COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF DIRECT ANTIVIRAL DRUGS IN THE TREATMENT OF CHRONIC VIRAL HEPATITIS C.

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Abstract. *Viral hepatitis C (HCV) is one of the most important problems of modern medicine. According to who statistics, there are between 500 and 700 million carriers of HCV.The aim of the study was to investigate clinical and immunological features of chronic viral hepatitis C, depending on the genotype of the virus, and to evaluate the diagnostic and prognostic value of immunological disorders.The research task was to study clinical and laboratory features of chronic hepatitis C in zavisimosti on the genotype of the virus. To study the immunological features of chronic hepatitis C in zavisimosti on the genotype of the virus. To determine the diagnostic and prognostic value of immunological indices as objective criteria for assessing the severity of the disease and prognosis.All of us were examined 83 patients with chronic viral hepatitis, 35-50 years with chronic viral hepatitis C, and 20 healthy persons of similar age and sex.Scientific novelty of the thesis is to explore was detected and clinical, laboratory and immunological features of chronic viral hepatitis C, depending on the genotype of the virus of hepatitis C.*

Keywords: *chronic viral hepatitis C, antiviral therapy, direct antiviral agents, treatment effectiveness.*

Actuality of the problem Over the past few years, the direction of antiviral treatment for patients with chronic HCV has changed rapidly due to an improved understanding of the biology of HCV replication and the identification of proteins that block key stages. Given the variability of complications of chronic hepatitis C virus - from minimal histological changes to extensive fibrosis and cirrhosis with hepatocellular carcinoma (HCC), a targeted and individual approach to prescribing antiviral therapy is the key to successful prevention. Care for patients with CHC-associated liver damage has improved significantly in recent years, which is associated with increasing our knowledge of the pathophysiology of this disease, as well as improving methods of diagnosis, treatment and prevention. The direction of antiviral treatment for patients with chronic HCV is changing rapidly due to improved understanding of the biology of HCV replication and the identification of proteins that block key steps. The use of two-component therapy in patients with genotype 1 (HCV-1), two-component therapy (DT) using PEG-IFN/RBV (active substance pegylated interferon alpha (PEG-IFN) and RBV (active substance riboverine) was changed to three-component therapy (TT) based on peginterferon with first-generation protease inhibitors (PIs). Recently, these regimens have been replaced by treatment regimens using NS3/4A protease inhibitors (the active substance simeprevir SIM or sofosbuvir (SOF)) [1,3].

The latter two regimens, in combination with PEG-IFN/RBV, resulted in changes in SVR rates from 30% to 92%, while reducing treatment duration and side effects. In patients with HCV genotypes 2 and 3, PEG-IFN/RBV strategies have been changed to SOF and RBV for patients with HCV-2, with SVR rates above 90% [1, 4], and to SOF and RBV, or SOF, and PEG-IFN/RBV for patients with HCV-3, where the addition of PEG-IFN increases SVR rates [1,5]. Data from

small groups of patients with HCV-4 showed that compared with dual therapy, triplet regimens based on SOF or SIM achieved SVR rates similar to those reported for patients with HCV-1 [2]. Until 2015, available regimens registered in Europe included SIM, SOF and (DAC) combined with PEG-IFN/RBV for patients with HCV-1 and HCV-4 with above-mentioned SVR rates, by off-label combination (SOF/SIM, or SOF/DAC, or DAC/SIM with without RBV in pilot studies of small groups of patients, or in combination with RBV for HCV-2 and HCV-3 patients (SOF only). Recent clinical studies have shown that all oral interferon-free regimens combining different direct-acting agents - SOF/ (LED) and (PAR active substance paritaprevir)/ (DAS active substance dasabuvir)/ (OMB active substance ombitasvir) achieve SVR rates that range from 90% to 100%, regardless of the severity of liver damage, the nature of the previous reaction to dual or first-generation PIs, and without significant side effects.2,3 The European Association for the Study of the Liver (EASL) presented updated recommendations for the treatment of hepatitis C adopted at a special meeting in Paris. The updated guidelines no longer provide for treatment of hepatitis C virus (HCV) with pegylated interferon-based regimens, thus ending the era of interferon therapy for hepatitis C in EU countries. Also excluded from the manual are modes based on one direct action agent. With the approval of new, highly effective treatment regimens for hepatitis C, access to therapy must be expanded. Most patients with CHC are unaware that they are infected. Today, there are different opinions about the role of the HCV genotype. During an in-depth examination of patients infected with strains with genotype 1b, researchers identified characteristic signs: patients, as a rule, were over 40 years old and had a longer duration of the disease, which indicated long-term persistence of the virus. In this case, as scientists point out, patients with chronic hepatitis C had a reduced response to interferon therapy. At the same time, when patients with chronic hepatitis C have other genotypes (3 and 2), on the contrary, a high response to antiviral therapy is observed, since in this case there is a smaller number of mutations. Of interest are reports that viruses belonging to different genotypes show varying degrees of interaction with antibodies. Thus, antibodies to NS4 epitopes in patients infected with viruses of genotypes 2, 3, 4 responded worse than with genotype 1. Similar data are provided by Toyoda et al. who note worse antibody reactivity to the C-terminus of the NS4a protein - recombinant protein 5-1-1 - in patients infected with genotypes 2b and 3a.

Purpose of the study. To determine the effectiveness of direct antiviral agents in the treatment of viral hepatitis C and to identify clinical and laboratory indicators characterizing the effectiveness of treatment.

Materials and methods of research. The studies were carried out at State Clinical Hospital No. 5, Research Institute of Virology. In order to study the effectiveness of various antiviral therapy regimens for chronic viral hepatitis C. We studied the anamnestic and clinical data in 83 patients with chronic viral hepatitis C. When studying the characteristics of the epidemiological history, it was revealed that in 43 patients the PEG-IFN/RBV regimen was used, they formed the first comparison group, and in 40 patients SOF/DAC formed the second group. 83 patients with chronic viral hepatitis C aged 35 to 50 years were examined. In the group of patients in the first group, 81.2% were men and 18.8% were women. Among the patients in the second group, 83.8% were men and 16.2% of patients were women.

We observed 83 patients with chronic viral hepatitis C; they were divided into two groups. The main group consisted of 43 patients with chronic viral hepatitis C on the PEG-IFN/RBV regimen. The second group consisted of 40 patients with chronic viral hepatitis C who were on the

SOF/DAC regimen. The diagnosis of chronic viral hepatitis C was established on the basis of clinical and epidemiological data from the study and was confirmed by the detection of anti-HCV IgM in the blood serum (ELISA). The diagnosis of chronic viral hepatitis B C was established on the basis of epidemiological, clinical, biochemical data and was confirmed by the detection of hepatitis C markers in the blood serum (anti-HCV IgG (total), qualitative and quantitative PCR, determination of the genotype of the blood virus.) in accordance with the order of the Ministry of Health of the Republic of Uzbekistan.

The criteria for assessing the severity of the disease were:

- severity of disease development,
- severity of intoxication and jaundice of the skin and sclera,
- enlargement of the liver and spleen,
- presence of hemorrhagic syndrome,
- involvement of the central nervous system in the pathological process,
- indicators of liver-specific enzymes,
- coagulogram.

A mild form of relapse of chronic viral hepatitis C in the icteric period was manifested by mild symptoms of intoxication (lethargy, nausea), slight icterus of the skin, moderate enlargement of the liver 1-3 cm below the edge of the right costal arch. Clinical manifestations of the moderate form of the disease were represented by moderately severe symptoms of intoxication, distinct jaundice of the skin, sclera of the eyes, and enlarged liver 2-4 cm below the edge of the costal arch. Distribution of clinical and laboratory parameters according to the degree of fibrosis (n=83)

Table 1.

Indicators	F0	F1	F2	F3	F4
n=	19	19	11	9	18
Age, years	40,9±3,1	37,1±2,5	49,8±3,6	52,7±2,3	56,9±2,6
Gender, male/female ratio	3/6	10/9	6/5	3/6	6/12
Cirrhosis of the liver				44,4±17,6	50,0±12,1
ALT, mol/l *	28,0±5,0	21,9±7,2	45,7±13,7	60,6±16,7	74,4±21,5
Total bilirubin, μmol/l	17,4±1,5	16,0±1,0	15,9±1,6	17,9±3,5	38,1±12,2
Protein, g/liter	73,1±0,9	73,4±1,6	73,3±3,3	68,4±2,9	71,3±1,6
Platelets, x 10^9 /l**	219,8±9,5	211,2±7,5	181,2±8,7	188,0±8,1	173,6±8,0
AFP, U/ml	3,3±0,7	3,0±0,8	2,4±0,4	6,1±1,1	151,1±8,1
HCV viral load, x 10^6 ME/ml	6,0±3,8	6,5±1,9	8,4±5,6	6,5±2,3	6,6±1,6

Half of the patients had an enlarged spleen. Distinctive clinical signs of a severe form of exacerbation of chronic viral hepatitis C were severe symptoms of intoxication (lethargy, repeated vomiting, anorexia), intense jaundice, hemorrhagic syndrome, the liver protruded from under the edge of the costal arch by 2-5 cm, and in some patients the spleen was enlarged.

Results and its discussion. In this paper, we present the evolution of etiotropic treatment of viral hepatitis C from the first experience with the use of interferon drugs to the results of new antiviral agents. There are three types of interferon: interferon-alpha (INF-α), interferon-beta (INF-β), interferon-gamma (INF-γ). All interferons have antiviral, immunomodulatory, antitumor and

antiproliferative effects. In addition to their common properties, interferons have a number of differences. The first positive results of the use of interferon (INF) alpha in patients with hepatitis B in the 80s served as the basis for studying the effectiveness of this drug in patients with chronic non-A, non-B hepatitis. Already the first studies showed that IFN alpha is effective in the treatment of this form of hepatitis, although the response response to therapy often turned out to be transient, and after its cessation a recurrence of infection developed. Monotherapy with IFN alpha was not very effective in the treatment of chronic hepatitis C, but the addition of the nucleoside analogue RB (active substance ribaverin) increased the rate of sustained virological response. IFN alpha therapy is accompanied by adverse reactions that can cause deterioration in quality of life and adherence to treatment. These include flu-like symptoms, fatigue and central nervous system reactions such as anxiety and depression. In large controlled trials, treatment with IFN alfa-2b and a protease inhibitor had to be discontinued more frequently due to adverse events than IFN alfa-2b monotherapy. RB causes reversible hemolytic anemia. In 9% of patients receiving IFN alfa-2b in combination with ribavirin at a dose of 1000 or 1200 mg/day for 48 weeks, the dose of the latter had to be reduced due to anemia. Over the past few years, the direction of antiviral treatment for patients with chronic HCV has changed rapidly due to an improved understanding of the biology of HCV replication and the identification of proteins that block key steps. In patients with genotype 1 (HCV-1), dual-component therapy (DT) using (PEG-IFN) and (RBV) was replaced by triple therapy (TT) based on peginterferon with first-generation protease inhibitors (PIs) -(VOS) or (TVR). Recently, these latter regimens have been replaced by (SIM) or α(SOF) regimens.

Characteristics of patients with chronic hepatitis C receiving DAA treatment (n=83)

Indicators	Meaning (M±m)
Age, years	46,3±1,5
Gender, male/female ratio	31/52
Cirrhosis of the liver,%	18,0±4,2
Genotype	
1b	81 (97,5%)
2	1 (1,2%)
3	1 (1,2%)
Fibrosis grade (F0-F5)	
F0	19 (25,0%)
F1	19 (25,0%)
F2	11 (14,5%)
F3	9 (11,8%)
F4	18 (23,7%)
ALT, mmol/l (normal 28 - 190 mmol/l	45,3±6,2
Total bilirubin, μmol/l (normal 3.4 – 17.1 μmol)	21,9±3,0
Protein, g/liter (norm 66 – 83 g/l	71,6±0,9

Platelets, x 10^9/л (norm 200 – 400 (m) 180 - 320 (g))	198,4 ±4,6
AFP, U/ml (norm < 10)	7,3±2,4
HCV viral load, x 10^6ME/ml	8,2±2,1

The latter two PEG-IFN/RBV combination regimens resulted in SVR rates ranging from 30% to 92%, while reducing treatment duration and side effects. In patients with HCV genotypes 2 and 3, PEG-IFN/RBV strategies were replaced by SOF, and RBV for patients with HCV-2 with SVR rates greater than 90%, and SOF and RBV, or SOF. and PEG-IFN/RBV for patients with HCV-3, where the addition of PEG-IFN increases SVR rates. Finally, data from small cohorts of HCV-4 patients showed that, compared with dual-drug therapy, SOF- or SIM-based triplet regimens achieved SVR rates similar to those reported for HCV-1 patients.

Recent clinical trials have shown that all oral interferon-free regimens combining different direct-acting agents achieve SVR rates that range from 90% to 100%, regardless of the severity of liver damage, the nature of previous response to dual therapy or first-generation PIs, and without significant side effects. The availability of interferon-free regimens confirmed that patients with HCV-2 are highly treatable, while the model for patients with HCV-3 was revised, compared with the “old, intractable” patients with HCV-1. In fact, with the availability of direct-acting antivirals today, patients with HCV-3 are the most difficult to treat. Results with the interferon-free regimen in patients with HCV-3 were initially quite encouraging in a small phase 2 study, indicating that the 12-week SOF/RBV regimen resulted in SVR for all patients with HCV-2 and 3. Other promising preliminary results, large phase 3 studies in treatment-naïve HCV-2 and 3 (Fission) treated patients and interferon intolerant or treatment unwilling patients (Positron) have been initiated to evaluate efficacy 12 -16-week SOF/RBV regimen. Overall, these studies surprisingly showed that a 12-week SOF/RBV regimen resulted in SVR in patients with HCV-2, regardless of previous exposure to PEG-IFN/RBV and severity of fibrosis, the latter 2 factors being significant for patients with HCV-3 . Specifically, 12-week treatment in untreated patients resulted in SVR in 61% and 34% of patients without and with cirrhosis, respectively. In addition, SVR rates in patients without cirrhosis were 37% and 63% in patients treated for 12 to 16 weeks, respectively, and 19% and 61% during 12 and 16 weeks in patients without cirrhosis, respectively. Notably, all treatment failures were due to relapse rather than virological breakthrough, confirming the high genetic barrier to resistance to SOF. Based on these results, strategies to improve SVR rates with SOF-containing regimens in patients with HCV-3 should consider the duration of previous treatment, or the addition of another anti-HCV drug (DAA or immunomodulator). Extension of treatment to a 24-week SOF/RBV regimen was evaluated in the Valence clinical trial, which resulted in an overall SVR rate of 83% [. This was particularly the result of high SVR rates in untreated patients (93% and 92% in non-cirrhotic and cirrhotic patients, respectively) and treated non-cirrhotic patients (87%), while rates were lower in patients with cirrhosis who received treatment (61%). These results identified a category of difficult-to-treat patients and suggested that SVR could be improved by adding another anti-HCV agent. This assumption was tested in 2 small studies. The Lonestar-2 trial tested TT using PEG-IFN/SOF/RBV for 12 weeks in treated patients with HCV-2 and 3 (22). SVR in patients with HCV-3 was 83%, with no difference relative to baseline cirrhosis (SVR 83% vs 83%, respectively). The second study tested the DAC/SOF combination, which resulted in an SVR of 89% in 18 untreated HCV-3 patients.

These data suggest that SOF/PEG-IFN/RBV is the most effective treatment for patients with cirrhosis who have been treated for HCV-3, and that the regimen is as effective for all other patients with HCV-3 as the 24-week course of SOF /RBV. Despite these strategies, certain unresolved problems remain, the inability to treat patients with advanced cirrhosis using an interferon regimen, and (ii) the high cost of a 24-week course of SOF. Therefore, further research on DAAs for patients with HCV-3 is necessary to substantiate the existing data in large groups of people and to test new promising DAA combinations, such as Grazoprevir/MK8742, SOF/GS5816 and others.

Генотип/режим	SOF+LED	SOF+VEL	PAR/r+OMB+DAS	PAR/r+OMB	GRZ+ELB	SOF+DAC	SOF+SIM
Генотип 1a	12 нед.	12 нед	12 нед	-	12 нед	12 нед	-
Генотип 1b	12 нед	12 нед	12 нед	-	12 нед	12 нед	-
Генотип 2	-	12 нед	-	-	-	12 нед	-
Генотип 3	-	12 нед	-	-	-	12 нед	-
Генотип 4	12 нед	12 нед	-	12 нед	12 нед	12 нед	12 нед
Генотип 5	12 нед	12 нед	-	-	-	12 нед	-

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With the introduction of interferon- and interferon-free regimens with new generation DAAs, the presence of patients with multidrug-resistant viral populations is expected. Therefore, the clinical significance of response to other antiviral strategies has not been sufficiently studied and data are limited. However, the low SVR rates observed in patients with HCV-1a replacement Q80K treated with SIM indicate the need for careful evaluation of this issue.

CONCLUSION

1. Adequate use of direct antiviral agents leads to a significant positive effect on the course of viral hepatitis and a sustained viral response in 100% of cases among patients.

2. It is recommended to treat with daas in accordance with the recommendations of the european association of liver diseases from 2016.

3. The use of daas for chronic viral hepatitis shows a high degree of effectiveness against fibrotic damage to liver tissue.

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