



# Clinical experience of using mineral water and vitafonotherapy in the complex treatment of patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease

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## Abstract

Chronic viral hepatitis C (CHC) remains a significant medical and social problem worldwide and is a leader in the structure of etiological factors in the development of diffuse liver diseases (NAFLD). The presence of NAFLD in patients with chronic hepatitis C accelerates the progression rate of HCV infection and reduces the effectiveness and tolerability of antiviral therapy. The above circumstances initiated us to the search for new non-drug technologies for the treatment of this category of patients. The purpose of these work is evaluate the effectiveness of the integrated use of standard antiviral therapy, the drinking of low-mineralized silicon sodium bicarbonate mineral water (MW), and vibroacoustic therapy (VT) in patients with chronic hepatitis C with concomitant NAFLD. Research methods: anamnestic and clinical, general clinical, biochemical, serological (markers of viral hepatitis C, HCV RNA PCR (qualitative and quantitative determination, genotyping), quantitative determination of total endogenous  $\alpha$ -interferon in the blood serum, ultrasonographic studies of the digestive system, statistical methods. Fifty patients with chronic hepatitis C (genotype 1b in the phase of replication, minimal and moderate activity) with concomitant NAFLD were examined. Patients were divided into two groups. Patients of the I (control) group (25 people) received the basic treatment complex, which included dietary nutrition (diet No. 5), standard antiviral therapy (AVT) (interferon alfa-2 b and ribavirin) for 12 months and internal intake of MW for the first month of treatment. Patients of group II (25 people), in addition to the basic complex of treatment, additionally received VT procedures, the course of which was six months. Evaluation of the effectiveness of treatment was carried out after 1, 3, 6, and 12 months from the start of treatment. The treatment in both groups was accompanied by the positive dynamics of most of the signs of the disease; however, a significant advantage of using VT was found. In patients of group II, the side effects of AVT - influenza-like and cytopenic syndromes - disappeared, interferonogenesis was stimulated, which made it possible to complete the AVT course in 92.00% of patients and obtain a virological response in 56.00% of patients. In other cases, reduce the virological load by no less than 2 log.

**Key words:** *chronic viral hepatitis C, non-alcoholic fatty liver disease, mineral water, vibroacoustic therapy,*

## Introduction

One of the urgent problems of modern hepatology remains the treatment of patients with chronic viral hepatitis C (CHC), which is associated with an increase in the incidence and development of complications - cirrhosis of the liver and hepatocellular carcinoma (1, 2). Non-alcoholic fatty liver disease (NAFLD) is also one of the most common diffuse liver diseases in the world, which is associated with the global epidemic of obesity 3, 4, 5). Due to the significant prevalence of CHC and NAFLD, according to various experts, it is expected that these two nosological forms will be determined together in a substantial number of patients. The average frequency of identifying NAFLD associated with chronic hepatitis C is about 55%, depending on the genotype of the virus and metabolic syndrome (6). The interaction between chronic hepatitis C and hepatic steatosis is essential when conducting

antiviral therapy (AVT), predicting the rate of progression of the fibrotic process, and assessing the risk of hepatocellular carcinoma (7, 8).

Our scientific research began in 2011 when the “gold standard” for the treatment of patients with chronic hepatitis C was the use of linear or pegylated interferons in combination with ribavirin. The effectiveness of such treatment, that is, the achievement of a stable virologic response (SVR), ranged from 40 to 60%. Meanwhile, such therapy had a large number of contraindications and several significant drawbacks, namely, the development of severe side effects. The lack of effectiveness and high cost of treatment forced some patients to prematurely terminate the AVT or to not agree to such treatment at all (9, 10, 11). The above circumstances initiated us to the search and development of new non-drug technologies for

treating patients with chronic hepatitis C with concomitant NAFLD to increase the effectiveness of therapy and improve the quality of life of patients.

The purpose of the work is to evaluate the effectiveness of the integrated use of standard AVT, drinking low-mineralized silicon sodium bicarbonate MW, and VT in patients with chronic hepatitis C with concomitant NAFLD.

**Materials and methods.** We examined 50 patients with chronic hepatitis C (genotype 1b in the replication phase, with a minimum and medium degree of activity) with concomitant NAFLD, who were monitored in the clinic for rehabilitation treatment of patients with a gastroenterological profile of the State Institution "Ukrainian Research Institute of MR and KM of Ukraine".

The study used methods such as anamnestic and clinical, surveyed general clinical, biochemical blood parameters, serological markers of viral hepatitis C, HCV PCR RNA (qualitative and quantitative determination, genotyping), quantitative determination of total endogenous  $\alpha$ -interferon in blood serum, ultrasonographic studies digestive organs, statistical methods.

Two groups of patients with chronic hepatitis C were formed with concomitant NAFLD. Patients of the 1st (control) group (25 people) were prescribed a basic treatment complex, which included dietary nutrition - diet No. 5, which corresponds to the Mediterranean diet (12), standard AVT (interferon alfa-2 b and ribavirin) for 12 months and internal administration mineral water (MW) during the first month of treatment. A prerequisite for our choice regarding the use of MW in the complex treatment of patients with chronic hepatitis C with concomitant NAFLD was the availability of data on the atherogenic, insulinotropic, lipid-lowering, cardioprotective properties of MV with a sufficient content of hydrocarbons, sodium and trace elements (13, 14, 15). The data on the mechanism of the influence of trace elements on NAFLD are presented, and the basis for their therapeutic appointment in a patient with NAFLD is established (16, 17).

We used packaged silicon low-mineralized bicarbonate sodium water of well No. 242, the village of Shayan, Khust district of the Transcarpathian region (Ukraine). The total mineralization of MW was 1.86 g/l. The main anions in the chemical composition of MW were  $\text{HCO}_3^-$  (1.187 g/l),  $\text{Cl}^-$  (0.095 g/l), and among the cations,  $\text{Na}^+$  and  $\text{K}^+$  ions (0.447 g/l). Other cations and

anions -  $\text{SO}_4^{2-}$  (0.059 g/l),  $\text{Ca}^{2+}$  (0.064 g/l) and  $\text{Mg}^{2+}$  (0.008 g/l) had insignificant concentrations. In MW, there are biologically active components and compounds that are standardized in balneology according to the legislation of Ukraine (18), and add specific properties to waters. Such components are  $\text{H}_2\text{SiO}_3$  (metasilicic acid) - 69.42 mg/l (silicones are considered MW with an  $\text{H}_2\text{SiO}_3$  content of 50 mg/l and  $\text{H}_3\text{BO}_3$  (Orthoboric acid) - 15.83 mg/l (boric ones are MW with an  $\text{H}_3\text{BO}_3$  content from 35 mg/l). Patients of 2 groups (25 people), in addition to the basic complex of treatment, were additionally prescribed the procedures of vibroacoustic therapy (VT), the course of which was six months. The procedures were performed using the apparatus "Vitaфон IR". The primary mechanism of action of vibroacoustic therapy is the ability of micro-vibration waves to reduce the hydrodynamic resistance of blood vessels. Due to this, the osmotic movement of the fluid is enhanced, and the rheological properties of the blood are improved, which leads to an intraorganic increase in capillary blood flow and lymph flow in a radius of 7-10 cm from the center of the vibraphone.

Strengthening the capillary and lymph flow in the affected organs and tissues is considered a necessary and essential direction of therapy for chronic inflammatory diseases, including chronic hepatitis C. It aims to achieve resorption of inflammatory edema and tissue revascularization, as well as improving the delivery of drugs to the site of inflammation. Also, the effect of this effect on interferonogenesis is not excluded due to the increased yield of immunocompetent cells in interstitium and an increase in the frequency of their contacts between themselves and liver cells (19).

Evaluation of the effectiveness of treatment was performed after 1, 3, 6, and 12 months from the start of therapy. The age of patients ranged from 18 to 59 years, and the average age was  $(43.15 \pm 11.32)$  years. The sex ratio was approximately the same: 27 women ( $54.00 \pm 7.05\%$ ) and 23 men ( $46.00 \pm 7.05\%$ ).

Statistical processing of the obtained data was carried out using the programs for biomedical research, Microsoft Excel 2010 and Statistica 6.0 (StatSoft, 2006). The average values are given in the form  $(M \pm m)$ , where M is the average value of the indicator, m is the standard error of the mean. Significant changes were considered to be those that were within the confidence limits according to Student's tables  $<0.05$ .

## Results and discussion.

Among the concomitant diseases of the digestive system, 50 patients examined more often had chronic pancreatitis - 36 (72.00 ± 6.35)% of cases, chronic non-calculous cholecystitis in 29 patients, chronic gastritis (atrophic and non-atrophic) was detected in 9 patients. When interviewing patients before treatment, most often ((94.00 ± 3.36)% of cases) some complaints characterize the asthenic syndrome. Manifestations of dyspeptic syndrome disturbed (74.00 ± 6.20)% of the respondents. Pain abdominal syndrome occurred in (68.00 ± 6.59)% of cases. Analysis of the leading indicators of the hemogram showed that almost a third of patients have signs of anemia and leukocytopenia (respectively (26.00 ± 6.20)% and (28.00 ± 6.35)%), a reduced platelet count was observed in 25% of the examined. In (16.00 ± 5.18)% of patients, an increase in ESR level was determined. In biochemical studies, cytotoxic syndrome was most often observed: an increase in transaminases to 2-3 N ((64.00 ± 6.79)% of patients; cholestasis syndrome was recorded less frequently - in (34.00 ± 6.69)% of patients. Thymol clouding was observed in ((38.00 ± 6.86)% of patients. Signs of dyslipidemia were observed in all patients and were characterized by an increase in total cholesterol (TCH) on average to (6.85 ± 0.17) mmol / l, lipoproteins low-density (LDL) (4.09 ± 0.21) mmol / L, a decrease in the level of high-density lipoproteins (1.49 ± 0.13) mol / L. The atherogenic coefficient was (4.55 ± 0.22) units. The plasma glucose level was (6.49 ± 0.33) mmol / L; the insulin concentration was slightly elevated and averaged (18.59 ± 0.86) μU / ml. In comparison the HOMA index was (5.27 ± 0.42) units, which indicated a pronounced insulin resistance (IR) in the examined patients.

Ultrasound examination of the abdominal organs revealed an increase in liver echogenicity and diffuse changes of varying severity in 86.00% of patients, which was accompanied by hepatomegaly in (68.00 ± 6.59)% of people. Sonographic signs of steatosis of the liver (distal attenuation of the echo signal, blurred vascular pattern, diffuse increase in the "brightness" of the hepatic parenchyma) were identified in all examined patients. Ultrasonographic signs of gallbladder pathology were noted in half (58.00 ± 6.98) % of patients, pancreas - in (52.00 ± 7.07)% of cases. Splenomegaly was detected in (12.00 ± 4.59) % of patients.

Assessment of interferon status demonstrated a significant decrease in the level of endogenous α-IFN in the absolute number of cases, with the average value being (1.57 ± 0.24) pg/ml, with reference values from 5 to 50 pg/ml. The treatment in both groups was accompanied by the positive dynamics of most of the signs of the disease; however, a detailed analysis revealed significant advantages in patients of group 2 with the use of VT. In patients of the 2nd group, after one month from the start of therapy, the manifestations of asthenic (p <0.05) and pain (p <0.05) syndromes significantly decreased, which was not observed in patients of the 1st group of the control, where only the trend was established (p > 0,05) to the dynamics of similar indicators. Positive dynamics of the syndrome of gastric and intestinal dyspepsia were observed in both groups. They were accompanied by normalization) of an acid-forming function of the stomach in most patients (p <0.001). Side effects typical of AVT, such as the flu-like syndrome, myalgia, joint pain in group I patients, were present in almost all patients and were leveled only after 3-5 injections of interferon. In patients of the 2nd group, flu-like syndrome was not observed in any case (p <0.05), myalgia, and joint pain in the vast majority of patients ((80.00 ± 8.16)%) were weakly expressed. Signs of a cytopenic syndrome in the form of leuko- and thrombocytopenia during treatment were recorded in (40.00 ± 10.00)% and (36.00 ± 9.79)% of patients in the control group, respectively. The course use of vibroacoustic therapy in persons of group 2 prevented the development of cytopenia; a decrease in the number of leukocytes and platelets was observed only in (12.00 ± 6.63)% of patients. A decrease in the severity of the syndrome of cytotoxic and cholestasis one month after the start of treatment in both groups did not occur. In patients of both groups during the entire course of treatment, there was a decrease in the concentration of total cholesterol and LDL (p <0.05). At the same time the values of other indicators of the lipid profile did not change. Analysis of the state of carbohydrate metabolism during all months of treatment showed a decrease in insulin resistance, including due to hyperinsulinemia. A tendency to a reduction of serum glucose (p > 0.05), a significant decrease in insulin concentration (p <0.05), primarily due to hyperinsulinemia, which decreased by 1.6 times, was established. Due to this, a decrease in the HOMA-IR index (p <0.05) was observed, although

reference values could not be achieved. During the first month of treatment in patients of groups 1 and 2, a significant ( $p < 0.05$ ) improvement in the ultrasound picture of the biliary system was determined, namely, a tendency to restore the size of the gallbladder and a decrease in cystic sediment. Sonographic characteristics of liver tissue have not changed.

The study of the level of endogenous  $\alpha$ -IFN showed the normalization of the process of interferonogenesis in both groups, and there were no significant differences between the groups. In group 1, the average level of endogenous interferon was  $20.41 \pm 2.87$  pg/ml, and in group II -  $25.00 \pm 3.93$  pg/ml ( $p > 0.2$ ). A quick virological response (1 month after the start of therapy) occurred equally often - in 32.00% for patients of groups I and II.

After three months, the positive effects of the clinical course of the disease and the functional state of the digestive system persisted in patients of both observation groups. However, in the 1st control group only after three months, it was possible to achieve a statistically significant positive dynamics of asthenic and pain syndromes. Three months after the start of treatment, an increase in the cytopenic syndrome was determined in group 1 (leuko- and thrombocytopenia were recorded in  $(64.00 \pm 9.79)\%$  of patients). In contrast, the use of BT in patients of group 2 made it possible to maintain the stability of hemogram indices, only in  $(8.00 \pm 5.53)\%$  of cases did the decrease in the number of leukocytes ( $p < 0.003$ ) occur. During the same treatment period, a statistically significant improvement in liver function tests was observed in both groups, although in group 1, it was slower for some indicators.

Improvement of ultrasonographic characteristics of the digestive system was more pronounced in group 2, where, along with the restoration of echogenicity and normalization of liver size, improved penetration of the echo signal into its deeper layers, the appearance of a homogeneous content in the gall bladder was observed in most patients ( $(80.00 \pm 8.16)\%$ ). In all patients during the study, the pancreas had standard sizes, even and precise contours. Homogeneous structures were observed in most cases ( $(32.00 \pm 9.52)\%$ ), although echogenicity of the gland in  $(20.00 \pm 8.16)\%$  of patients remained elevated.

An early virological response (after three months from the start of treatment) was recorded in 8.00% and 20.00% of cases in patients of groups 1 and 2, respectively, which indicates the use of

vibroacoustic therapy in standard antiviral treatment. A study of the state of interferonogenesis after three months of treatment showed further stimulation of endogenous  $\alpha$ -IFN in patients of group 2. This effect is an adequate response to persistent viremia and proves the pathogenetic effect of the proposed method. In patients of group 1, a similar effect was not observed (table. 1). Control observation after six months of treatment indicated the preservation of the positive effects of the clinical course of the disease in the 2nd group of patients ( $p < 0.001$ ). The stability of hemogram indicators, the functional state of the liver and its sonographic characteristics, and the restoration of the state of the system of endogenous  $\alpha$ -IFN were observed. In contrast, patients of group 1 retained signs of a cytopenic syndrome, the biochemical response was slower, and there was no adequate response of the endogenous  $\alpha$ -IFN system to persistent viremia. The achievement of a slow virological response after six months from the start of treatment was determined by 12.00% and 4.00% for groups 1 and 2 of patients, respectively. It should be noted that at the same time, there was a restoration of the functional state of the digestive system in patients with concomitant gastroduodenal and pancreatobiliary pathology, expressed more in patients of the 2nd group.

Further treatment in patients of group 1 during the 6th-12th months led to the development of some side complications characteristic of AVT, which forced to cancel therapy in  $(20.00 \pm 7.94)\%$  of people. A third of patients in this group who continued to receive standard antiviral treatment experienced biochemical disturbances in the functional state of the liver (an increase in ALT and AsAT levels, an increase in the concentration of total bilirubin). The average level of  $\alpha$ -IFN did not significantly differ from the previous indicator and amounted to  $(42.36 \pm 3.89)$  pg/ml. A virological study continued to record a negative HCV PCR RNA in 52.00% of people. The remaining patients ( $(28.00 \pm 8.92)\%$ ) experienced a decrease in viral load, while in 3 patients, a reduction of 1 log was observed, and in 4 patients, a decrease of 2 logs. In patients of 2 groups after six months of treatment in 2 people ( $8.00 \pm 5.33$ ), increased cytopenic syndrome, which did not allow continued AVT. But all other patients in this group ( $(92.00 \pm 5.33)\%$  of people) completed antiviral treatment after 48 weeks. Moreover, over the next six months, a stable biochemical response was observed in patients of this group. Assessment of interferon status after 12



months showed further stimulation of the level of endogenous  $\alpha$ -IFN ( $p < 0.02$ ). This situation may explain the results of the analysis of virological load in patients in whom HCV PCR RNA continued to be determined ( $36.00 \pm 9.55\%$ ). All patients had a decrease in HCV RNA level by at least 2 logs. Virological response after 12 months continued to be recorded in 56.00% of patients in this group. Thus, the use in the complex treatment of patients with chronic viral hepatitis C with concomitant non-alcoholic fatty liver disease, mineral waters, and vibrotherapy causes the development of a stable biochemical response, eliminates the side effects of AVT as flu-like and cytopenic syndromes, and stimulates interferonogenesis.

### Conclusions.

1. The use of silicon low-mineralized sodium bicarbonate MW and vibroacoustic therapy in complex treatment helps to significantly reduce the clinical signs of the disease ( $p < 0.001$ ), eliminate the cytolysis syndrome and cholestasis ( $p < 0.001$ ), which occurred against the background of the restoration of ultrasonographic parameters of the pancreatobiliary system.

2. It is proved that vibroacoustic therapy eliminates the manifestations of the flu-like syndrome and eliminates the signs of cytopenia (leukocyte and thrombocytopenia), which allowed to complete the course of antiviral therapy in 92.00% of patients of group 2.

3. The ability of vibroacoustic therapy to stimulate endogenous interferonogenesis has been proven, which made it possible to obtain a virological response in 56% of patients in this study and to reduce the virological load in other patients by at least 2 logs.

### Prospects for further research.

After the elimination of the hepatitis C virus, there remains a high risk of further progression of liver fibrosis, which is associated with the preservation of NAFLD in the majority of examined patients. This circumstance stimulates us to continue our scientific research and develop new methods of internal use of mineral water and the use of other physiotherapeutic methods.

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