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# Use of antiviral therapy in patients with chronic hepatitis C

**Abstract:** Introduction: The presence of background HCV infection cannot be overestimated in view of the prevalence of chronic hepatitis C and the risk of adverse outcomes of this disease. Purpose of this study was to evaluate the effectiveness of the combined use of antiviral therapy (Roferon + Vero-Ribavirin) and resort factors in patients with chronic hepatitis C in the phase of replication.
Material and methods: We observed 48 patients with chronic hepatitis C; the minimum level of activity of the process defined the phase of replication. Markers of HCV infection were determined by enzyme linked immunosorbent assay (ELISA) (a-HCV and HCV-Ig M). HCV RNA was determined twice by the polymerase chain reaction (PCR). Genotyping of hepatitis C virus was performed. Biochemical blood analysis and the study of HCV infection markers were carried out four times. Results of therapy were assessed immediately after the end of the resort (spa) treatment, then at 3, 6 and 12 months after starting treatment. At 12 months after starting treatment, all the observed patients had persistent clinical and biochemical remission. Elimination of the virus from the blood was noted in 56% of the control group and 74% of patients in the study group.
Conclusions: For patients with moderately active HCV, the replication phase was characterized by asthenic-vegetative syndrome (100% of patients) with severe depression (22.92%), pain (77.08%) and dyspeptic syndrome (33.33%), moderate hypertransferaseemia (100%), slightly pronounced cholestasis (33% of patients), and signs of mesenchymal-inflammatory response.

**Keywords:** Antiviral therapy, health resort factors, chronic hepatitis C

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## 1 Introduction

The presence of background hepatitis C virus (HCV) infection cannot be overestimated in view of the prevalence of chronic hepatitis C (CHC) and the risk of adverse outcomes of this disease.

Experts predict that in 10-20 years HCV infection will be an immense medical, social and economic problem [1-8]. At present, 0.5-2% of the population has been diagnosed with CHC. The frequency of newly diagnosed cases of HCV infection in developed countries ranges from 1 to 5 cases per 100 000 population (true frequency exceeds these indicators by 5-8 times). For the Commonwealth of Independent States (CIS), the incidence of newly diagnosed cases of HCV infection is 60-80 per 100 000 people [6]. Even worse statistics exist for Ukraine. In recent years, the prevalence of HCV in Ukraine amounted to 612 people per 100 000 [5, 6].

According to several studies [1, 7, 9], in approximately 80% of patients with acute hepatitis C, the disease becomes chronic. Cirrhosis develops in 10-20% of HCV patients and is detected usually 10-20 years after infection. The cirrhosis may involve complications such as jaundice, ascites, bleeding from esophageal varices, and

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encephalopathy, indicating the transition to the phase of disease decompensation.

End-stage HCV is a major indication for liver transplantation. Unfortunately, for most patients with CHC in Ukraine, this operation is not available. Pathogenic treatment of CHC is based on antiviral therapy, aimed at the elimination of the virus, slowing the progression of the disease, and reducing the risk of hepatocellular carcinoma.

Currently, standard treatment for CHC is a combination of a-interferon (a-IFN) plus ribavirin for 24-48 weeks. At the same time, sustained virological response is achieved in 40-45% of cases and is accompanied by favorable dynamics of the histological parameters [7, 8, 12, 16]. The use of pegylated interferon alpha in patients with HCV genotype 1b HCV increases the effectiveness of combination antiviral therapy (70-75% systemic vascular resistance (SVR) rate) [2, 8, 11-15, 17, 18].

Serious deficiencies in today's regimens include the high cost of modern drugs used for treatment of HCV, longer duration of treatment and the high frequency of adverse reactions during treatment with antiviral drugs (flu-like symptoms with fever, myalgia, depression, psychosis, decrease in white blood cells, thrombocytopenia, anemia, and autoimmune reactions). Thus, these data suggest the need to develop effective and affordable methods of pathogenic therapy for the volume of cases of HCV. Currently, treatment options for HCV patients worldwide are associated only with the use of drugs, without considering whether to use resort (spa) resources with these patients [19-23].

Therefore, the purpose of this study was to evaluate the effectiveness of combined use of antiviral therapy interferon alfa-2a=Roferon + Ribavirin=Vero-ribavirin and resort factors in patients with CHC in the replication phase.

## 2 Material and methods

We observed 48 patients with CHC; the minimum activity of the process was the phase of replication. Of these, 26 men and 22 women were aged from 35 years to 58 years. The diagnosis was verified based on a comprehensive examination including the history, physical examination, and accepted clinical, biochemical and instru¬mental methods. Markers of HCV infection were determined by enzyme linked immunosorbent assay (ELISA) (a-HCV and a-HCV Ig M). HCV RNA was determined twice by the polymerase chain reaction (PCR). Genotyping of HCV was performed. Morphofunctional state of the gastroduodenal system was evaluated on the basis of esophagogastroduodenofibroscopy (EGDFS) and computed pH-metry (the method by V.M. Chernobrovy).

In 4 patients (before treatment, after 24 days and 3 months, 6 months and 12 months) biochemical blood analysis and the study of HCV infection markers were carried out. All the patients were randomly divided into 2 groups. The first group (control group, 17 patients) comprised those who received outpatient a-IFN 2a as Interferon alfa-2a = Roferon drug (company „Hoffmann - La Roche", Switzerland) at 3 IU, intramuscularly or subcutaneously, every other day in combination with Vero-ribavirin („Veropharm", Russia) 800-1200 mg/day (depending on the patient's body weight). The second group (study group of 31 patients) consisted of patients who received combination therapy in the form of a complex combination of drugs Interferon alfa-2a = Roferon + Ribavirin = Vero-ribavirin, along with the factors of resort (spa) treatment (psychotherapy, climatotherapy, diet, oxygen baths, indoor reception of low-mineralized mineral water (2.5 g/l), sulphate-bicarbonate-chloride-sodium composition of 200 ml 3 times a day for 30-45-60 min before a meal (depending on the level of basal acid formation), water temperature 38-40°C). The course of sanatorium-and-spa treatment in a Gastroenterological Sanatorium (Odessa) was 24 days.

More patients in both groups continued to receive conventional therapy in a combination with Interferon alfa-2a = Roferon + Ribavirin = Vero-ribavirin for 12 months, while the study group continued to receive domestic mineral water still within a month.

Patients in both groups were comparable in age, sex, and severity of disease. The inclusion of factors in the resort complex of antiviral therapy of HCV patients was based on our earlier data [4-6], indicating the effectiveness of these resort factors in patients after viral hepatitis. The results of therapy were assessed immediately after the end of resort (spa) treatment, then at 3, 6 and 12 months after start of treatment.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration.

**Table 1:** Evolution of the functional status of the liver under influence of the standard antiviral therapy in patients with chronical viral hepatitis C, (M±m), n = 17 (the control group).

| Index | Before treatment | After treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Through 1 month | $p_1$ | Through 3 months | $p_2$ | Through 6 months | $p_3$ | Through 12 months | $p_4$ |
| AlAT, mmol/(h l) | 2,86±0,41 | 1,52±0,15 | <0,05 | 1,18±0,26 | <0,05 | 0,64±0,13 | <0,001 | 0,63±0,09 | <0,001 |
| AsAT, mmol/(h l) | 1,42±0,35 | 0,89±0,03 | <0,02 | 0,68±0,1 | <0,05 | 0,41±0,1 | <0,01 | 0,35±0,07 | <0,01 |
| Gamma-Glutamyl TransPeptidase, u/l | 140,3±4,3 | 141,5±4,22 | >0,5 | 92,3±2,3 | <0,001 | 70,8±3,4 | <0,001 | 69,4±5,38 | <0,001 |
| AlP, u/l | 206,4±6,38 | 204,8±6,73 | >0,5 | 180,6±4,2 | <0,001 | 128,3±5,63 | <0,001 | 126,4±5,53 | <0,001 |
| Total bilirubin, µmol/l | 29,28±3,38 | 29,13±3,64 | >0,5 | 28,25±4,83 | >0,5 | 24,12±3,28 | >0,5 | 20,18±3,05 | <0,05 |
| Thymol test, u. (S-H) | 12,21±2,15 | 7,68±2,13 | >0,2 | 5,28±0,24 | <0,001 | 4,63±1,28 | <0,01 | 4,24±0,84 | <0,001 |

Amount (p) was counted between before and after treatment.

**Table 2:** Evolution of the functional status of the liver under influence of the standard antiviral therapy and resort (spa) treatments in patients with chronic viral hepatitis C, (M±m), n = 31 (the basic group).

| Index | Before treatment | After treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Through 1 month | $p_1$ | Through 3 months | $p_2$ | Through 6 months | $p_3$ | Through 12 months | $p_4$ |
| AlAT, mmol/(h l) | 2,84±0,43 | 1,1±0,1 | <0,001 | 0,58±0,11 | <0,003 | 0,5±0,03 | <0,003 | 0,44±0,13 | <0,003 |
| AsAT, mmol/(h l) | 1,32±0,11 | 0,51±0,04 | <0,001 | 0,36±0,81 | <0,003 | 0,31±0,17 | <0,003 | 0,21±0,04 | <0,003 |
| Gamma-Glutamyl TransPeptidase, u/l | 142,0±95,35 | 92,3±40,3 | <0,05 | 53,4±8,05 | >0,2 | 45±4,15 | >0,2 | 41,87±6,2 | >0,2 |
| AlP, u/l | 193,5±44,3 | 167,7±43,35 | <0,05 | 108,7±8,15 | <0,05 | 104,5±7,35 | <0,05 | 99,0±5,4 | <0,02 |
| Total bilirubin, µmol/l | 29,34±3,46 | 18,54±0,87 | <0,003 | 16,3±1,05 | <0,003 | 16,0±1,2 | <0,003 | 14,3±1,25 | <0,003 |
| Thymol test, u. (S-H) | 12,0±2,58 | 6,64±0,48 | <0,05 | 4,34±0,13 | <0,05 | 3,05±0,25 | <0,001 | 3,0±0,23 | <0,001 |

Amount (p) was counted between before and after treatment.

## 3 Statistical analysis

The statistical analysis was done with Statistica 10.0 PL software. The analysis outcome was presented as a proportion or average with standard variations. To compare the variables, the ANOVA test and Tukey's test were run. The value $p < 0.05$ was accepted as significant. The results are presented in the tables.

## 4 Results

HCV RNA was detected in all 48 patients examined. In determining the genotype of the virus, we most frequently encountered genotype 1b (42 patients) and least frequently genotypes 2a and 3a (6 patients). It should be noted that according to the Odessa regional sanitary station, in Odessa the predominant genotype is 1b.

Prior to treatment, all patients had the most characteristic manifestations of asthenic-vegetative syndrome in the form of severe general weakness, fatigue (100%), and depression (22.92%). Pain in the right hypochondrium occurred in most of the patients (77.08%). Less severe complaints were pain in the epigastric and pyloroduodenal

zones (31.25% of cases) and in the left upper quadrant of the abdomen (29.16%). Dyspeptic syndrome occurred equally often as bitterness in the mouth and nose (33.33%) and belching and heartburn (31.25%).

Objective examination of the vast majority of patients (89.58%) showed increased liver size with solid consistency and pain on palpation, and 1/4 of patients had a painful, enlarged spleen.

In more than half of the patients, dysfunction of the bowel in the form of constipation (56.25% individuals) was observed, which in some patients (35.42%) was accompanied by intestinal dyspepsia manifesting as swelling and flatulence or stomach pain during bowel movements (27.08%). Pain on palpation of the colon was found in two thirds (64.58%) of observations.

Analysis of laboratory parameters revealed in all patients hypertransferaseemia as AlAT increased to an average of 2.84 ±0.43 mmol/(h l) and AsAT averaged 1.32 ±0.11 mmol/(h l). In one-third of patients (35.41%), there was cholestasis, which was characterized by increased levels of alkaline phosphatase (ALP) to 1.5-2 N, y-glutamyl transpeptidase up to 2 N, and the indicators of direct bilirubin averaged 29.34±3.46 mmol/l. In 79.16% of the patients, we observed an increase of thymol in samples (with an average of 12.0 ±2.58 units (SH)) and in the level of gamma globulin (28.24±4.36%), reflecting the presence of a mesenchymal-inflammatory response.

According to the results of endothelial-derived growth factors testing, at the beginning of treatment, the vast majority of persons surveyed (68.75%) had severe congestion of the mucous membrane of the gastroduodenal zone, which in some patients (43.75%) was accompanied by minimum hyperacidity of gastric juice (mean pH value was 1.41 ±0.03 U); 39.58% of patients had initial hypoacidity, whereas the normal pH values were recorded only in 8 patients.

Micro-biocenosis intestinal disorders occurred in varying severity in 100% of HCV patients; 18.75% of patients were diagnosed with grade one, 54.16% with grade 2, and 27.08% with grade 3 of intestinal dysbacteriosis.

It was found that the degree of impairment of intestinal micro-biocenosis increased in proportion to the severity of functional disorders of the liver, as well as the severity of inflammatory changes in the mucous membrane of the gastroduodenal zone. It was most often determined by growth inhibition of Escherichia coli (68.75% of patients), bifidobacteria (81.25%) and lactobacilla (70.83%). There was significant growth of E. coli with hemolyzing properties (56.25% of observations). At the same time, an increased number of other opportunistic pathogens and aerobic microorganisms, such as Klebsiella, Staphylococcus, Proteus and fungi of the genus Candida, were shown.

By the end of resort (spa) treatment, there were significant differences in the clinical course of disease in patients in the primary and control groups.

## 5 Discussion

First of all, it should be noted that in the second group, even at 7-10 days of stay in the sanatorium, patients reported significant improvement in overall health, with reduced overall weakness, improved sleep and mood, and increased efficiency.

It is extremely important that all patients who had resort (spa) treatment better tolerated antiviral therapy compared with those of the control group. Thus, in the main group, effects of myalgia, temperature reaction, and joint pain were significantly less pronounced compared with the control group, and the disappearance of the manifestations of influenza-like syndrome was observed after the third injection of Roferon. In the basic group, there were no other adverse reactions to interferon therapy, such as anemia, leuko- and thrombocytopenia. At the same time, in 2 control subjects after 2 months of starting treatment, hemoglobin concentration decreased to 112 g/l and platelet count to 150 g/l.

Cases of intolerance or the appearance of certain side effects of Vero-ribavirin were not identified in any of the investigated patients.

The astheno-vegetative nature of the treatment effects in the main group of patients was demonstrated only in 12.90% of cases, whereas in control subjects there was a tendency to reduction of overall weakness, fatigue, and depressive symptoms ($p < 0.01$). Pain syndrome, as pain in the right upper quadrant, remained in 35.48% of the basic group, which was not observed in the control group, whereas pain in the right upper quadrant, although of lesser intensity, continued to occur in practically all patients ($p < 0.003$).

Marked improvement of dyspeptic complaints in the study group was manifested as a significant decrease in bitter taste in the mouth, heartburn, belching, and bloating after 24 days of treatment ($p < 0.05$). These positive changes in the control group were characterized by a tendency to decrease ($p > 0.05$). Also worth noting was a significant improvement in bowel function in patients in the primary group, where there was normalization of stools ($p < 0.05$) and marked ($p < 0.05$) decrease or disappearance

of pain along the intestine in the majority of patients with flatulence ($p < 0.05$).

The positive dynamics of clinical manifestations of disorders of bowel function was accompanied by positive changes in the intestinal micro-biocenosis, shown as an increase in the concentration of the total number of E. coli, bifidobacteria and lactobacilli, as well as a significant decrease in the concentration of hemolytic E. coli and other opportunistic and pathogenic microorganisms. At the same time, in the control subjects significant positive changes in bowel function were noted.

In addition, in patients in the control group an increased tenderness to palpation of the liver remained, while in the main group by the end of the course of resort (spa) treatment, despite the persistence of pathological size of the liver in most patients, palpation in a third of patients was painless, and consistency of liver tissue was softer.

At discharge from the sanatorium, patients in the second group showed a significant reduction of AlAT level in comparison with the beginning of the treatment (mean - 1.10 ±0.10 mmol/(h l), $p < 0.001$) and AsAT (average - 0.51 ±0.04 mmol/(h l), $p < 0.001$), and the complete normalization of these parameters was observed. At the same time we noted the normalization of total bilirubin concentration to an average of 18.54 ±0.87 mmol/l ($p < 0.003$) and the tendency to reduction of activity of ALP and y-glutamyl transpeptidase ($p > 0.05$). There was improved performance of the mesenchymal-inflammatory response of the liver. Thus, the indicator thymol by the end of treatment decreased by 1.8 times ($p < 0.05$) and amounted to 6.64 ±0.48 U (SH), and y-globulin levels averaged 25.32 ±0.38%.

At the same time (1 month from the start of antiviral therapy) in the control group of patients, changes in the functional state of the liver were significantly less important in comparison with indicators of the second group of patients. For example, AlAT and AsAT activity was, respectively, 1.52 ±0.15 mmol/(h l) ($p < 0.05$) and 0.89 ±0.03 mmol/(h l) ($p < 0.001$).

In addition, one should note, according to EGDFS and pH-metry, the normalization of acid-forming functions of the stomach in all of the main group, which in most cases was accompanied by the disappearance or significant reduction in inflammatory changes of the gastroduodenal mucosa ($p < 0.003$).

Survey results of patients 3 months after start of treatment showed a significant advantage of the resort factors used.

First of all, this advantage showed significant differences between the indices of the functional state of the liver in patients in the primary and control groups. Thus, the average level of AlAT and AsAT in the main group was within normal limits (0.58 ±0.11 mmol/ (h l) and 0.36 ±0.81 mmol/(h l), $p < 0.003$), respectively. At the same time in one patient with genotype 2a and 2 patients with genotype 3a, HCV RNA and HCV-and Ig M levels were not determined.

Patients continued to receive antiviral therapy for an additional 3 months.

Positive dynamics in hypertransferaseemia in the study group was accompanied by normalization of the mesenchymal-inflammatory reaction, as evidenced by normal levels of AlAT and AsAT, as well as thymol and y-globulin ($p < 0.05$). The same tendency was noted in the study of indicators of cholestasis; in the study group there was complete normalization of alkaline phosphatase activity and y-glutamyl transpeptidase at 82.35% in those with initially higher rates. Unlike the main group, in the control group, similar changes were observed; the average cytolysis syndrome only slightly decreased (AlAT - 1.18 ±0.26 mmol/(h l), $p > 0.05$, AsAT - 0.68 ±0.10 mmol/ (h l), $p < 0.05$) but continued to be above acceptable values. Standards and indicators of cholestasis were not reached; the level of alkaline phosphatase and y-glutamyl transpeptidase was 1.3-1.5 N. With regard to mesenchymal-inflammatory response, its manifestations were observed in most patients, although much less pronounced. Thus, the average thymol was 5.28 ±0.24 units (SH), and the level of y-globulin was 24.38 ±0.46%, significantly higher than those levels in the main group of patients.

At 3 months after starting treatment, in 3 pa¬tients in the basic group and 1 patient in the control group, markers of HCV replication were not determined.

At 6 months after starting treatment, on the background of persistent clinical and biochemical remission, markers of activity of viral hepatitis C (HCV RNA PCR, anti-HCV Ig M) were not determined in 48% of patients in the basic group and in 32% in the control group.

At 12 months after the start of treatment, all the observed patients showed persistent clinical and biochemical remission. Elimination of the virus from the blood was noted in 56% of the control group and in 74% of the basic group.

## 6 Conclusion

In patients with HCV in the stage of moderate activity, the replication phase was characterized by asthenic-vegetative syndrome (100%) with severe depression

(22.92%), pain syndrome (77.08%) and dyspeptic syndrome (33.33%), moderate hypertransferaseemia (100%), slightly pronounced cholestasis (1/3 of patients), and signs of mesenchymal-inflammatory response. More than half of patients had disturbances of bowel function, often in the form of constipation (56.25%) and bloating, pain in the epigastrium pyloroduodenal zone observed (31.25%), largely due to impaired intestinal micro-biocenosis (100%) and breaches of the morpho-functional status of the gastroduodenal zone. It is established that in patients with HCV the degree of impairment of intestinal micro-biocenosis increases in proportion to the severity of functional disorders of the liver, as well as the severity of inflammatory changes of gastric mucosa and duodenum. Combination antiviral therapy (Roferon + Vero-ribavirin) promotes early (after 6 months) elimination of the virus from the blood in patients with genotype 2a and 3a HCV-resistant clinical and biochemical remission in patients with different genotypes, and the disappearance of markers of replication in 56% of patients. Antiviral therapy for most patients with HCV can be recommended because of its tolerability and reasonable cost of treatment and relatively high efficacy.

The use of resort factors (low-mineralized mineral water, oxygen baths, diet, climatotherapy, psychotherapy) in combination with antiviral therapy (Roferon + Vero-ribavirin) eliminates the side effects of treatment and increases its efficiency to 74% of favorable outcomes.

**Conflict of interest:** The authors state that they have no conflicts of interest.

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