Mariam Mgeladze
Master of Public Health, PhD, Assistant Professor,
European University, Tbilisi, Georgia

LONG-TERM OUTCOME OF PATIENTS WITH ADVANCED LIVER FIBROSIS TREATED IN THE HEPATITIS C ELIMINATION PROGRAM

Abstract

The hepatitis C elimination program has enabled thousands of HCV-infected people to receive treatment. The main objective of our study was to evaluate the effect of long-term treatment in patients with advanced liver fibrosis who achieved a sustained viral response (SVR) after receiving direct antiviral medication (DAA) and to evaluate the role of socio-demographic characteristics and clinical/laboratory data in changing the level of liver fibrosis. The study cohort included patients from a hepatitis C elimination program treated with direct-acting antivirals (DAAs), high-grade elastography-defined liver fibrosis (> = F3), and patients with a FIB4 score greater than 3.25 and a sustained viral response achieved 12-24 weeks after treatment. A total of 150 patients were selected. The data was processed in SPSS statistical software. Among the statistical tests, the Wilcoxon Signed Ranks test was used. The research was conducted in 2020-2021. These data were determined both before and after treatment. After treatment with metavir, the level of liver damage improved in 51.7% of patients. Statistical analysis showed that the change in the level of fibrosis after treatment was statistically significant (P < 0.001).

Introduction

An estimated 130-150 million people worldwide are living with hepatitis C virus (HCV), and more than 700,000 people die each year from HCV-related liver disease. [1] Of these, 80% of infected people live in low- and middle-income countries. Hepatitis C virus (HCV) has a leading role in the development of liver-related diseases. [2] Hepatitis C (HCV) is an infectious disease caused by the hepatitis C virus. Hepatitis C is a disease caused by an RNA (ribonucleic acid) virus that damages the liver and is diagnosed in both acute and chronic forms and causes serious health problems. Unfortunately, the problem of hepatitis C is exacerbated by the fact that until now, preventive measures such as vaccination or specific immunoglobulin have not been developed. The situation in the country in the 1990s, of course, had an impact on the healthcare system as well. In particular, the poor quality of health care services led to the breakdown of infection control and safe blood donation systems in medical institutions. Also, the practice of sharing needles, syringes and other injecting equipment among injecting drug users has increased, further increasing the spread of infection. In 2015, a population study of seroprevalence conducted by the National Public Health Center for Disease Control of Georgia, the US Centers for Disease Control and Prevention (CDC) showed that the prevalence in the country is high and amounts to 7.7%, and the active form of hepatitis C is 5.4% of the population [3]. Taking into account the results of the mentioned study, in April 2015, the basis was laid for the Hepatitis C Elimination Program, [4] which aimed to reduce the prevalence to 0.5% by 2020 using both preventive and curative strategies.

The main objective of our study was to evaluate the effect of long-term treatment in patients with advanced liver fibrosis who achieved a sustained viral response (SVR) after direct antiviral medication (DAA). We evaluated the role of socio-demographic characteristics and clinical/laboratory data in changing the level of liver fibrosis.

Research methods

The presented research was carried out at the base of the clinic "Neolab" included in the program of elimination of hepatitis C. The study cohort included patients who were treated with direct antiviral drugs as part of an elimination program, had a high threshold (>=F3) or FIB4 score greater than 3.25 on liver elastography, and achieved stable viral respond within 12-24 weeks after treatment. Based on the principle of randomness, study cases were selected retrospectively from the clinic lists. The main criterion for inclusion in the study is to perform a full course of direct antiviral treatment (DAA), to achieve a sustained viral response (SVR) within 12-24 weeks after the end of treatment. A total of 150 patients should be examined in the study. Study participants were recruited into the group after signing an informed consent form specifically designed for the study. The cohort study pooled data from medical records. Baseline data were determined before treatment and included HCV genotyping, viral load, liver function tests, complete blood count, and abdominal ultrasound. Pre-treatment history, including refusal of previous treatment programs and injection drug use, was also reviewed from medical records.

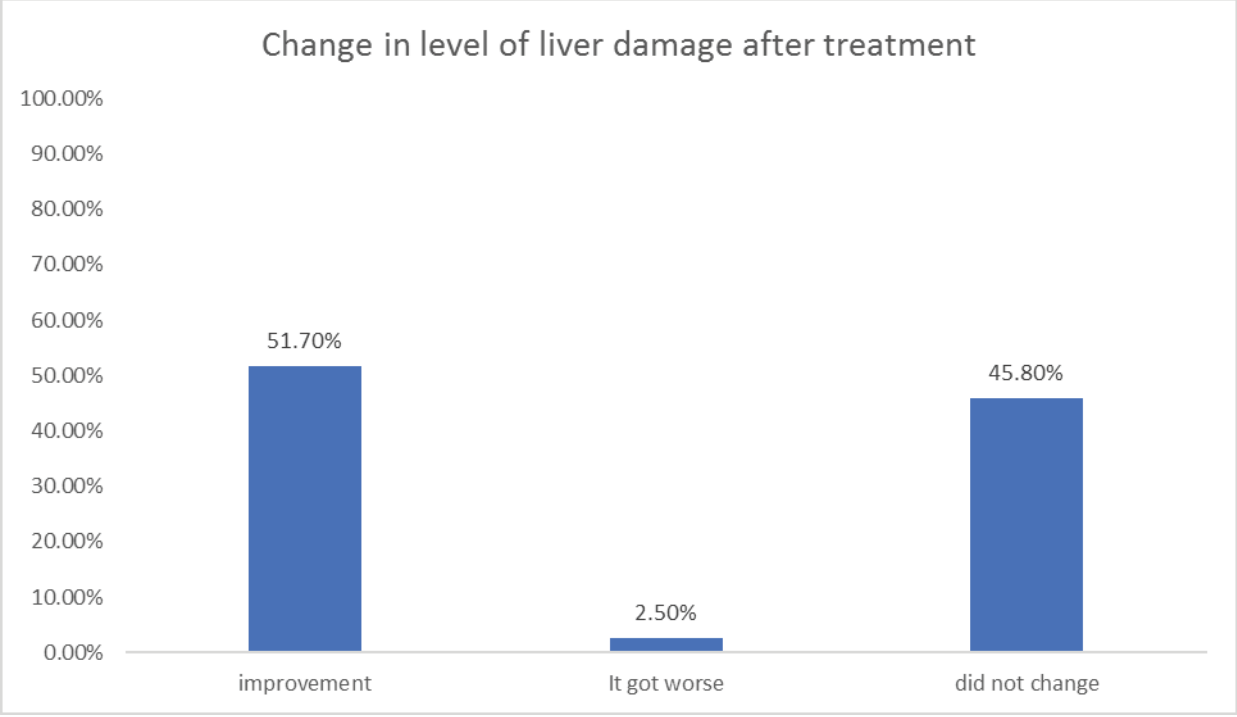
Levels of liver fibrosis according to the FIB4 scale were determined in all patients prior to inclusion in the elimination program. The FIB4 score is based on ALT, AST, and absolute platelet counts. It can be interpreted as follows: low (<1.45), medium (1.45-3.25) and high (>3.25). In patients whose FIB4 level is within the average range, liver elastography is additionally performed. Liver elastography was used to assess METAVIR liver fibrosis stage F0–F1: 2.5–6.9 kPa; F2: 7.0–9.4 kPa; F3: 9.5–12.4 kPa; F4: ≥12.5 kPa.

Post-study anthropometric, laboratory, and clinical parameters were prospectively collected. Blood serum (10 ml) was collected from study participants for laboratory testing. The mentioned study started work in the same clinic where patients are treated within the elimination program.

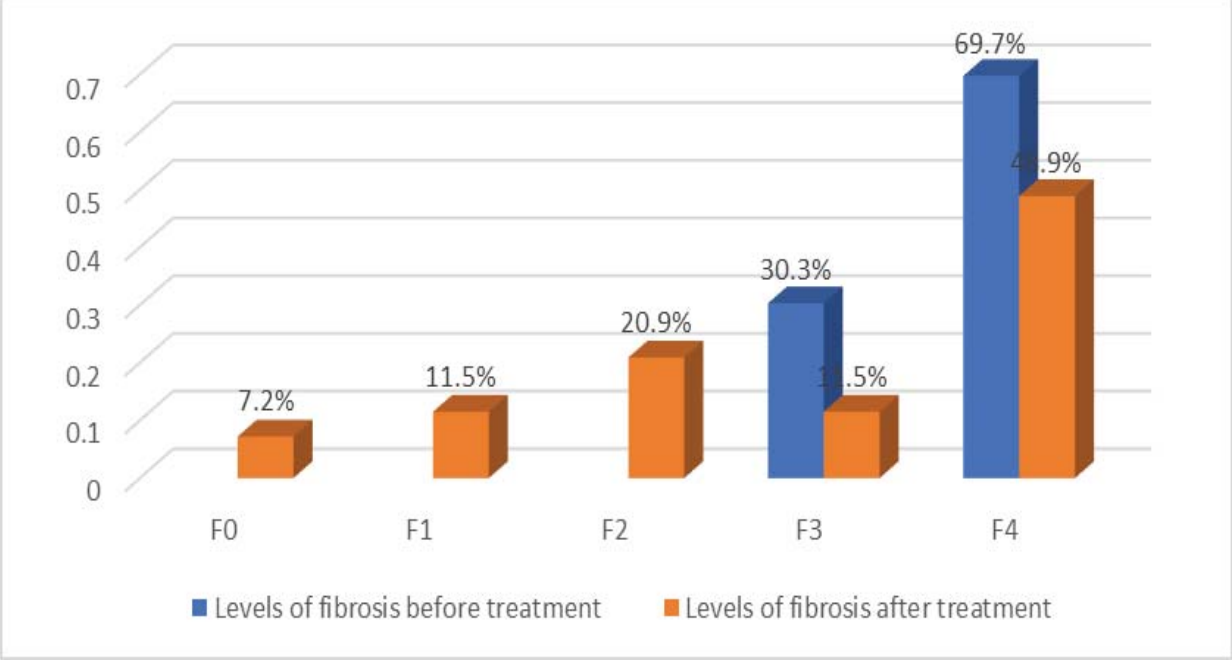
Standard statistical software (e.g. SPSS) is used for statistical analysis and data management. Baseline and follow-up values (at least two years after treatment), liver fibrosis levels (via elastography and FIB4), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count (PLT), spleen size, and ascites were assessed among study participants. Basic descriptive statistics were performed for all variables, and bivariate analysis was used to assess the association between factors such as baseline liver disease severity, behavioral characteristics, and the effect of changes in laboratory data on the level of liver fibrosis.

Results

A total of 150 patients were studied who were assigned a high threshold (>=F3) or FIB4 score greater than 3.25 by elastography measurement and achieved a sustained viral response 12-24 weeks after treatment. The average age of the patients included in the study was 48.8 years. Most of them, 88.7%, were men. According to nationality, the majority of patients included in the study group, 143 (95.3%) were Georgians. Respondents were asked questions related to harmful habits, namely tobacco, injection drug and alcohol use. In particular, whether they have been users, or if they have been users in the past. As a result of the research, it was found that every tenth patient (10.7%) had used injectable drugs at the time of treatment initiation, 42% (63 patients) had used them in the past, and 47.3% (71 patients) had never used them. Before treatment, 72% (108) were smokers, and after treatment, their number decreased to 52%. According to the results of liver elastography, 30.3% (36) and 69.7% (83) had F3 level damage, and 51.7% of the patients had improved liver damage after treatment. The change was statistically significant (P< 0.001).



Fibrosis levels as measured by FIB4 were also reduced after treatment. The average of this indicator before and after treatment decreased by 2.03 units.



Within the research, the changes in laboratory research indicators are as follows.

Characteristic	Unit	Baseline (mean)	Follow-up (mean)	Mean difference	95% CI	p-value
Liver stiffness	kPa	22.64	15.43	7,21	5,36-8,33	< .0001
FIB-4 score		5,26	3,23	2,03	2,00-3,37	< .0001
ALT	U/mL	110	29.2	80.8	63,57-87.14	< .0001
AST	U/mL	98.62	33.53	65.09	53.34-71,31	< .0001
PLTS	10^9/L	166.40	195.60	29.2	17,13-41,13	< .005
Hb	g/dL	15.06	14.94	0.12	0,90-2,10	0.31
Spleen length	mm	125,08	123,85	1,22	1,50-3,96	0.36
Spleen width	mm	49,46	49,38	0,08	1,34-1,68	0,992

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at the beginning of treatment were 110 U/mL and 98.62 U/mL, and after treatment decreased to 29.2 U/mL and 33.53 U/mL (p< .0001). The average value of hemoglobin before treatment was 15.06, and after treatment was 14.94 (p< 0.31). The mean absolute platelet count (PLTS) before treatment was 166.4 and after treatment was 195.6 (p< .005). The mean spleen size (the length of the spleen times its width) decreased slightly, but there was no significant change in spleen size as a result of the treatment. (p =0.36, p =0.992, p =0.341).

Information on patients' weight was collected before and after treatment. The mean weight for the whole group was 90.2 kg before treatment and 87.32 kg after treatment. The observed change in patients' weight after treatment is statistically significant (P<0.001).

Analysis of changes in body mass index before and after treatment showed an increase in the proportion of patients whose weight is within the normal range. After treatment, the body mass index (BMI) level of 22.67% of patients decreased.

Also, interestingly, the study identified factors such as tobacco, alcohol, injecting drug use or obesity as risk factors for fibrosis. It was found that none of them, overweight (OR = 1.816 (95% CI 0.751-4.390; Mantel-Haensze Chi2-test = 1.233; p = 0.267), alcohol (OR = 0.628 (95% CI 0.267-1.4777; Mantel-Haensze Chi2) -test = 0.725; p = 0.395), injection drugs (OR = 1.160 (95% CI 0.562 - 2.396; Mantel-Haensze Chi2-test = 0.046; p = 0.830), high alt level (OR = 1.1) CI 0.326 - 3.944 ; Mantel-Haensze Chi2-test = .014; p = 0.906), high level of AST (OR = 0.204 (95% CI 0.023 - 1.800; Mantel-Haensze Chi2-test = 1.303; 5 = 1.303). There are no risk factors for reducing the level of fibrosis as a result of treatment. Therefore, the reduction of the level of fibrosis does not depend neither on the patient's weight, nor on tobacco consumption, nor on the high level of ALT or AST, etc.

Conclusion

The hepatitis C elimination program has enabled the treatment and follow-up of HCV-infected patients with advanced fibrosis until a durable viral response is achieved. Our study aimed to evaluate

modifications in liver stiffness, measured by liver elastography or FIB-4 score, with clinical and laboratory parameters as indicators of liver disease severity and portal hypertension. As a result of the observation, it can be said that we achieve a solid viral response after the use of direct antiviral drugs in HCV patients with high liver fibrosis rates, leading to a significant improvement in the level of liver fibrosis 12-24 weeks after the end of the treatment course. There are various studies reporting regression of liver fibrosis and improvement of portal hypertension. [4] [5] Along with the improvement in liver fibrosis, our study also revealed normalization of liver function tests, increase in platelet count, normalization of ALT, AST, reduction of splenomegaly after achieving solid viral response. Similar results have been obtained by other studies as well. [6] The major conclusion of the study is that achieving SVR after direct antiviral treatment among HCV patients with advanced liver fibrosis leads to a significant improvement in the level of liver fibrosis 2 years after the end of the treatment course.

References:

1. World Health Organization. Hepatitis C. Key Facts 9 July 2019. Available at: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-c
2. Graham CS, Swan T. A path to eradication of hepatitis C in low- and middle-income countries. Antiviral Res. 2015 Jul; 119:89-96. doi: 10.1016/j.antiviral.2015.01.004. Epub 2015 Jan 20.
3. Gvinjilia L, Nasrullah M, Sergeenko D, Tsertsvadze T, Kamkamidze G, Butsashvili M, et al. National Progress Toward Hepatitis C Elimination—Georgia, 2015–2016. MMWR Morb Mortal Wkly Rep. 2016;65: 1132–1135.
4. Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, De Ledinghen V, Larrey D, Haour G, Bronowicki JP, Zoulim F, Asselah T, Marcellin P, Thabut D, Leroy V, Tran A, Habersetzer F, Samuel D, Guyader D, Chazouilleres O, Mathurin P, Metivier S, Alric L, Riachi G, Gournay J, Abergel A, Cales P, Ganne N, Loustaud-Ratti V, D'Alteroche L, Causse X, Geist C, Minello A, Rosa I, Gelu-Simeon M, Portal I, Raffi F, Bourliere M, Pol S; French ANRS CO22 Hepather cohort. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet. 2019 Apr 6;393(10179):1453-1464. doi: 10.1016/S0140-6736(18)32111-1. Epub 2019 Feb 11.
5. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2011 Nov;9(11):923-30. doi: 10.1016/j.cgh. 2011.05.028. Epub 2011 Jun 13.
6. Giannini EG, Crespi M, Demarzo M, Bodini G, Furnari M, Marabotto E, Torre F, Zentilin P, Savarino V. Improvement in hepatitis C virus patients with advanced, compensated liver disease after sustained virological response to direct acting antivirals. Eur J Clin Invest. 2019 Mar; 49(3):e13056. doi: 10.1111/eci.13056. Epub 2018 Dec 19.