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Efficiency of Antiviral Therapy and Non-Invasive Diagnostics of Liver Fibrosis in Patients with Chronic Hepatitis C

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Summary: Under observation were 319 patients aged 19-55 years with HCV infection, of which 110 (34.5%) male patients and 209 (65.5%) female patients. All patients were under dispensary observation in polyclinics of the Bukhara region. The first genotype of the virus was detected in 63.9% (n=204) of patients, the second genotype in 0.5% (n=18); 21.9% (n=70) have the third genotype, 0.8% (n=27) have the fourth genotype. Before antiviral therapy in the main group of patients, 22 (20%) patients had F0 fibrosis, 30 (27%) F1, 36 (31.8%) F2, and 23 (21%) F3 patients. Fibrosis F4 stage was observed in 2 (0.2%) patients. With the use of sofosbuvir + ledipasvir, an early virological response was noted in 204 (100%) patients, of which 200 (98%) patients were confirmed to have no recurrence of HCV RNA viremia, a rapid virological response was noted in 195 (95.6%) patients. In parallel with the improvement in the results of HCV treatment with antiviral therapy, a decrease in the progression of liver fibrosis was also noted.

Keywords: HCV infection, elastometry, sofosbuvir, treatment dynamics.

Relevance. Hepatitis C virus (HCV) infection is one of the most common infectious diseases. To date, the number of people infected with hepatitis C virus (HCV) has reached more than 180 million in the world, most of them develop chronic hepatitis, less often cirrhosis (liver cirrhosis), hepatocellular carcinoma. Due to the lack of an effective vaccine, a significant decrease in the incidence of CHC is unlikely to be expected, which determines the importance of developing and improving antiviral therapy regimens [1,2,11]. Chronic viral hepatitis is a risk of developing cirrhosis of the liver (LC) and its complications, hepatocellular carcinoma (even without the formation of LC) [3-6]. Therefore, the clinician who first identifies chronic HCV infection in a patient needs to assess the patient's possible individual prognosis and indications for antiviral therapy. Currently, the standard of antiviral therapy (AVT) for chronic hepatitis C (CHC) is a combination of pegylated interferon-alpha (Peg-INF-alpha) and ribavirin, which provides 40-50% in the frequency of achieving a persistent viral response in HCV genotype 1 infection with the duration of treatment within 48 weeks and 70-90% for infection with HCV genotypes 2 and 3 and treatment for 24 weeks [10].

Standard antiviral therapy (AVT) for chronic hepatitis C is pegylated-interferon-alpha and ribavirin, and with the HCV-1 genotype, treatment within 48 weeks is 40-50% or with treatment of HCV-2 and 3 within 24 weeks reaches 70-90 % efficiency.

The formation of a stable virological response is now equated with the eradication of HCV infection, > 99% of patients have long-term resistance to aviremia, no detection of HCV RNA in liver tissues

and peripheral mononuclear cells, normalization of the amount of aminotransferase, improvement of histological data and, most importantly, a decrease in the incidence of cirrhosis liver [7-9].

A great achievement of modern AVT is the development of an algorithm for the "basics of AVT virological response" in HCV, which will be presented on the basis of an individual approach to the treatment of patients, the prognostic value of the HCV genotype and the amount of virus in the dynamics of treatment.

Purpose of the study: To identify an early and persistent virological response, as well as the development of fibrosis when using combined antiviral drugs (sofosbuvir, ledipasvir) in patients with chronic hepatitis C on an outpatient basis.

Materials and methods of research: HCV RNA-positive patients (319) aged 18-71 years, caused by HCV genotypes 1, 2, 3, who had not previously received AVT, were examined. Applicants in urban and rural family clinics in 2018-2019 110 of them are men, 209 are women, the average age is 32.5 (25-40) years. The duration of the disease is from 8 to 15 years, on average 9.5 (9-11) years. Patients with a body mass index of more than 30, alcoholic, drug-induced liver damage, as well as patients with pulmonary, cardiac, and renal insufficiency of more than 1 degree were excluded.

Patients underwent a standard examination, including the collection of complaints and anamnesis on the underlying and concomitant diseases, a medical examination with a targeted assessment of possible "liver" signs and signs of fibrosis using elastomerty (fibroscan). Biochemical examination determined indicators of cytolytic, cholestatic, mesenchymal-inflammatory syndrome and violations of the synthetic function of the liver.

The inclusion criteria for the study are serological confirmation of the presence of hepatitis C antibody by ELISA, qualitative and quantitative determination of HCV RNA by polymerase chain reaction, no changes in hematopoietic organs, the number of neutrophils in the kidneys, thyroid gland more than 3*109 g/l, platelets 100*109 g / l, hemoglobin more than 110 g / l in women, more than 120 g / l in men, normal creatinine and TSH.

Etiological verification of hepatitis was carried out by serological methods, with the detection of anti-HCV-core, unprotected proteins NS3, NS4, NS5, molecular-polymer chain reaction of the IQ5 CUCLER genotype at the time of nucleic acid amplification. This level of liver fibrosis (according to the METAVIR F0, F1, F2, F3, F4 scale) was measured using ultrasound liver elastometry. In the treatment of patients with an identified genotype, preparations containing Sofosbuvir and Ledipasvir (Sofoled, Sofas, Virpas) were prescribed. Patients show a rapid viral response within 4 weeks, and a late virological response after 12 weeks. Efficacy of antiviral therapy in the presence of an early virological response - increase in viremia by 100 times or more (> 2 log10) after 4 weeks of treatment, late viral response by 100 times or more (> 2 log10) treatment within 12 weeks no HCV-RNA immediately after the end of antiviral therapy (24 or 48 weeks, depending on the genotype of viral hepatitis C). Results of the study and their discussion. 319 patients selected for clinical studies were examined from an epidemiological point of view and the data are presented in the table. According to the information shown in the table, 110 of the patients under control were men (34.5%) and 209 (65.5%) women. The patients were divided into cities and districts according to the table as follows: By sex, the patients were distributed as follows: Analyzes show that 50 people were examined in the city of Bukhara, of which 72% were women and 28% were men, and in the Gijduvan district - 36, 69.4% and 30.6%, Bukhara region 29.62%, 38%, in Peshku region 31.51.6% and 48.4%. Low incidence rates were noted in Karaulbazar district - 7, 42.8% and 57.2%, as well as in Shafirkan district - 10, 70% and 30%. According to the results of the distribution of patients into groups with minimal, moderate and severe AF (groups 1,2,3), the duration of the disease, age, body mass index, MD, spleen area, de Rites coefficient, cholesterol, alkaline phosphatase, fibrinogen, PTI, thrombin time (Table 1).

Table 1. The most significant indicators of routine research methods in HCV infection.

Indicators	Function	
	1	**2**
Disease duration, years	0,367	0,074
Age, years	-0,030	-0,080
Body mass index, kg/m2	0,177	-0,364
MD - liver density according to AGK, units.	-0,156	0,172
Spleen area, cm2	0,066	-0,076
De Ritis coefficient	1,336	2,183
Cholesterol, mol/l	-0,333	-0,664
Alkaline phosphatase, U/l	0,003	0,011
Fibrinogen, g/l	-5,502	-5,612
PTI %	-0,072	0,029
Thrombin time, s	0,131	0,438

When analyzing the PCR data presented in the table, 1 genotype was detected in 204 patients, genotype 2 in 18, genotype 3 in 70, and genotype 27 was absent.

In the study of subtypes of genotypes, genotype 1A was detected in 15 (7.4%) cases, 1B in 185 (90.7%) and 1AB in 4 cases (1.9%) in patients with genotype 1. Of the 3, genotypes 3 in 20 (28.6%), 3B in 15 (21.4%), 3 in 22 (31.4%) subtypes were detected, and 13 (18.6%) subtypes were not detected.

Among control patients, a high viral particle (400,000 IU/ml) was observed in 9 patients (43%), a low viral particle in 12 patients (57%). Most patients in the control group had a low content of viral particles.

As a non-invasive assessment of liver fibrosis, patients underwent elastometry. According to elastometry data, in patients with chronic HCV infection there are significant differences ($p<0.05$) in elastometry parameters depending on the stage of liver fibrosis (AF), stage of chronic hepatitis (stages 1-3 according to Metavir) and LC (stage 4 according to Metavir).

Before starting antiviral therapy, 113 patients (61%) were examined in the control group: 22 patients (20%) had fibrosis of the F0 level, 30 patients (27%) had the F1 level, 36 patients (31.8%) had the F2 level, 23-(21%) have F3 level. Fibrosis F4 degree developed in 2 patients (0.2%). Early virological response in patients was assessed 4 weeks after treatment. During 4 weeks of treatment, 90 (44.1%) of the observed patients did not detect HCV RNA, and 90 (44.1%) patients experienced a 2-log decrease in viral load: 195 patients (95.6%) achieved an early virological response.

In the analysis of the late virological response (within 12 weeks from the start of treatment), complete eradication of HCV RNA was observed in 200 patients (98%), with a 2 log or greater decrease in viral load in 4 patients; A decrease in the stage of fibrosis was noted in more than half of the patients. Also, it was revealed that a long-term persistent viral response reduces the risk of developing late complications of chronic hepatitis C.

Conclusions:

1. Most of the chronic viral hepatitis reported in the region are caused by genotype 1 hepatitis C virus.
2. The effectiveness of the antiviral drug - sofosbuvir + ledipasvir, leads to the elimination of viruses, causing a persistent virological response in 98% of patients. which has a direct impact on outpatient care
3. It is important to substantiate approaches to conducting AVT in chronic viral hepatitis based on non-invasive monitoring of the dynamics of liver fibrosis in terms of elastometry. Also, non-invasive methods for diagnosing liver fibrosis in outpatient practice can be used not only for diagnosis, but also for monitoring patients.

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