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# Study Of Indirect Fibromarkers in Identifying the Degree of Liver Fibrosis During Antiviral Therapy Of Patients With Hepatitis HCV Etiology

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**Abstract:** This work examined the diagnostic role of biomarkers - APRI, alpha-fetoprotein – AFP and gammaglutamine transpeptidase – GGTP before and after antiviral therapy in patients with different degrees of liver fibrosis. At the same time, there was a decrease in these indicators after treatment, which indicates a reverse development of liver fibrosis after specific therapy. During therapy, a significant decrease in APRI from 0.67 to 0.33 ($p<0.05$), AFP from 4.82 to 1.77 ($p<0.01$) and GGTP from 42.4 to 26.8 was established ($p<0.05$). Thus, APRI, AFP and GGTP indicators can be used as dynamic markers for assessing the antifibrotic effect of etiotropic therapy for hepatitis C.

**Key words:** hepatitis C virus, fibrosis, APRI, AFP, GGTP, antiviral therapy, PCR, regression, viral load.

**Introduction.** Today it is known that antiviral treatment of hepatitis C leads to the reverse development of liver fibrosis and hepatocellular carcinoma, which leads to a reduction in the patient's risk of death from complications of liver cirrhosis by 74% [1, 8, 11]. Unfortunately, in a number of countries, due to late diagnosis of hepatitis C, the number of patients with cirrhosis and liver cancer is increasing [4, 5, 12, 13]. Studying the antifibrotic effectiveness of antiviral therapy with DAAs for chronic viral hepatitis C in patients during treatment and subsequently after therapy is one of the main objectives of the hepatitis C virus elimination program in Uzbekistan.

New opportunities for science are opening up the introduction into practice of the combination of antiviral drugs Sofosbuvir 400mg + Daclatasvir 60mg [6, 9]. Currently, clinical trials have shown the high effectiveness of the combination Sofosbuvir 400 mg + Daclatasvir 60 mg in patients with genotypes 1-4 of the hepatitis C virus in people with liver cirrhosis and after liver transplantation [2, 7, 10]. Sofosbuvir is an antiviral drug, a pangenotypic inhibitor of the RNA-dependent RNA polymerase NS5B of HCV.

With the help of NS5B polymerase, GS-461203 can integrate into the HCV RNA chain and terminate the chains. Daclatasvir, an antiviral drug against HCV, is an inhibitor of the NS5A protein encoded by HCV. It binds to NS5A and inhibits virion assembly. Daclatasvir is used as part of complex therapy for hepatitis C in combination with the drug Sofosbuvir [3].

In order to clarify the possibility of using fibromarkers to assess the dynamics of liver fibrosis after treatment for hepatitis C, initially and after completion of the course of therapy, liver elasticity, rate of fibrosis progression, indirect fibrosis marker - APRI, regeneration index - AFP, cytolysis markers - alanine aminotransferase (ALT) and aspartate aminotransferase (AST), parameters cholestasis – alkaline phosphatase, gammaglutamyl transpeptidase. We observed 23 patients with hepatitis C receiving antiviral therapy.

At the time of prescription of therapy, the estimated duration of HCV infection according to anamnesis ranged from 4 to 15 years, which averaged 7.35±2.66 years.

In the examined patients, concomitant pathologies were identified to varying degrees (Table 1).

Table 1
General characteristics of the examined patients

| Indicators | Patients with hepatitis C (n=23) | % |
|---|---|---|

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| | | |
|---|---|---|
| Diabetes mellitus | 3 | 13,0 |
| Gallstone disease | 1 | 4,30 |
| Chronic cholecystitis | 4 | 17,4 |
| Chronic pyelonephritis | 3 | 13,0 |
| Chronic gastritis | 6 | 26,0 |
| Chronic pancreatitis | 5 | 21,7 |
| Anemia | 4 | 17,3 |
| Arthritis | 2 | 8,69 |
| Arterial hypertension | 3 | 13,0 |

As can be seen from Table 1, the most common diseases in the examined patients with chronic hepatitis C were chronic gastritis (26.0%), chronic pancreatitis (21.7%), chronic cholecystitis and anemia (17.3% and 17.3% respectively). The incidence of diabetes mellitus, chronic pyelonephritis and arterial hypertension was 13.0% each. During the examination, clinical manifestations of dyspeptic and asthenovegetative syndromes were identified in all patients. 56.5% of patients had pain in the right hypochondrium and pain in the joints and muscles. 13.0% of patients had complaints of weight loss. In 73.9% of patients, hepatomegaly and jaundice of the sclera were detected, in 26.0 cases splenomegaly was noted.

An ultrasound examination of the liver of the examined patients revealed a change in the liver in 43.4% of patients - diffuse compaction of the liver parenchyma with varying degrees of density, and 13.0% of patients had uneven contours and heterogeneity of the structure of the liver with portal hypertension. Patients received Sofosbuvir 400 mg + Daclatasvir 60 mg orally, 1 tablet once a day, 1-2 hours after meals. The duration of therapy for chronic hepatitis C and with compensated liver cirrhosis of HCV etiology of Child-Pugh class A, regardless of the genotype of the virus - 1a, 1b, 2 and 3a, was 12 weeks (with the exception of patients with compensated liver cirrhosis with HCV genotype 3). Monitoring the effectiveness of antiviral therapy with direct-acting drugs for chronic viral hepatitis C was carried out using a molecular genetic research method - polymerase chain reaction (PCR) (less than 10 IU/ml). The data obtained - the average viral load of the hepatitis C virus (HCV) and the elastometry values of the liver tissue using the Fibroscan device (France) in the examined patients are presented in Table 2.

Table 2
Viral load of hepatitis C virus and liver elastography indices in patients

| Indicators | Patients with hepatitis C (n=23) |
|---|---|
| HCV viral load, copies/ml | |
| $\leq 2{,}0 \times 10^6$ | 34,7% |
| $>2{,}0 \times 10^6$ | 56,5% |
| Initial data on liver fibrosis according to the METAVIR scale, (%) | |
| $F_0$ (without fibrosis) | 17,4% |
| $F_1$ (1-degree fibrosis) | 26,0% |
| $F_2$ (2-degree fibrosis) | 17,3% |
| $F_3$ (3-degree fibrosis) | 10,9% |
| $F_4$ (4-degree fibrosis) | 8,69% |

The viral load of the virus in the blood was 3.44±1.12×106 copies/ml. A high viral load (VL) of HCV was observed in more than half of the patients (13 people - 56.5%). An increase in the activity of transaminases - ALT and AST was observed before therapy in 52.1% of patients, the average ALT was 39.8 ± 5.93 U/L, AST - 36.2 ± 4.76 U/L.It must be said that before therapy, men had higher ALT levels compared to women ($p < 0.05$), which indicates the severity of hepatocyte cytolysis.

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Half of the examined patients had moderate liver fibrosis (F1-F2) before treatment. In patients before treatment, according to elastometry, the liver density was 8.84±3.62 kPa. At the same time, before the start of therapy, men had higher liver density values compared to women: 11.0±2.45 kPa and 7.89±1.81 kPa, respectively ($p < 0.05$).

During therapy, rapid recovery of liver function was noted. During treatment, signs of hepatomegaly decreased. The average platelet count in the blood of patients after antiviral therapy averaged 229.5 cells/μL (this indicator before antiviral therapy averaged 149.7 cells/μL).

In 52.1% of patients there was a decrease in the severity of liver fibrosis. After the end of antiviral therapy, positive dynamics were obtained in the regression of liver fibrosis according to elastometry data ($p < 0.05$) (Fig. 1).

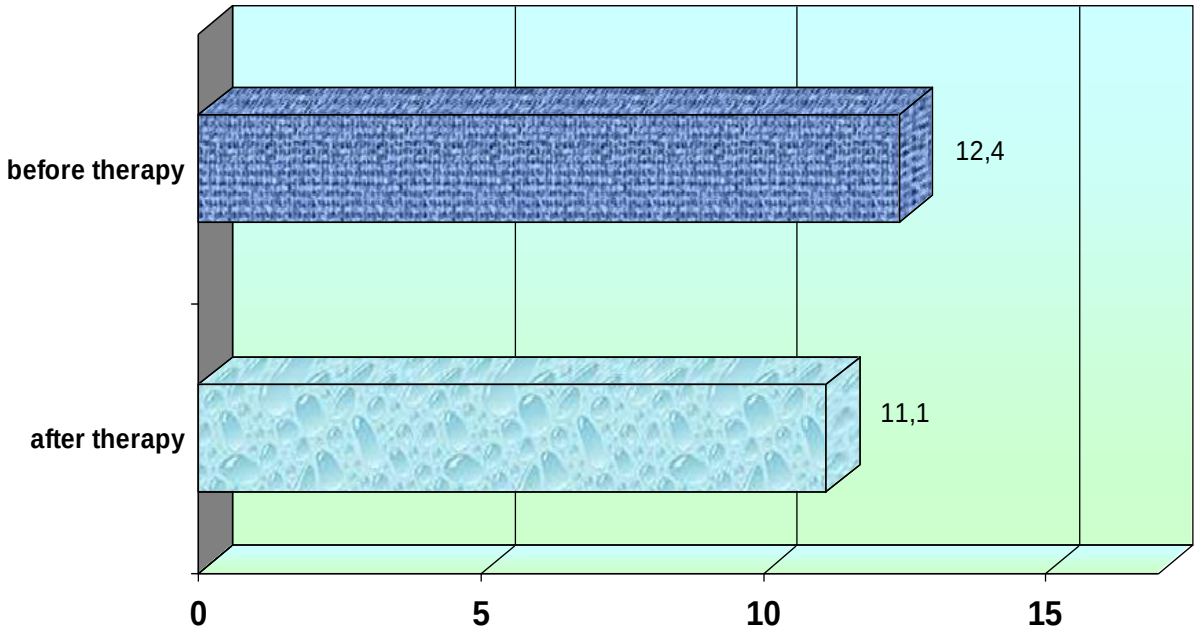


Figure 1. Dynamics of liver density during antiviral therapy in patients with hepatitis C

When studying the dynamics of the fibromarker APRI during antiviral therapy, a significant decrease in its level was found on average by 2 times: before treatment – 0.67±0.09, after – 0.33±0.11 ($p < 0.05$) (Fig. 2), which coincides with the stages of liver fibrosis according to elastometry data.

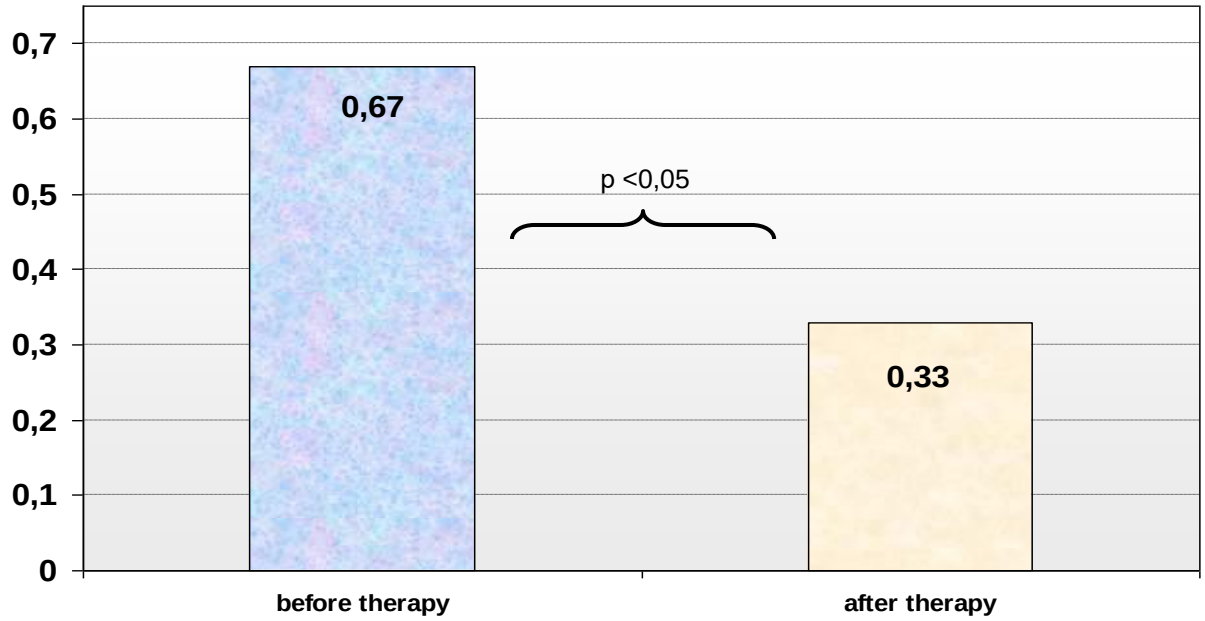


Figure 2. Dynamics of the APRI index during antiviral therapy in patients with hepatitis C

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Before the start of etiotropic antiviral therapy, there were no differences in APRI values between men and women (p > 0.05). After the course of therapy, the level of the APRI index in men decreased by 2.4 times (p <0.05), and in women by 2 times (p <0.05) (Fig. 3).

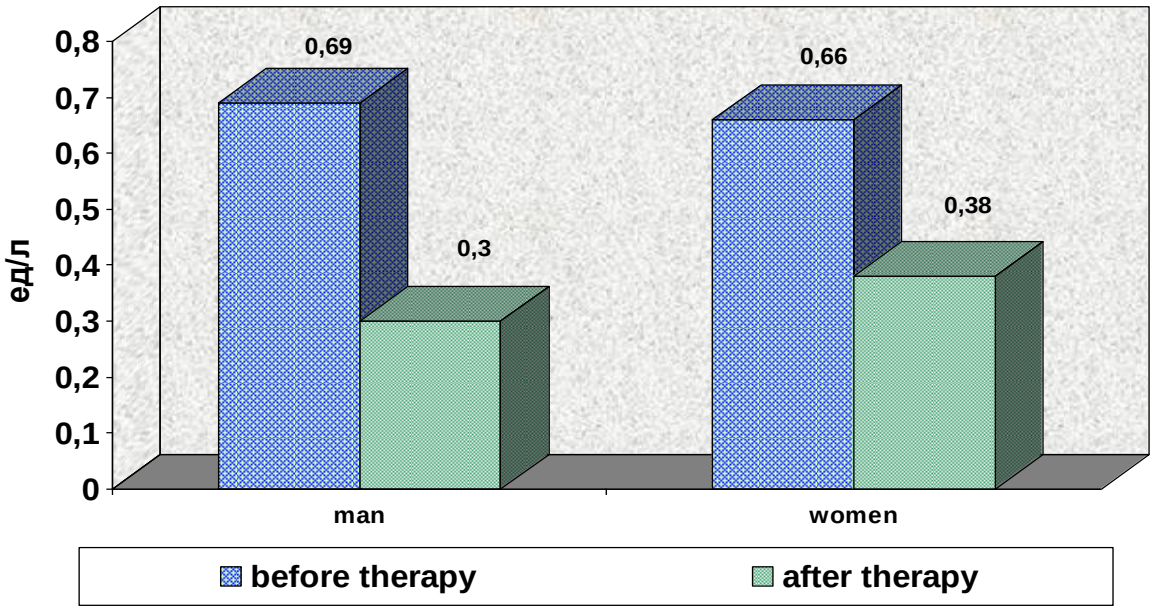


Figure 32. Dynamics of the APRI index in patients with hepatitis C depending on the gender of patients

In laboratory analysis of markers of liver regeneration - alpha-fetoprotein (AFP) and cholestasis (stagnation of bile), regenerative activity of liver tissue at the end of antiviral therapy in the examined patients with chronic viral hepatitis C, a significant decrease in the APRI index (P <0,05) and alpha-fetoprotein (AFP) index was noted (p <0, 05) and gammaglutamine transpeptidase (GGTP), at P <0,05.

At the same time, the albumin content in the peripheral blood of patients increased significantly (p <0.05) (Table 3).

Table 3

Laboratory parameters in examined patients with chronic viral hepatitis C before and after antiviral therapy with direct-acting drugs

| Indicator | before antiviral therapy | after antiviral therapy | P |
|---|---|---|---|
| APRI | 0,67±0,09 | 0,33±0,11 | <0,05 |
| AFP, IU/ml | 4,82±1,09 | 1,77±0,39 | <0,01 |
| GGTP, units/l | 42,4±11,6 | 26,8±8,02 | <0,05 |
| Albumin, g/l | 32,0±6,87 | 41,8±7,63 | <0,05 |

The results of this study indicate a significant decrease in the severity of cholestasis syndrome, the activity of inflammation and regeneration during the normalization of the mechanisms of antioxidant function of the liver, which is accompanied by a decrease in the severity of liver fibrosis and the rate of its development.

A comprehensive analysis of the antifibrotic effectiveness of etiotropic therapy for chronic viral hepatitis C with direct-acting drugs is presented in Table 4.

Table 4

Antifibrotic efficacy of antiviral therapy for chronic hepatitis C

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| Indicator | | Efficiency (n=23) |
|---|---|---|
| Antifibrotic effect, % | | 52,1% |
| Liver density, кПа | before treatment | 12,4±3,03 |
| | after treatment | 11,1±2,08 |
| | P | >0,05 |
| Fibrosis progression rate, points/year, M±σ | before treatment | 0,26±0,09 |
| | after treatment | 0,12±0,04 |
| | P | <0,05 |

Thus, monitoring indicators of the rate of progression of liver fibrosis will allow assessing the progression of liver fibrosis, and fibromarkers APRI, alpha-fetoprotein – AFP and GGTP can be used as dynamic criteria for assessing the antifibrotic effect of etiotropic therapy for hepatitis C. Positive dynamics of the indirect marker of liver fibrosis APRI and a decrease in the rate of progression of liver fibrosis during antiviral therapy indicate a reverse development of the fibrogenesis process, which coincided with elastometry data. Along with a decrease in fibrosis, indicators of cholestasis and cytolysis improved with the normalization of other liver functions.

**Literature:**

1. Afdhal N., Everson G. T., Calleja J. L. et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. J. Viral. Hepat, 2017. - № 24(10). – C. 823-831.
2. Antonini T. M., Coilly A., Rossignol E. et al. ANRS C023 CUPILT study group. Sofosbuvir-based regimens in HIV/HCV coinfected patients after liver transplantation: results from the ANRS CO23 CUPILT study. Transplantation, 2018. – N 102(1). - P. 119-126.
3. Foster G. R., Pianko S., Brown A. et al. BOSON Study Group. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology, 2015. – N 149(6). – P. 1462-1470.
4. Ganesan M. K. Matrix stiffness regulate apoptopic cell death in HIV-HCV co-infected hepatocytes: Importance for liver fibrosis progression. Biochem Biophys Res Commun, 2018. – N 500. – P. 717-722.
5. Hezode C. Effectiveness of Telaprevir or Boceprevir in Treatment-Experienced Patients with HCV Genotype 1 Infection and Cirrhosis / Gastroenterology, 2014. - V. 147. - № 1. - P. 132-142.
6. Konerman M. A., Mehta S. H., Sutcliffe C. G. et al. Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfected adults: prospective analysis of liver biopsy pairs. Hepatology, 2014. - V.59. - N3. - P. 767-775.
7. Lafeuillade A. Eliminating the HIV reservoir. Curr HIV/AIDS Rep., 2012. Jun. – N. 9 (2). – P. 121-131.
8. Lo Re V., Kallan M. J., Tate J. P. et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study // Ann Intern Med., 2014. Mar 18. - Vol. 160 (6). - P. 369-379. doi: 10.7326/M13-1829.
9. Poordad F., Schiff E. R., Vierling J. M. et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology, 2016. – N 63(5). – P. 1493-1505.
10. Roger Ch., Ngoc W. Blood Tests to Diagnose Fibrosis or Cirrhosis in Patients With Chronic Hepatitis C Virus Infection. Ann Intern Med, 2013. - Vol. 158. – N 11. – P. 807-820.
11. Sulkowski M. S. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients coinfected with HIV-1: a randomized trial. JAMA, 2015. - Vol. 313 (12). - P 223-1231.
12. Terilli R. R., Cox A. L. Immunity and hepatitis C: a review. Curr. HIV/AIDS Rep., 2013. - Vol. 10. - N 1. – P. 51-58.

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13. Wolffran I. Prevalence of elevated ALT values, HBsAg, and anti-HCV in the primary care setting and evaluation of guideline defined hepatitis risk scenarios / J. of Hepatology, 2015. - № 62. – P. 1256-1264.