased 1.4 times and the activity of ALP also grew, but the level of ALT decreased 1.4 times, AST - 1.2, GGTP - 1.1, which indicates a decrease in the intensity of cytolysis and increased cholestatic component. At this stage an increase in creatinine concentration (by 1.1 times) and a decrease in glucose content (by 1.1) were observed. Other studies have reported an increase in glucose tolerance after hepatitis C virus eradication [9].

After 12 weeks of treatment in patients in group II compared to 4 weeks there was a decrease in the amount of total bilirubin (by 1.2 times), ALT activity (1.6), AST (1.3), GGTP (1.4), creatinine (1.1), glucose (1.1), with ALT, AST, and GGTP levels lower than those before treatment (correspondingly 2.2 times; 1.6; 1.5), with ALT and AST levels higher than normal (1.4 and 1.2). During this period, an increase in the De Ritis Ratio compared to 4 weeks (1.2) and with the beginning of antiviral therapy (1.3) was observed.

Table 1 - Changes in clinical blood analysis in patients with CVHC on the received antiviral therapy

Indicator	Groups, (n), survey period										
	Practically virus-free individuals (n=55)	I (n=131)	II (n=84)			III (n=25)			IV (n=47)		
			Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy
1	2	3	4	5	6	7	8	9	10	11	12
Leukocytes $1 \times 10^9/l$	5,50 (4,80-6,80)	5,39 (4,13-6,61) (p ₁ =0,126)	5,15 (4,41-6,00) (p ₁ =0,011*, p ₂ =0,447)	3,40 (3,10-3,90) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***)	4,20 (3,10-4,90) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***, p ₄ =0,000****)	5,90 (4,48-7,26) (p ₁ =0,689, p ₂ =0,156)	3,60 (3,15-4,82) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***)	3,35 (2,71-4,15) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***, p ₄ =0,023****)	5,40 (4,30-6,89) (p ₁ =0,442, p ₂ =0,475)	5,51 (4,50-6,50) (p ₁ =0,650, p ₂ =0,252, p ₃ =0,891)	5,34 (4,50-7,16) (p ₁ =0,603*, p ₂ =0,485, p ₃ =0,899, p ₄ =0,386)
Erythrocytes $1 \times 10^{12}/l$	4,66 (4,32-5,05)	4,45(4,04-4,86)(p ₁ =0,002*)	4,95 (4,46-5,27) (p ₁ =0,032*, p ₂ =0,000**)	4,36 (3,90-4,83) (p ₁ =0,001*, p ₂ =0,502, p ₃ =0,001***)	4,07 (3,59-4,50) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***, p ₄ =0,000****)	5,18 (4,86-5,38) (p ₁ =0,000*, p ₂ =0,000**)	4,63 (4,14-5,03) (p ₁ =0,652, p ₂ =0,105, p ₃ =0,001***)	4,25 (3,88-4,71) (p ₁ =0,002*, p ₂ =0,383, p ₃ =0,000***, p ₄ =0,006****)	4,58 (4,21-5,04) (p ₁ =0,458, p ₂ =0,043**)	4,57 (4,12-4,86) (p ₁ =0,082, p ₂ =0,333, p ₃ =0,014***)	4,34 (4,09-4,76) (p ₁ =0,002*, p ₂ =0,704, p ₃ =0,003, p ₄ =0,197)
Hemoglobin g/l	138,00 (130,00-146,00)	136,00 (123,00-148,00) (p ₁ =0,165)	146,50 (136,00-159,75) (p ₁ =0,004*, p ₂ =0,000**)	130,50 (124,00-137,75) (p ₁ =0,000, p ₂ =0,062, p ₃ =0,000***)	123,50 (113,00-133,50) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***, p ₄ =0,000****)	155,00 (146,50-159,5) (p ₁ =0,000*, p ₂ =0,000**)	135,00 (126,00-147,50) (p ₁ =0,421, p ₂ =0,759, p ₃ =0,000***)	126,00 (119,00-140,50) (p ₁ =0,002*, p ₂ =0,110, p ₃ =0,000***, p ₄ =0,018****)	140,00 (129,00-151,00) (p ₁ =0,655, p ₂ =0,065)	146,00 (125,00-155,00) (p ₁ =0,227, p ₂ =0,017*, p ₃ =0,874)	136,00 (126,00-145,00) (p ₁ =0,361, p ₂ =0,738, p ₃ =0,044***, p ₄ =0,006****)
Platelets $1 \times 10^9/l$	221,00 (195,00-265,00)	170,00 (135,00-224,00) (p ₁ =0,000*)	174,50 (140,00-210,25) (p ₁ =0,000*, p ₂ =0,977)	146,50 (131,25 - 162,50) (p ₁ =0,000*, p ₂ =0,001**, p ₃ =0,067)	139,00 (114,00-153,00) (p ₁ =0,000*, p ₂ =0,000**, p ₃ =0,000***, p ₄ =0,007****)	185,00 (137,50-231,50) (p ₁ =0,016*, p ₂ =0,453)	174,00 (123,50-207,50) (p ₁ =0,001*, p ₂ =0,820, p ₃ =0,067)	150,00 (117,50-198,00) (p ₁ =0,000*, p ₂ =0,356, p ₃ =0,046***, p ₄ =0,242****)	191,00 (153,00-246,00) (p ₁ =0,007*, p ₂ =0,163)	191,00 (154,00-233,00) (p ₁ =0,015*, p ₂ =0,063, p ₃ =0,718)	195,00 (155,00-239,00) (p ₁ =0,010*, p ₂ =0,057, p ₃ =0,475, p ₄ =0,904)
Rod-core %	4,00 (3,00-6,00)	5,00 (3,00-7,00) (p ₁ =0,021*)	3,00 (2,00-4,00) (p ₁ =0,001*, p ₂ =0,000**)	5,00 (3,00-6,00) (p ₁ =0,043*, p ₂ =0,772, p ₃ =0,000***)	4,00 (3,00-6,00) (p ₁ =0,458, p ₂ =0,097, p ₃ =0,000***, p ₄ =0,095)	2,00 (2,00-3,50) (p ₁ =0,002*, p ₂ =0,000**)	5,00 (3,00-7,00) (p ₁ =0,168, p ₂ =0,842, p ₃ =0,000***)	5,00 (3,00-6,00) (p ₁ =0,180, p ₂ =0,799, p ₃ =0,001***, p ₄ =0,863)	4,00 (2,00-5,00) (p ₁ =0,627, p ₂ =0,019*)	3,00 (2,00-5,00) (p ₁ =0,349, p ₂ =0,07**, p ₃ =0,900)	4,00 (3,00-5,00) (p ₁ =0,992, p ₂ =0,052, p ₃ =0,668, p ₄ =0,436)

1	2	3	4	5	6	7	8	9	10	11	12
Segment-nuclear %	55,00 (50,00-59,00)	48,00 (41,00-55,00) (p ₁ =0,000*)	44,50 (37,00-53,75) (p ₁ =0,000*,p ₂ =0,042**)	37,50 (33,00-42,00) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,011***)	43,00 (40,00-48,00) (p ₁ =0,000*,p ₂ =0,001**,p ₃ =0,672,p ₄ =0,000****)	48,00 (41,50-59,50) (p ₁ =0,064,p ₂ =0,378)	42,00 (36,00-48,00) (p ₁ =0,000*,p ₂ =0,037**,p ₃ =0,011***)	42,00 (34,50-49,00) (p ₁ =0,000*,p ₂ =0,028**,p ₃ =0,003***,p ₄ =0,819)	50,00 (44,00-59,00) (p ₁ =0,053,p ₂ =0,136)	50,00 (46,00-54,00) (p ₁ =0,002*,p ₂ =0,254,p ₃ =0,654)	49,00 (44,00-52,00) (p ₁ =0,000*,p ₂ =0,665,p ₃ =0,221,p ₄ =0,639)
Eosinophils %	2,00 (1,00-4,00)	2,00 (1,00-4,00) (p ₁ =0,454)	2,00 (1,00-3,00) (p ₁ =0,100,p ₂ =0,387)	1,00 (0,00-2,00) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,057)	1,00 (0,00-2,00) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,000***,p ₄ =0,610)	2,00 (0,50-4,00) (p ₁ =0,309,p ₂ =0,585)	1,00 (0,00-2,00) (p ₁ =0,001*,p ₂ =0,006**,p ₃ =0,057)	1,00 (0,00-2,00) (p ₁ =0,000*,p ₂ =0,002**,p ₃ =0,110,p ₄ =0,486)	2,00 (0,00-3,00) (p ₁ =0,020,p ₂ =0,080)	1,00 (0,00-2,00) (p ₁ =0,003*,p ₂ =0,010**,p ₃ =0,938)	1,00 (0,00-2,00) (p ₁ =0,000*,p ₂ =0,002**,p ₃ =0,439,p ₄ =0,834)
Basophils %	0,00 (0,00-0,00)	0,00 (0,00-1,00) (p ₁ =0,050)	0,00 (0,00-0,00) (p ₁ =0,476,p ₂ =0,100)	0,00 (0,00-0,00) (p ₁ =0,807,p ₂ =0,100,p ₃ =0,029)	0,00 (0,00-0,00) (p ₁ =0,487,p ₂ =0,100,p ₃ =0,833,p ₄ =0,617)	1,00 (0,00-1,00) (p ₁ =0,100,p ₂ =0,147)	0,00 (0,00-1,00) (p ₁ =0,400,p ₂ =0,553,p ₃ =0,092)	0,00 (0,00-0,50) (p ₁ =0,031,p ₂ =0,306,p ₃ =0,157,p ₄ =1,000)	0,00 (0,00-1,00) (p ₁ =0,100,p ₂ =0,553)	0,00 (0,00-1,00) (p ₁ =0,100,p ₂ =0,939,p ₃ =0,441)	0,00 (0,00-1,00) (p ₁ =0,100,p ₂ =0,939,p ₃ =0,470,p ₄ =0,988)
Lymphocytes %	31,00 (28,00-34,00)	36,00 (28,00-41,00) (p ₁ =0,001*)	35,00 (28,00-41,75) (p ₁ =0,003*,p ₂ =0,790)	45,00 (40,00-50,00) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,004***)	40,50 (37,00-45,75) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,000***,p ₄ =0,000****)	33,00 (29,00-41,50) (p ₁ =0,060,p ₂ =0,625)	42,00 (38,00-48,50) (p ₁ =0,000*,p ₂ =0,003**,p ₃ =0,004****)	43,00 (35,00-45,50) (p ₁ =0,000*,p ₂ =0,035,p ₃ =0,007***,p ₄ =0,443)	35,00 (27,00-40,00) (p ₁ =0,049,p ₂ =0,424)	35,00 (31,00-41,00) (p ₁ =0,000*,p ₂ =0,716,p ₃ =0,240)	36,00 (31,00-42,00) (p ₁ =0,000*,p ₂ =0,475,p ₃ =0,122,p ₄ =0,772)
Monocytes %	7,00 (6,00-10,00)	8,00 (6,00-11,00) (p ₁ =0,491)	6,00 (5,00-9,00) (p ₁ =0,226,p ₂ =0,022**)	10,00 (7,00-11,00) (p ₁ =0,003*,p ₂ =0,007**,p ₃ =0,841)	9,00 (7,25-10,00) (p ₁ =0,014*,p ₂ =0,064,p ₃ =0,000***,p ₄ =0,186)	8,00 (6,00-11,00) (p ₁ =0,245,p ₂ =0,421)	9,00 (6,00-11,50) (p ₁ =0,143,p ₂ =0,277,p ₃ =0,841)	10,00 (7,00-12,50) (p ₁ =0,006*,p ₂ =0,195,p ₃ =0,415)	8,00 (6,00-11,00) (p ₁ =0,312,p ₂ =0,679)	8,00 (6,00-11,00) (p ₁ =0,409,p ₂ =0,773,p ₃ =0,879)	8,00 (6,00-12,00) (p ₁ =0,175,p ₂ =0,330,p ₃ =0,645,p ₄ =0,465)
ESR mm/h	5,00 (3,00-11,00)	9,00 (5,00-20,00) (p ₁ =0,000*)	6,00 (4,00-8,75,00) (p ₁ =0,443,p ₂ =0,000**)	13,00 (8,00-16,00) (p ₁ =0,000*,p ₂ =0,220,p ₃ =0,000***)	11,25 (4,00-24,00) (p ₁ =0,000*,p ₂ =0,000**,p ₃ =0,000***,p ₄ =0,000****)	5,00 (4,00-8,00) (p ₁ =0,598,p ₂ =0,002**)	14,00 (10,00-18,50) (p ₁ =0,000*,p ₂ =0,110,p ₃ =0,000**)	16,00 (10,00-20,00) (p ₁ =0,000*,p ₂ =0,058,p ₃ =0,000***,p ₄ =0,287)	8,00 (4,00-11,00) (p ₁ =0,034*,p ₂ =0,066)	12,00 (7,00-19,00) (p ₁ =0,000*,p ₂ =0,341,p ₃ =0,002**)	12,00 (7,00-16,00) (p ₁ =0,000*,p ₂ =0,411,p ₃ =0,003,p ₄ =0,231)

Notes. Significant difference compared to: * - indicator of group of practically virus-free individuals (p₁<0,05, calculated according to the Mann-Whitini criterion); ** - with indicator in the group that did not receive antiviral therapy (p₂<0,05, calculated according to the Mann-Whitney criterion), *** - with indicator before therapy (p₃<0,05, calculated according to Wilcoxon criterion), * *** - with an indicator after 4 weeks of antiviral therapy (p₄<0,05, calculated according to Wilcoxon criteria).

Table 2 - Changes in the biochemical analysis of blood in patients with CVHC on the received antiviral therapy

Indicator	Groups, (n), survey period										
	Practically virus-free individuals (n=55)	I (n=131)	II (n=84)			III (n=25)			IV (n=47)		
			Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy
1	2	3	4	5	6	7	8	9	10	11	12
Total protein (g/l)	71,30 (68,30-73,90)	72,50 (68,30-75,70) (p ₁ =0,450)	72,00 (70,00-76,45) (p ₁ =0,133; p ₂ =0,335)	73,00 (69,25-77,00) (p ₁ =0,096; p ₂ =0,228; p ₃ =0,684)	73,00 (68,00-77,45) (p ₁ =0,126; p ₂ =0,225; p ₃ =0,959; p ₄ =0,983)	75,10 (72,50-79,90) (p ₁ =0,000*; p ₂ =0,002**)	75,10 (71,35-78,80) (p ₁ =0,021*; p ₂ =0,054; p ₃ =0,162)	71,80 (70,10-74,10) (p ₁ =0,655; p ₂ =0,674; p ₃ =0,003***; p ₄ =0,106)	75,00 (71,00-77,70) (p ₁ =0,006*; p ₂ =0,014*)	75,20 (71,80-79,20) (p ₁ =0,000*; p ₂ =0,054; p ₃ =0,354)	73,70 (71,00-77,00) (p ₁ =0,002*; p ₂ =0,011**; p ₃ =0,874; p ₄ =0,385)
Total bilirubin (μmol/l)	14,40 (12,40-17,90)	17,30 (12,10-25,10) (p ₁ =0,018*)	13,00 (10,00-18,00) (p ₁ =0,051; p ₂ =0,000**)	18,00 (13,00-25,93) (p ₁ =0,002*; p ₂ =0,497; p ₃ =0,000***)	14,50 (11,08-17,18) (p ₁ =0,351; p ₂ =0,002**; p ₃ =0,975; p ₄ =0,000****)	15,50 (12,30-20,60) (p ₁ =0,550*; p ₂ =0,283)	18,90 (16,00-23,35) (p ₁ =0,000*; p ₂ =0,311; p ₃ =0,045***)	14,00 (11,00-16,90) (p ₁ =0,299; p ₂ =0,020**; p ₃ =0,226; p ₄ =0,001)	15,80 (10,70-24,60) (p ₁ =0,162; p ₂ =0,869)	15,20 (10,00-18,50) (p ₁ =0,922; p ₂ =0,055; p ₃ =0,018***)	14,30 (10,80-19,60) (p ₁ =0,984; p ₂ =0,043**; p ₃ =0,068; p ₄ =0,887)
ALT (IU/l)	22,70 (18,30-28,16)	55,00 (32,00-98,00) (p ₁ =0,000*)	69,00 (40,00-124,25) (p ₁ =0,000*; p ₂ =0,095)	50,00 (28,25-84,50) (p ₁ =0,000*; p ₂ =0,180; p ₃ =0,000***)	31,50 (19,00-46,00) (p ₁ =0,002*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,000****)	58,00 (38,50-156,50) (p ₁ =0,000*; p ₂ =0,179)	32,00 (22,00-41,50) (p ₁ =0,008*; p ₂ =0,000**; p ₃ =0,000***)	40,00 (23,00-47,00) (p ₁ =0,001*; p ₂ =0,002**; p ₃ =0,001***; p ₄ =0,559)	75,00 (44,00-158,00) (p ₁ =0,000*; p ₂ =0,018)	25,00 (19,00-38,00) (p ₁ =0,092; p ₂ =0,000**; p ₃ =0,000***)	27,00 (19,00-36,00) (p ₁ =0,043; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,697)
AST (IU/l)	24,40 (21,40-28,00)	52,00 (33,00-76,00) (p ₁ =0,000*)	45,00 (33,25-73,00) (p ₁ =0,000*; p ₂ =0,514)	37,00 (25,00-52,75) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	29,00 (22,00-39,00) (p ₁ =0,006*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,007****)	45,00 (30,00-78,50) (p ₁ =0,000*; p ₂ =0,631)	32,00 (23,00-44,00) (p ₁ =0,002; p ₂ =0,000**; p ₃ =0,002***)	35,00 (24,00-45,50) (p ₁ =0,002*; p ₂ =0,000**; p ₃ =0,020***; p ₄ =0,657)	52,00 (39,00-101,00) (p ₁ =0,000*; p ₂ =0,213)	29,00 (22,00-38,00) (p ₁ =0,014*; p ₂ =0,000**; p ₃ =0,000***)	30,00 (23,00-40,00) (p ₁ =0,005; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,759)
GGTP (IU/l)	26,00 (18,00-35,00)	46,00 (25,00-81,00) (p ₁ =0,000*)	36,50 (24,00-66,50) (p ₁ =0,001*; p ₂ =0,320)	33,50 (22,00-59,25) (p ₁ =0,007*; p ₂ =0,049*; p ₃ =0,000***)	24,00 (16,00-33,00) (p ₁ =0,201; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,000****)	61,00 (35,50-92,00) (p ₁ =0,000*; p ₂ =0,093)	43,00 (33,00-50,00) (p ₁ =0,000; p ₂ =0,597; p ₃ =0,002***)	31,00 (20,50-42,00) (p ₁ =0,219; p ₂ =0,020; p ₃ =0,001***; p ₄ =0,002****)	67,00 (35,00-93,00) (p ₁ =0,000*; p ₂ =0,011)	43,00 (30,00-61,00) (p ₁ =0,000*; p ₂ =0,996; p ₃ =0,000***)	38,00 (22,00-56,00) (p ₁ =0,002*; p ₂ =0,369; p ₃ =0,000***; p ₄ =0,078)

Continuation of Table 2

1	2	3	4	5	6	7	8	9	10	11	12
ALP (IU/l)	90,00 (80,00-112,00)	85,00 (60,00-110,00) (p ₁ =0,026*)	69,00 (57,70-80,75) (p ₁ =0,000*; p ₂ =0,000**)	71,00 (65,00-81,55) (p ₁ =0,000*; p ₂ =0,007**; p ₃ =0,004***)	71,00 (63,00-80,03) (p ₁ =0,000*; p ₂ =0,001; p ₃ =0,585; p ₄ =0,696)	85,00 (74,00-96,00) (p ₁ =0,102; p ₂ =0,750)	88,00 (72,50-95,00) (p ₁ =0,161; p ₂ =0,961; p ₃ =0,518)	76,00 (62,50-89,50) (p ₁ =0,001*; p ₂ =0,226; p ₃ =0,055; p ₄ =0,170)	92,00 (67,20-115,00) (p ₁ =0,528; p ₂ =0,176)	73,00 (59,00-86,00) (p ₁ =0,000*; p ₂ =0,012; p ₃ =0,000***)	67,00 (56,00-90,00) (p ₁ =0,000*; p ₂ =0,017**; p ₃ =0,001***; p ₄ =0,981)
Creatinine μmol / l	82,90 (72,90-100,70)	78,00 (65,00-92,00) (p ₁ =0,062)	76,00 (62,25-89,75) (p ₁ =0,005*; p ₂ =0,285)	80,50 (67,25-93,75) (p ₁ =0,160; p ₂ =0,398; p ₃ =0,000***)	72,50 (61,75-87,00) (p ₁ =0,002*; p ₂ =0,195; p ₃ =0,952; p ₄ =0,028****)	78,00 (64,00-89,50) (p ₁ =0,096; p ₂ =0,728)	78,00 (67,00-81,50) (p ₁ =0,023*; p ₂ =0,502; p ₃ =0,391)	71,00 (63,00-86,00) (p ₁ =0,007*; p ₂ =0,165; p ₃ =0,339; p ₄ =0,545)	77,00 (66,00-85,00) (p ₁ =0,035*; p ₂ =0,695)	76,00 (69,00-88,00) (p ₁ =0,051; p ₂ =0,916; p ₃ =0,702)	78,00 (69,00-91,00) (p ₁ =0,181; p ₂ =0,565; p ₃ =0,438; p ₄ =0,211)
Glucose mmol/l	5,20 (4,59-5,70)	5,20 (4,60-5,80) (p ₁ =0,821)	5,04 (4,70-5,56) (p ₁ =0,776; p ₂ =0,473)	4,80 (4,43-5,30) (p ₁ =0,029*; p ₂ =0,003*; p ₃ =0,000***)	4,75 (4,10-5,19) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,004****)	4,90 (4,30-5,45) (p ₁ =0,220; p ₂ =0,146)	4,80 (4,40-5,70) (p ₁ =0,262; p ₂ =0,182; p ₃ =0,893)	5,10 (4,20-5,43) (p ₁ =0,232; p ₂ =0,181; p ₃ =0,864; p ₄ =0,840)	5,30 (4,80-5,80) (p ₁ =0,648; p ₂ =0,794)	5,00 (4,70-5,70) (p ₁ =0,925; p ₂ =0,578; p ₃ =0,588)	4,90 (4,60-5,60) (p ₁ =0,612; p ₂ =0,376; p ₃ =0,476; p ₄ =0,197)
De Ritis Ratio	1,07 (0,86-1,31)	0,93 (0,71-1,17) (p ₁ =0,005*)	0,70 (0,57-0,86) (p ₁ =0,000*; p ₂ =0,000**)	0,78 (0,59-1,02) (p ₁ =0,000*; p ₂ =0,007*; p ₃ =0,074)	0,94 (0,83-1,22) (p ₁ =0,093; p ₂ =0,210; p ₃ =0,000***; p ₄ =0,000****)	0,65 (0,53-0,84) (p ₁ =0,000*; p ₂ =0,002*)	1,00 (0,83-1,30) (p ₁ =0,455; p ₂ =0,213; p ₃ =0,003***)	0,92 (0,77-1,12) (p ₁ =0,075; p ₂ =0,820; p ₃ =0,819; p ₄ =0,819)	0,76 (0,62-0,95) (p ₁ =0,000*; p ₂ =0,020**)	1,19 (0,88-1,41) (p ₁ =0,670; p ₂ =0,578; p ₃ =0,000***)	1,16 (0,85-1,36) (p ₁ =0,745; p ₂ =0,007**; p ₃ =0,000***; p ₄ =0,718)

Notes. Significant difference compared to: * - indicator of group of practically virus-free individuals (p₁<0,05, calculated according to the Mann-Whitini criterion); ** - with indicator in the group that did not receive antiviral therapy (p₂<0.05, calculated according to the Mann-Whitney criterion), *** - with indicator before therapy (p₃<0.05, calculated according to Wilcoxon criterion), * *** - with an indicator after 4 weeks of antiviral therapy (p₄<0.05, calculated according to Wilcoxon criteria).

Among patients on triple therapy after 4 weeks of treatment, the total bilirubin increased 1.2 times and the De Ritis ratio 1.5 times, the ALT activity decreased 1.8 times, the AST and GGTP - 1.4 times.

After 12 weeks of therapy, the level of GGTP decreased 1.4 times compared to 4 weeks, other indicators remained at the previous level. However, compared to the beginning of treatment, ALT decreased 1.5 times, AST 1.3 times, and GGTP 2 times.

In patients from group IV after 4 weeks of therapy the amount of total bilirubin decreased by 1.1 times, ALT activity - 3.0, AST - 1.8, GGTP - 1.6, ALP - 1.3, and the De Ritis ratio increased 1.6 times. Normalization of ALT and AST was observed in other studies, but bilirubin reduction was only found in patients with combination of sofosbuvir with symprevir [14]. At 12 weeks of treatment, the values of all biochemical parameters did not differ from the previous levels, but the activity of ALT, AST, GGTP, ALP were significantly lower, and the De Ritis ratio was higher than at the beginning of therapy.

In groups of patients with CVHC, IST and entropy levels were higher than in the comparison group, which is explained by an increase in ESR and impaired normal ratios of leukocytes in patients.

In patients at all stages of treatment, the following observations were made: increase in indices of nonspecific reactivity (RC - by 1.2-2.1 times) and inflammatory activity (ILG - by 1.2-2.0); decrease in indexes of endogenous intoxication (ISL - by 1.1-1.9), which confirms the prevalence of the autoimmune component of intoxication syndrome, and also indicates the severity of inflammation [15].

No changes in the levels of IR and LMR were observed, and other integrative indicators revealed changes depending on the type of therapy and the period of treatment.

Patients from groups I, II, III and IV before receiving antiviral therapy had: increase of the following indices of nonspecific reactivity: RC (from 1.2 to 1.4 times), Ilymph (1.2-1.6), NI (1.4 times), and in groups III and IV there was a decrease); decrease in NLR (1.1-1.3), ISEL (1.6-2). Among the indexes of activity of inflammation in these patients, an increase in TII (I - 1.2 times) or a decrease (II, III, IV - 1.1), an increase in KI (1.2-1.4) and ILESR (1.2-1.7), and decrease in ILG (1.2-1.4) were established. Among the indexes of endogenous intoxication, only a decrease in ISL (1.2-1.3) and NRR (1.2-2.7) was found.

In patients receiving dual antiviral therapy after 4 weeks of treatment, ISI (1.1) increased compared with pre-treatment data, but the entropy of leukocyte formula was normalized. Among nonspecific reactivity indices, the KI increased by 1.5 times, 1.4 - Ilymph, 1.9 - NI, there was a decrease in the NLR - by 1.7 times and ISEL - by 2.5, indicating an increase in the influence of cellular immunity, compared with humoral, and left shift in the granulocyte-macrophage system [15]. Among the inflammation activity indexes, increased: TII (1.1 times), ILG (1.4), ILESR (1.7); only KI (1.4)

decreased, confirming increased inflammation due to the autoimmune component [15]. Indices of endogenous intoxication decreased: 1.4 times - ISL and 1.9 - NRR. These data confirm the decrease in immunological reactivity with adequate treatment.

After 12 weeks, ISI treatment increased by 1.1 times compared with 4 weeks and before treatment. The entropy of the leukocyte formula also went beyond normal (increased 1.2 times relative to 4 weeks). RC decreased during this period (1.3 times), but remained higher than normal and at the beginning of therapy. Also, when comparing to 4 weeks, the ILG (1.2 times) and NLR (1.1) increased, while the lower values were Ilimph (1.3), IA (1.2), NI (1.4), which indicates a weakening of cellular immunity at this stage. Among the indices of inflammatory activity, TII increased by 1.1 comparing to the 4th week and by 1.2 comparing to the beginning of therapy, KI increased by 1.2, but remained lower than before treatment, ILG decreased by 1.2, remaining higher than before therapy, ILESR increased by 1.6 compared with 4 weeks and by 2.7 than before therapy. All indexes of endogenous intoxication at the 12th week of therapy in comparison with 4 weeks increased (LII - by 1.3 times, Iagr - by 1.4, HII - by 1.6, LSI - by 1.2, IIS - by 2.1) and the NRR level has not changed.

Patients in group III after 4 weeks of therapy had similar changes: ISI increased by 1.1 times, entropy of leukocyte formula decreased by 1.1 times. Among the nonspecific reactivity indices, the following indicators have changed: the KI increased 1.4 times, the Ilimph - 1.3, the NI - 2.8, and the ISEL decreased 1.3 times. Among the activity indexes, ILG inflammation increased one and a half times, ILESR 1.3 times, and KI decreased 1.3 times. From the indexes of endogenous intoxication, after 4 weeks of therapy, only ISL decreased by 1.5 times.

At week 12 of treatment, there were some differences in the nonspecific reactivity indices: KI, Ilimf, and NI remained at the same level, but they were higher than values before therapy. Indices of activity of inflammation and endogenous intoxication did not change compared to week 4.

In patients receiving interferon-free antiviral regimens, the ISI significantly increased at 4 weeks and remained at the same level until the end of treatment, the entropy of the leukocyte formula was higher than in the comparison group, but did not change in the observation process as in the previous groups. All integrative indicators did not change during therapy except ILESR (increased by 1.6 at 4 weeks of treatment).

Table 3 - Changes in integrative parameters in patients with CVHC on the received antiviral therapy

Indicator	Groups, (n), survey period										
	Practically virus-free individuals (n=55)	I (n=131)	II (n=84)			III (n=25)			IV (n=47)		
			Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy	Prior to antiviral therapy	After 4 weeks of antiviral therapy	After 12 weeks of antiviral therapy
1	2	3	4	5	6	7	8	9	10	11	12
General integrative indices											
ISI	13,83 (13,58-14,56)	14,29 (13,77-15,66) (p ₁ =0,000*)	13,94 (13,69-14,39) (p ₁ =0,205; p ₂ =0,000**)	14,78 (14,23-15,21) (p ₁ =0,000*; p ₂ =0,147; p ₃ =0,000***)	15,38 (14,23-15,21) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,000****)	13,85 (13,63-14,20) (p ₁ =0,579; p ₂ =0,005**)	14,94 (14,35-15,63) (p ₁ =0,000*; p ₂ =0,153; p ₃ =0,000***)	15,08 (14,43-15,61) (p ₁ =0,000*; p ₂ =0,045**; p ₃ =0,000***; p ₄ =0,326)	14,19 (13,70-14,58) (p ₁ =0,018*; p ₂ =0,208)	14,70 (14,22-15,57) (p ₁ =0,000*; p ₂ =0,178; p ₃ =0,002***)	14,69 (14,08-15,19) (p ₁ =0,000*; p ₂ =0,284 p ₃ =0,002***; p ₄ =0,232)
ELF	21,05 (18,30-24,15)	26,79 (22,44-33,96) (p ₁ =0,000*)	23,85 (17,05-32,04) (p ₁ =0,094 p ₂ =0,003**)	20,03 (20,23-23,98) (p ₁ =0,137; p ₂ =0,000**; p ₃ =0,133)	23,59 (21,39-25,79) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,890; p ₄ =0,011****)	25,83 (23,44-35,89) (p ₁ =0,000*; p ₂ =0,463)	24,86 (21,58-26,53) (p ₁ =0,002*; p ₂ =0,076; p ₃ =0,037***)	22,53 (20,39-27,61) (p ₁ =0,012*; p ₂ =0,030**; p ₃ =0,032***; p ₄ =0,968)	27,16 (23,00-35,07) (p ₁ =0,000*; p ₂ =0,409)	27,95 (24,30-31,13) (p ₁ =0,000*; p ₂ =0,691 p ₃ =0,409)	26,16 (23,53-29,93) (p ₁ =0,000*; p ₂ =0,720 p ₃ =0,176; p ₄ =0,649)
Nonspecific reactivity indices											
RC	0,57 (0,49-0,66)	0,71 (0,51-1,00) (p ₁ =0,000*)	0,81 (0,56-1,06) (p ₁ =0,000*; p ₂ =0,363)	1,19 (0,96-1,49) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	0,95 (0,77-1,19) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,012***; p ₄ =0,000****)	0,69 (0,50-0,96) (p ₁ =0,046*; p ₂ =0,552)	1,00 (0,76-1,29) (p ₁ =0,000*; p ₂ =0,006**; p ₃ =0,003***)	1,02 (0,71-1,30) (p ₁ =0,000*; p ₂ =0,025; p ₃ =0,002***; p ₄ =0,657)	0,70 (0,45-0,92) (p ₁ =0,035*; p ₂ =0,296)	0,70 (0,57-0,96) (p ₁ =0,000*; p ₂ =0,695 p ₃ =0,397)	0,73 (0,58-0,98) (p ₁ =0,000*; p ₂ =0,831 p ₃ =0,141; p ₄ =0,661)
IR	4,63 (3,40-6,40)	4,66 (3,12-7,40) (p ₁ =0,734)	5,37 (3,74-7,38) (p ₁ =0,107; p ₂ =0,146)	4,86 (4,00-6,67) (p ₁ =0,176; p ₂ =0,256; p ₃ =0,510)	5,11 (4,06-5,85) (p ₁ =0,274; p ₂ =0,456; p ₃ =0,051; p ₄ =0,474)	5,25 (2,74-6,55) (p ₁ =0,872; p ₂ =0,416)	5,13 (3,36-7,17) (p ₁ =0,663; p ₂ =0,796; p ₃ =0,360)	3,83 (3,00-4,85) (p ₁ =0,164*; p ₂ =0,114; p ₃ =0,397; p ₄ =0,063)	4,16 (3,16-7,42) (p ₁ =0,564; p ₂ =0,376)	5,14 (3,33-6,60) (p ₁ =0,827; p ₂ =0,913 p ₃ =0,756)	4,14 (3,33-6,40) (p ₁ =0,768; p ₂ =0,561 p ₃ =0,891; p ₄ =0,495)
NLR	7,88 (5,60-10,67)	7,00 (4,50-10,33) (p ₁ =0,044*)	7,50 (5,00-9,80) (p ₁ =0,144; p ₂ =0,564)	4,51 (3,66-6,02) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	5,53 (4,20-6,81) (p ₁ =0,000*; p ₂ =0,003**; p ₃ =0,000***; p ₄ =0,005****)	6,25 (4,56-8,50) (p ₁ =0,037*; p ₂ =0,416)	5,89 (4,07-8,08) (p ₁ =0,006*; p ₂ =0,120; p ₃ =0,545)	4,70 (2,86-7,35) (p ₁ =0,000*; p ₂ =0,004**; p ₃ =0,123; p ₄ =0,376)	6,30 (5,00-9,85) (p ₁ =0,112; p ₂ =0,769)	6,25 (5,00-9,83) (p ₁ =0,101; p ₂ =0,853 p ₃ =0,882)	6,11 (4,23-9,71) (p ₁ =0,030*; p ₂ =0,557 p ₃ =0,502; p ₄ =0,579)

Continuation of Table 3

1	2	3	4	5	6	7	8	9	10	11	12
LMR	4,25 (3,00-5,83)	4,42 (2,87-7,00) (p ₁ =0,702)	5,18 (3,58-7,00) (p ₁ =0,075; p ₂ =0,112)	4,76 (3,90-6,42) (p ₁ =0,055; p ₂ =0,093; p ₃ =0,919)	5,00 (3,83-5,66) (p ₁ =0,090; p ₂ =0,205; p ₃ =0,159; p ₄ =0,477)	4,75 (2,54-6,26) (p ₁ =0,752; p ₂ =0,520)	4,70 (3,36-7,10) (p ₁ =0,375; p ₂ =0,535; p ₃ =0,231)	3,80 (3,00-4,85) (p ₁ =0,314; p ₂ =0,208; p ₃ =0,527; p ₄ =0,048***)	4,00 (2,75-7,40) (p ₁ =0,714; p ₂ =0,517)	4,56 (3,10-6,60) (p ₁ =0,582; p ₂ =0,882 p ₃ =0,802)	4,00 (3,00-6,00) (p ₁ =0,914; p ₂ =0,751 p ₃ =0,783; p ₄ =0,492)
I_{lymph}	0,54 (0,47-0,60)	0,66 (0,48-0,90) (p ₁ =0,000*)	0,76 (0,54-0,99) (p ₁ =0,000*; p ₂ =0,151)	1,05 (0,87-1,33) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	0,84 (0,72-1,05) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,050; p ₄ =0,000****)	0,67 (0,47-0,91) (p ₁ =0,027*; p ₂ =0,765)	0,89 (0,69-1,23) (p ₁ =0,000*; p ₂ =0,006**; p ₃ =0,009***)	0,91 (0,63-1,17) (p ₁ =0,000*; p ₂ =0,030**; p ₃ =0,006***; p ₄ =0,677)	0,64 (0,43-0,80) (p ₁ =0,050*; p ₂ =0,350)	0,66 (0,52-0,84) (p ₁ =0,000*; p ₂ =0,925 p ₃ =0,305)	0,67 (0,54-0,87) (p ₁ =0,000*; p ₂ =0,745 p ₃ =0,130; p ₄ =0,653)
ELR	0,08 (0,04-0,11)	0,06 (0,02-0,10) (p ₁ =0,150)	0,05 (0,25-0,99) (p ₁ =0,016*; p ₂ =0,454)	0,02 (0,00-0,05) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	0,02 (0,00-0,05) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,466)	0,04 (0,01-0,12) (p ₁ =0,175*; p ₂ =0,670)	0,03 (0,00-0,05) (p ₁ =0,000*; p ₂ =0,001**; p ₃ =0,016***)	0,02 (0,00-0,05) (p ₁ =0,000*; p ₂ =0,001**; p ₃ =0,083; p ₄ =0,566)	0,04 (0,00-0,09) (p ₁ =0,006*; p ₂ =0,079)	0,04 (0,00-0,08) (p ₁ =0,001*; p ₂ =0,012** p ₃ =0,697)	0,03 (0,00-0,07) (p ₁ =0,000*; p ₂ =0,002** p ₃ =0,342; p ₄ =0,717)
IA	0,99 (0,78-1,18)	1,08 (0,75-1,56) (p ₁ =0,052)	1,23 (0,89-1,71) (p ₁ =0,003*; p ₂ =0,335)	1,23 (1,05-1,64) (p ₁ =0,000*; p ₂ =0,021**; p ₃ =0,519)	1,05 (0,86-1,40) (p ₁ =0,043*; p ₂ =0,717; p ₃ =0,024***; p ₄ =0,000****)	1,17 (0,73-1,46) (p ₁ =0,230*; p ₂ =0,657)	1,08 (0,91-1,38) (p ₁ =0,128*; p ₂ =0,998; p ₃ =0,798)	1,00 (0,86-1,36) (p ₁ =0,235; p ₂ =0,660; p ₃ =0,798; p ₄ =0,778)	0,92 (0,69-1,40) (p ₁ =0,619; p ₂ =0,043**)	0,89 (0,72-1,29) (p ₁ =0,596; p ₂ =0,045** p ₃ =0,966)	0,97 (0,72-1,28) (p ₁ =0,778; p ₂ =0,048** p ₃ =0,966; p ₄ =0,970)
NI	0,07 (0,05-0,10)	0,10 (0,05-0,15) (p ₁ =0,000*)	0,07 (0,05-0,08) (p ₁ =0,179; p ₂ =0,000**)	0,13 (0,09-0,17) (p ₁ =0,000*; p ₂ =0,026**; p ₃ =0,000***)	0,09 (0,06-0,16) (p ₁ =0,016*; p ₂ =0,385; p ₃ =0,000***; p ₄ =0,001****)	0,04 (0,02-0,06) (p ₁ =0,007*; p ₂ =0,000**)	0,11 (0,07-0,15) (p ₁ =0,008*; p ₂ =0,817; p ₃ =0,000***)	0,11 (0,08-0,16) (p ₁ =0,001*; p ₂ =0,612; p ₃ =0,001***; p ₄ =1,000)	0,06 (0,04-0,10) (p ₁ =0,833; p ₂ =0,004**)	0,06 (0,04-0,10) (p ₁ =0,655; p ₂ =0,002** p ₃ =0,824)	0,08 (0,05-0,12) (p ₁ =0,324; p ₂ =0,034** p ₃ =0,505; p ₄ =0,394)

1	2	3	4	5	6	7	8	9	10	11	12
Indices of activity of inflammation											
III	6,95 (6,33-7,69)	7,44 (6,42-8,27) (p ₁ =0,045*)	6,07 (5,48-6,72) (p ₁ =0,000*; p ₂ =0,000**)	6,51 (5,92-7,28) (p ₁ =0,042*; p ₂ =0,000**; p ₃ =0,001***)	6,99 (6,28-7,83) (p ₁ =0,745*; p ₂ =0,073; p ₃ =0,000***; p ₄ =0,025****)	6,66 (6,10-7,04) (p ₁ =0,050*; p ₂ =0,001**)	7,05 (5,91-7,55) (p ₁ =0,637; p ₂ =0,077; p ₃ =0,074)	6,41 (5,81-7,62) (p ₁ =0,231; p ₂ =0,020; p ₃ =0,510; p ₄ =0,510)	6,73 (6,30-7,94) (p ₁ =0,893; p ₂ =0,147)	7,11 (6,46-7,99) (p ₁ =0,398; p ₂ =0,448 p ₃ =0,391)	6,92 (6,59-7,78) (p ₁ =0,287; p ₂ =0,457 p ₃ =0,330; p ₄ =0,771)
KI	1,85 (1,65-2,11)	1,51 (1,10-2,06) (p ₁ =0,000*)	1,32 (1,01-1,86) (p ₁ =0,000*; p ₂ =0,151)	0,96 (0,75-1,15) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	1,19 (0,96-1,39) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,005***; p ₄ =0,000****)	1,48 (1,09-2,09) (p ₁ =0,027*; p ₂ =0,765)	1,12 (0,81-1,45) (p ₁ =0,000*; p ₂ =0,006**; p ₃ =0,017***)	1,09 (0,85-1,59) (p ₁ =0,000*; p ₂ =0,030; p ₃ =0,032***; p ₄ =0,619)	1,54 (1,25-2,32) (p ₁ =0,050; p ₂ =0,350)	1,51 (1,20-1,91) (p ₁ =0,000*; p ₂ =0,925 p ₃ =0,166)	1,50 (1,15-1,85) (p ₁ =0,000*; p ₂ =0,745 p ₃ =0,064; p ₄ =0,508)
ILG	5,17 (4,46-5,76)	6,42 (4,51-8,29) (p ₁ =0,000*)	7,24 (5,09-9,25) (p ₁ =0,000*; p ₂ =0,096)	10,11 (8,32-12,82) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	8,20 (6,97-10,16) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,016***; p ₄ =0,000****)	6,00 (4,58-8,54) (p ₁ =0,045*; p ₂ =0,624)	8,78 (6,89-11,52) (p ₁ =0,000*; p ₂ =0,002**; p ₃ =0,003***)	9,15 (6,21-11,54) (p ₁ =0,000*; p ₂ =0,016**; p ₃ =0,002***; p ₄ =0,696)	6,25 (4,19-7,69) (p ₁ =0,049; p ₂ =0,391)	6,42 (5,16-8,20) (p ₁ =0,000*; p ₂ =0,896 p ₃ =0,290)	6,55 (5,26-8,40) (p ₁ =0,000*; p ₂ =0,530 p ₃ =0,125; p ₄ =0,575)
ILES R	0,28 (0,18-0,58)	0,48 (0,29-0,99) (p ₁ =0,000*)	0,26 (0,19-0,44) (p ₁ =0,046*; p ₂ =0,000**)	0,44 (0,27-0,58) (p ₁ =0,027*; p ₂ =0,108; p ₃ =0,000***)	0,70 (0,45-1,07) (p ₁ =0,000*; p ₂ =0,014**; p ₃ =0,000***; p ₄ =0,000****)	0,33 (0,22-0,50) (p ₁ =0,174; p ₂ =0,002**)	0,43 (0,36-0,67) (p ₁ =0,010*; p ₂ =0,987; p ₃ =0,000***)	0,53 (0,30-0,68) (p ₁ =0,017*; p ₂ =0,860; p ₃ =0,000***; p ₄ =0,819)	0,39 (0,21-0,75) (p ₁ =0,002*; p ₂ =0,104)	0,64 (0,45-1,02) (p ₁ =0,000*; p ₂ =0,061 p ₃ =0,000***)	0,64 (0,38-0,95) (p ₁ =0,000*; p ₂ =0,165 p ₃ =0,000***; p ₄ =0,103)
Indices of endogenous intoxication											
LII	0,45 (0,33-0,78)	0,43 (0,23-0,78) (p ₁ =0,328)	0,44 (0,24-0,65) (p ₁ =0,226; p ₂ =0,765)	0,47 (0,30-0,78) (p ₁ =0,732; p ₂ =0,500; p ₃ =0,573)	0,61 (0,32-1,06) (p ₁ =0,139; p ₂ =0,033**; p ₃ =0,031***; p ₄ =0,016****)	0,50 (0,22-0,84) (p ₁ =0,640; p ₂ =0,785)	0,49 (0,38-1,02) (p ₁ =0,430; p ₂ =0,333; p ₃ =0,861)	0,63 (0,32-0,92) (p ₁ =0,337; p ₂ =0,158; p ₃ =0,657; p ₄ =0,339)	0,63 (0,30-1,14) (p ₁ =0,189; p ₂ =0,049)	0,77 (0,34-1,06) (p ₁ =0,051; p ₂ =0,018** p ₃ =0,680)	0,74 (0,37-1,02) (p ₁ =0,050; p ₂ =0,013** p ₃ =0,966; p ₄ =0,849)
Iagr	0,63 (0,44-1,09)	0,65 (0,32-1,12) (p ₁ =0,330)	0,58 (0,34-0,94) (p ₁ =0,175; p ₂ =0,615)	0,64 (0,41-1,04) (p ₁ =0,608; p ₂ =0,559; p ₃ =0,559)	0,87 (0,42-1,45) (p ₁ =0,221; p ₂ =0,043**; p ₃ =0,026***; p ₄ =0,013****)	0,62 (0,29-1,15) (p ₁ =0,510; p ₂ =0,979)	0,64 (0,50-1,49) (p ₁ =0,537; p ₂ =0,378; p ₃ =0,696)	0,84 (0,45-1,30) (p ₁ =0,256; p ₂ =0,134; p ₃ =0,397; p ₄ =0,313)	0,82 (0,41-1,56) (p ₁ =0,303; p ₂ =0,080)	1,00 (0,42-1,50) (p ₁ =0,158; p ₂ =0,040** p ₃ =0,849)	0,98 (0,48-1,36) (p ₁ =0,094; p ₂ =0,026 p ₃ =0,916; p ₄ =0,743)

Continuation of Table 3

1	2	3	4	5	6	7	8	9	10	11	12
HII	0,46 (0,30-0,70)	0,45 (0,23-0,94) (p ₁ =0,789)	0,45 (0,23-0,66) (p ₁ =0,437; p ₂ =0,217)	0,52 (0,31-0,83) (p ₁ =0,381; p ₂ =0,588; p ₃ =0,217)	0,81 (0,41-1,25) (p ₁ =0,001*; p ₂ =0,004**; p ₃ =0,001***; p ₄ =0,002****)	0,46 (0,20-0,80) (p ₁ =0,807; p ₂ =0,719)	0,56 (0,42-1,12) (p ₁ =0,108; p ₂ =0,282; p ₃ =0,798)	0,73 (0,36-1,10) (p ₁ =0,032*; p ₂ =0,117; p ₃ =0,264; p ₄ =0,183)	0,67 (0,28-1,42) (p ₁ =0,063; p ₂ =0,117)	0,85 (0,41-1,34) (p ₁ =0,001*; p ₂ =0,048** p ₃ =0,452)	0,81 (0,37-1,23) (p ₁ =0,004*; p ₂ =0,017** p ₃ =0,966; p ₄ =0,866)
LSI	1,56 (1,38-1,78)	1,27 (0,96-1,77) (p ₁ =0,000*)	1,18 (0,89-1,66) (p ₁ =0,000*; p ₂ =0,204)	0,82 (0,64-0,99) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***)	0,98 (0,82-1,16) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,000***; p ₄ =0,000****)	1,38 (1,08-1,77) (p ₁ =0,022*; p ₂ =0,915)	0,93 (0,75-1,14) (p ₁ =0,000*; p ₂ =0,002**; p ₃ =0,012***)	1,00 (0,70-1,38) (p ₁ =0,000*; p ₂ =0,010**; p ₃ =0,025***; p ₄ =0,706)	1,38 (1,04-1,77) (p ₁ =0,027*; p ₂ =0,483)	1,28 (1,00-1,50) (p ₁ =0,000*; p ₂ =0,034** p ₃ =0,169)	1,17 (0,96-1,44) (p ₁ =0,000*; p ₂ =0,345 p ₃ =0,069; p ₄ =0,400)
IIS	0,12 (0,06-0,31)	0,18 (0,08-0,53) (p ₁ =0,011*)	0,14 (0,06-0,28) (p ₁ =0,931; p ₂ =0,006**)	0,20 (0,11-0,32) (p ₁ =0,098; p ₂ =0,464; p ₃ =0,185)	0,41 (0,21-0,73) (p ₁ =0,000*; p ₂ =0,002**; p ₃ =0,000***; p ₄ =0,000****)	0,17 (0,07-0,43) (p ₁ =0,516; p ₂ =0,253)	0,27 (0,13-0,49) (p ₁ =0,023*; p ₂ =0,614; p ₃ =0,527)	0,23 (0,15-0,50) (p ₁ =0,015*; p ₂ =0,347; p ₃ =0,183; p ₄ =0,326)	0,18 (0,07-0,44) (p ₁ =0,011*; p ₂ =0,609)	0,47 (0,24-0,71) (p ₁ =0,000*; p ₂ =0,457 p ₃ =0,083)	0,34 (0,18-0,84) (p ₁ =0,000*; p ₂ =0,013 p ₃ =0,380; p ₄ =0,546)
NRR	11,28 (7,14-16,71)	9,26 (3,38-21,51) (p ₁ =0,160)	4,13 (1,83-10,12) (p ₁ =0,000*; p ₂ =0,002**)	2,15 (0,00-6,21) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,008***)	2,04 (0,00-5,99) (p ₁ =0,000*; p ₂ =0,000**; p ₃ =0,008***; p ₄ =0,655)	8,87 (3,18-17,38) (p ₁ =0,007*; p ₂ =0,078)	3,17 (0,00-9,34) (p ₁ =0,000*; p ₂ =0,006**; p ₃ =0,181)	2,23 (0,00-8,03) (p ₁ =0,000*; p ₂ =0,001**; p ₃ =0,338; p ₄ =0,741)	9,26 (3,41-17,40) (p ₁ =0,001*; p ₂ =0,015**)	4,38 (0,00-12,22) (p ₁ =0,000*; p ₂ =0,745 p ₃ =0,493)	3,54 (0,00-12,24) (p ₁ =0,000*; p ₂ =0,003** p ₃ =0,871; p ₄ =0,777)

Notes. Significant difference compared to: * - indicator of group of practically virus-free individuals (p₁<0,05, calculated according to the Mann-Whitini criterion); ** - with indicator in the group that did not receive antiviral therapy (p₂<0,05, calculated according to the Mann-Whitney criterion), *** - with indicator before therapy (p₃<0,05, calculated according to Wilcoxon criterion), * *** - with an indicator after 4 weeks of antiviral therapy (p₄<0,05, calculated according to Wilcoxon criteria).

Conclusions

1 In patients with CVHC, there is a predominance of young and middle-aged men without obesity. In most cases, viral hepatitis is caused by 1b and 3a genotypes, and undergoes with minimal activity and moderate fibrotic changes in the liver. Among the probable ways of infection indicated by patients, the treatment of the dentist (29.79% - 76.34%), surgical interventions and manipulations (44.00% - 74.81%) predominate.

2 There is a decrease in platelet counts and segmented neutrophils, as well as an increase in lymphocyte counts ($p < 0.05$) in pre-treatment patients compared with healthy ones. After 4 weeks of treatment, the subjects receiving double and triple therapy reduced the number of leukocytes, erythrocytes, and ESR, and with double therapy - an additional number of platelets ($p < 0.05$). With the use of DAAs, only erythrocyte content decreased after one month and ESR increased, and hemoglobin content decreased by 12 weeks ($p < 0.05$).

3 Before treatment, blood biochemical analysis is characterized by an increase in bilirubin concentration, ALT activity, AST ($p < 0.05$). After the fourth week of treatment in patients undergoing dual and triple therapy, the activity of ALT, AST, GGTP decreased, while bilirubin and ALP increased ($p < 0.05$). At 12 weeks, total bilirubin, ALT, AST, GGTP, creatinine decreased, but the De Ritis ratio increased ($p < 0.05$). Patients on interferon-free therapy after 4 weeks experience a decrease in the concentration of total bilirubin, the activity of ALT, AST, GGTP, ALP and increase the De Ritis ratio ($p < 0.05$) that remains stable until the end of treatment.

4 Changes in integrative parameters indicate the prevalence of cellular immunity, a clear inflammation with a predominance of the autoimmune component. In patients undergoing interferon-containing therapy, indicators demonstrating the dominance of cellular immunity are increased, and at 12 weeks are reduced. Indices that indicate inflammation of the autoimmune genesis remain elevated throughout the treatment period. People receiving DAAs have increased rates that indicate an increase in inflammation by 4 weeks and intoxication caused by the autoimmune process.

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