

Gavryliuk Nadiia, Hospodarskyi Ihor, Prokopchuk Oksana, Krekhovska-Lepiavko Olha, Lokay Borys, Havrylyuk Mykhailo. Comparative effectiveness of anti-fibrosis treatment in patients after HCV infection and in patients with non-alcoholic fatty liver disease (NAFLD). *Journal of Education, Health and Sport*. 2021;11(2):222-229. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2021.11.02.022> <https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.02.022> <https://zenodo.org/record/5038644>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8.2) and § 12.1.2) 22.02.2019.

© The Authors 2021;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland  
Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 11.01.2021. Revised: 10.02.2021. Accepted: 26.02.2021.

## **Comparative effectiveness of anti-fibrosis treatment in patients after HCV infection and in patients with non-alcoholic fatty liver disease (NAFLD)**

**Nadiia Gavryliuk<sup>1</sup>, Ihor Hospodarskyi<sup>1</sup>, Oksana Prokopchuk<sup>1</sup>,  
Olha Krekhovska-Lepiavko<sup>1</sup>, Borys Lokay<sup>1</sup>, Mykhailo Havrylyuk<sup>2</sup>**

**<sup>1</sup>I.Ya.Horbachevskiy Ternopil National Medical University, Department of clinical immunology, allergology and general patients' care, Ternopil, Ukraine**

**<sup>2</sup>I.Ya. Horbachevskiy Ternopil National Medical University, Department of Internal Medicine No.1, Ternopil, Ukraine**

### **Abstract**

Due to the high prevalence of NAFLD and CHC, these two pathologies will progress and contribute to the progression of fibrosis. Unfortunately, nowadays there is no single treatment strategy for such patients. That is why, in most cases a variety of treatment regimens on the base of different hepatoprotectors are prescribed. Instead, there is evidence that the use of some hepatoprotectors has no influence on fibrotic processes in the liver or can even exacerbate them. In order to study the antifibrotic effect of hepatoprotectors in patients with posthepatic fibrosis after HCV infection and in patients with NAFLD, we studied the results of prescribing the hepatoprotective drug bicyclol.

**Keywords: posthepatic fibrosis; NAFLD; overweight; elastography; index NFS; bicyclol.**

**Topicality.** Up to 3% of the human population suffers from CHC in the world [1], the number of patients with NAFLD, overweight and obesity is constantly increasing, which is an

important medical and social problem [2, 3]. Due to the high prevalence of NAFLD and CHC, these two pathologies will progress and contribute to the progression of fibrosis, and depending on the genome of the virus and metabolic syndrome, even after achieving a stable virological response, there is a high risk of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) [4].

There is evidence in the literature that the hepatitis C virus as a comorbid factor in NAFLD may interfere with triglyceride (TG) metabolism and secretion of very low density lipoproteins (VLDL), leading to increased fatty changes in hepatocytes and even the development of atherosclerosis [5]. Increasing the load of free fatty acids and TG oxidation leads to fatty degeneration of the liver and due to the oxidation of by-products there is the appearance and progression of fibrosis [6]. On the background of an increase in the number of people with diabetes, coronary heart disease, MS in the coming decades, there is a possibility of higher incidence of NAFLD with more serious complications [7, 8]. If the situation does not change, then according to British hepatologists-transplantologists from London's King's College Hospital in the next 20-30 years, obesity will cause LC, which will require a liver transplant [9].

Unfortunately, nowadays there is no single treatment strategy for such patients. One of the common options is waiting tactics. However, this approach does not provide any positive clinical and laboratory effect, at the same time it has significant disadvantages, especially in the presence of comorbidities and other disorders, such as - diabetes, metabolic syndrome, obesity, thyroid pathology, etc. [10-12].

That is why, in most cases a variety of treatment regimens on the base of different hepatoprotectors are prescribed. Some of them (bioflavonoid drugs) have a proven effect on cytolysis, others - also a pronounced effect on fibrotic processes and cytokine balance (amino acids, ursodeoxycholic acid). Instead, there is evidence that the use of some hepatoprotectors has no influence on fibrotic processes in the liver or can even exacerbate them [9-15].

A number of previous studies have shown the antifibrotic effect of bicyclol, in particular in the treatment of chronic hepatitis C. However, similar studies have not been performed in patients with NAFLD, and the mechanisms of antifibrotic action of this medicine remain unclear. In order to study the antifibrotic effect of hepatoprotectors in patients with posthepatic fibrosis after HCV infection and in patients with NAFLD, we studied the results of prescribing the hepatoprotective drug bicyclol.

## Materials and methods

Forty-five patients with post-hepatitis fibrosis after HCV infection and completion of antiviral treatment as well as patients with NAFLD with F2-F3 liver fibrosis and concomitant overweight and grade I obesity were selected. All patients were recommended to use a comprehensive non-drug therapy (CST), which included the correction of nutrition and increased physical activity in order to stabilize the metabolism in the body and stimulate weight loss. Patients were divided into two groups. Group I included 26 patients who, in addition to CST in order to study the possibilities of antifibrotic therapy, were prescribed the hepatoprotective drug bicyclol at a dose of 25 mg 3 g / d for 3 months. 19 patients from group II received only CST.

All patients had their energy needs calculated based on gender, age, height, body weight, and physical activity. Waist circumference (WC), hip circumference (HC) and WC/HC index were also determined. Then it was calculated and subtracted 15% of kcal from daily calories. According to the recommendations of nutritionists, such a deficit is safe and provides a reduction in body weight by about 800 - 1200 g during the week.

Basic dietary recommendations:

1. reduction of the daily number of calories to obtain an energy deficit (the average diet of patients had 1200-1800 kcal/day);
2. a low-carb diet (limited consumption of sugar, honey, berries and fruits with medium and high glycemic index, sweets, juices, jams);
3. exclusion of smoked meats, hot dogs, sausages, semi-finished products, mayonnaise sauce and other sauces, margarine;
4. restriction of high-fat foods and fatty meats;
5. recommended Mediterranean diet;
6. number of meals - 4 (3 main meals and 1 snack) at the same time with intervals between meals of not less than 2.5 hours and not more than 4 hours;
7. method of cooking: steam cooking, stewing, baking;
8. adhere to an adequate drinking regime: 1.5-2.0 l / d;

Physical activity included:

- daily walks for 30 minutes with an intensity at which the heart rate was 60-70% of maximum heart rate;
- aerobic exercise of medium intensity  $\geq 150$  minutes per week (divided into 3 or more sessions);
- intensive training more than 2 times a week;

- restriction of daytime sleep and reduction of periods of inactivity.

Patients were monitored for 12 weeks, visiting every 14 days to adjust the daily calorie intake, get answers to questions and motivation. After treatment, a set of clinical, laboratory and instrumental examinations was repeated for comparative analysis of the effectiveness of the therapy.

Prior to treatment, multifactor regression analysis was performed for patients with different trophological status and the most significant predictors of the predicted risk of liver fibrosis and steatosis were selected.

### Study outcomes

The analysis showed that in both groups, regardless of the choice of drug therapy, there was a tendency to decrease body weight ( $p < 0.01$ ). In group I, BMI decreased in 65.38% of subjects, and in group II - 94.74%. The number of patients with abdominal obesity also decreased significantly in the study groups ( $p < 0.01$ ). Spearman's correlation analysis found a significant association between BMI and WC, indicating an increase in abdominal obesity with increasing BMI ( $p < 0.01$ ,  $r = 0.43$ ). Average levels of it are presented in Table 1.

Table 1. Average levels of anthropometric indicators in I and II groups

Indices	Group I		Group II	
	Before treatment	After treatment	Before treatment	After treatment
WC	97,19±2,37	88,37±2,29	108,21±1,84	95,65±2,14
	p<0,01*		p<0,01*	
HC	111,19±1,80	103,58±2,23	112,16±1,90	106,6±1,97
	p<0,01*		p<0,01*	
WC/HC	0,91±0,04	0,87±0,03	0,97±0,02	0,89±0,01
	p<0,01*		p<0,01*	
Body weight, kg	88,46±2,77	83,19±2,67	96,16±2,32	90,32±2,03
	p<0,01*		p<0,01*	
BMI	30,92±0,68	28,95±0,69	32,75±0,34	31,16±0,57
	p<0,01*		p<0,01*	

Note. The significance of the difference in groups I and II by Wilcoxon test -  $p < 0.05$ .

Following the recommendations of the CNT and treatment with bicyclol in patients of group I, the indexes of WC, IWH, and BMI were significantly lower (respectively  $p < 0,045$ ;  $p < 0,024$ ;  $p < 0,038$ ;  $p < 0,049$  by Mann-Whitney test) compared to patients of group II, which received only CNT.

In order to determine fibrosis at this stage of the study, non-invasive methods were used. NFS indices were calculated, and pSWE-elastography was performed in all patients who received treatment for 3 months.

The results of studies of the NFS index in the examined patients of the two groups before and after treatment in Table 2.

Table 2. Mean NFS index values in groups I and II before and after treatment.

Index	Group I		Group II	
	Before treatment	After treatment	Before treatment	After treatment
NFS	-1,09±0,08	-1,65±0,05	-0,61±0,01	-1,26±0,12
	p<0,01*		p<0,01#	
Note. The significance of the difference was calculated by the paired Student's T-test: * – p<0,05; the significance of the difference was calculated by Wilcoxon test: # – p<0,05				

After treatment, it was observed a tendency to decrease the NFS index in both groups, but a statistically significant difference was obtained while taking bicyclol (p<0.042).

Spearman's correlation analysis found a direct moderate correlation between NFS with BMI and WC (p<0.05, r = 0.37), which confirms the high risk of steatosis and liver fibrosis in overweight patients, especially in patients with abdominal obesity.

The results of elastography studies in the examined patients of two groups before and after treatment in Table 3.

Table 3. The average values of elastography in groups I and II before and after treatment.

Index	Group I		Group II	
	Before treatment	After treatment	Before treatment	After treatment
Elastographic density of the liver, m / s	1,49±0,03	1,29±0,01	1,46±0,01	1,34±0,02
	p<0,01#		p<0,01#	
Note. The significance of the difference was calculated by Wilcoxon test: # – p<0,05				

A direct strong link between elastography and NFS (p<0.05, r = 0.60) has been established, which allows us to assert the feasibility of using a combination of these methods to verify the presence and stage of liver fibrosis.

In two groups there was a tendency to the reduction of the shear wave, but in the group receiving additional drug therapy, the liver density was significantly lower ( $p < 0,041$ ). In 69% of treated patients there was a significant decrease in the stage of liver fibrosis by one degree ( $p < 0,05$ ).

According to the results of prognostic analysis, we identified the main predictors of progression of hepatic steatosis (BMI, blood glucose, HDL cholesterol, TG) and liver fibrosis (BMI, age, platelet count, total bilirubin, ACT activity) in NAFLD and posthepatic fibrosis on the background of overweight and obesity. On the basis of those results the logistic regression models were built for their prediction with high sensitivity and specificity: for the model for predicting the risk of fibrosis (97.8% and 91.3%, respectively) and for the model of hepatic steatosis (respectively 96.8% and 89.3%).

### **Conclusions**

1. It was established a direct moderate correlation between liver fibrosis according to NFS with BMI and WC ( $p < 0.05$ ,  $r = 0.37$ ), which confirms the high risk of steatosis and liver fibrosis in overweight patients, especially in patients with abdominal type of obesity.

2. The use of comprehensive non-drug treatment, which included the prescription of lifestyle modifications, weight loss, and dietary adjustments, led to significant improvement in clinical and anthropometric data and the decrease in liver density ( $p < 0.01$ ).

3. The administration of bicyclol in combination with CST for at least 12 weeks in overweight and obese patients leads to the significant reduction of liver density with a regression of fibrosis by one degree ( $p < 0.05$ ).

4. The main predictors of progression of hepatic steatosis (BMI, blood glucose, HDL cholesterol, TG) and liver fibrosis (BMI, age, platelet count, total bilirubin, ACT activity) in NAFLD and posthepatic fibrosis of the liver on the background of overweight and obesity were figured out.

### **References**

1. World Health Organization (WHO). Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. –2018.

2. Williams, C.D. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study / C.D. Williams [et al.] // *Gastroenterology*. – 2011. – № 140. – P. 124–131.

3. Havrylyuk N.M., Hospodars'kyy I.Ya., Prokopchuk O.V., Havrylyuk M.Ye. Otsinka vplyvu nayavnosti u patsiyentiv nadlyshkovoyi masy tila na fibroz pechinky // Zdobutky klinichnoyi i eksperymental'noyi medytsyny. – 2020. – # 4. – S.50-60.
4. Adinolfi, L.E. NAFLD and NASH in HCV Infection: Prevalence and Significance in Hepatic and Extrahepatic Manifestations / L.E. Adinolfi [et al.] // International Journal of Molecular Sciences. – 2016. – № 6 (17). – P. 803.
5. Amarapurka D.N. Non-alcoholic steatohepatitis (NASH) with diabetes: predictors of liver fibrosis / D.N. Amarapurka, A.D. Amarapurkar, N.D. Patel, Agal, R. Baigal, P. Gupte, S. Pramanik // Ann Hepatol. – 2006. – Vol.5. – P.30-33.
6. Patel, A. Hepatitis C virus infection and nonalcoholic steatohepatitis / A. Patel, S.A. Harrison // Gastroenterology & Hepatology. – 2012. – № 5 (8). – P. 305–312.28
7. Buyeverova E.L. Narusheniya lipidnogo obmena u bol'nykh s metabolicheskimi sindromom / E.L. Buyeverova, O.M. Drapkina, V.T.Ivashkin // Ros. meditsin. vesti. – 2014. – T.19, № 2. – S. 23-32.
8. Khullar V. Pre-and-post transplant considerations in patients with non-alcoholic fatty liver disease / V. Khullar, A. Dolganiuc, R.J. Firpi // World J Transplant. – 2014. – Vol.4 (2). – P.81-92
9. Charlton M.R. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States / M.R. Charlton, J.M. Burns, R. A. Pedersen, K.D. Watt, J.K. Heimbach, R.A. Dierkhising // Gastroenterology. – 2011. – Vol. 141. – P.1249-1253.
10. Faustini A., Colais P., Fabrizi E. et al. Hepatic and extra-hepatic sequelae, and prevalence of viral hepatitis C infection estimated from routine data in at-risk groups // BMC Infect. Dis. – 2010. – Vol. 10. – P. 97.
11. Gospodarskiy I.Ya., Volynets' K.V., Grushko V.V. Osobennosti lecheniya bol'nykh gepatitom V i S pri soputstvuyushchey krioglobulinemii // Eksperymental'naya i klinicheskaya farmakologiya. – 2013. - № 12. – S. 34-37.
12. Ivanov A.V., Bartosch B., Smirnova O.A. HCV and Oxidative Stress in the Liver // Viruses. – 2013. – Vol. 5 (2). – P. 439–469.
13. Hawke R.L., Schrieber S.J., Soule T.A. Silymarin Ascending Multiple Oral Dosing Phase I Study in Noncirrhotic Patients With Chronic Hepatitis C // J. Clin. Pharmacol. – 2010. – Vol. 50 (4): - P. 434–449.

14. Reddy K.R., Belle S.H. Rationale, challenges, and participants in a Phase II trial of a botanical product for chronic hepatitis C // *Clin. Trials.* – 2012. – Vol. 9 (1). – P. 102–112.
15. Kolesnikova E. V. Sovremennyy patsiyent s zabolevaniyem pecheni i patologiyey serdechno-sosudistoy sistemy: kakoy vybor sdelat'? // *Suchasna gastroenterologiya.* - 2014. - № 2 (76) – S. 85-94.
16. Paris A.J., Snapir Z., Christopherson C.D.A Polymorphism that Delays Fibrosis in Hepatitis C Promotes Alternative Splicing of *AZIN1*, Reducing Fibrogenesis // *Hepatology.* – 2011. – Vol. 54(6). – P. 2198–2207.
17. Pharmacological therapy of non-alcoholic steatohepatitis / Ratzin et al. // *Clin.Liver Dis.* - 2009. – Vol. 13 (4). - P. 667-688.
18. Duong FH, Christen V, Filipowicz M, Heim MH. S-Adenosylmethionine and betaine correct hepatitis C virus induced inhibition of interferon signaling in vitro // *Hepatology.* – 2006. - Vol. 43 (4). – P. 796-806.
19. Lioznov D.A., Geyvandova N.I., Morozov V.G. Otsenka effektivnosti original'nogo gepatoprotektornogo preparata Bitsiklol u bol'nykh khronicheskim virusnym gepatitom S // *Ukrains'kiy medichniy chasopis.* – 2014. - № 6 (104). – S. 14-17.