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THERAPEUTIC EFFICACY OF DIRECT-ACTING ANTIVIRALS IN PATIENTS WITH HEPATIC CIRRHOSIS BY HEPATITIS C VIRUS

321.09 – INFECTIOUS, TROPICAL DISEASES AND MEDICAL PARASITOLOGY

Doctoral thesis summary in medical sciences

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The thesis was developed within the Department of infectious diseases, tropical and medical parasitology and the Doctoral School in the Field of Medical Sciences, State University of Medicine and Pharmacy "Nicolae Testemitanu"

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CONTENTS

CONCEPTUAL LANDMARKS OF RESEARCH

Topic actuality. Viral hepatitis C is a disease with a significant impact worldwide, approximately 71 million people worldwide infected with hepatitis C virus (HCV) [1]. In the Republic of Moldova, the prevalence of HCV infection in the general population was estimated at 4.5-5.0%, with genotype 1b predominant - 98% [2; 3; 4].

The opportunity to administer direct-acting antivirals (DAA) is a major advantage in the treatment of chronic HCV infection, as the duration of treatment with minimal adverse reactions is reduced, it is possible to administer orally, with the possibility of administration, high SVR rate, decreased liver stiffness, improved liver function [5]. Currently, the SVR rate reaches up to 85-98% with DAA treatment even so in patients with cirrhosis [6; 7].

Description of the situation in the field of research and identification of research issues. Assessment of the efficacy and safety of DAA therapy in patients with hepatitis C cirrhosis are important, in particular for the development of control measures and the application of different antiviral treatment regimens in order to achieve sustained virologic response. Evolutionary particularities in patients with cirrhosis following DAA therapy and the risk of developing hepatocarcinoma in such patients are currently insufficiently studied. Therefore, long-term surveillance of these patients remains mandatory.

Work purpose. Study of the effectiveness of antiviral treatment with direct-acting antivirals in patients with cirrhosis (by evaluation of clinical, biochemical parameters, molecular biology and imaging tests), to optimise the supervision and implementation of effective treatment schemes.

Research objectives:

1. Assessment of clinical data, biochemical, haematological and other paraclinical parameters in hepatitis C cirrhosis patients at initiation of antiviral therapy.
2. Assessment of the efficacy of antiviral regimens: Sofosbuvir and Daclatasvir/Ledipasvir with Ribavirin and Sofosbuvir and Daclatasvir/Ledipasvir without Ribavirin in patients with HCV cirrhosis by assessment of biochemical indices, haematology and molecular biology tests 1.3, 6, 12 months after initiation of antiviral therapy.
3. Assessment of Fibroscan-evaluated hepatic fibrosis at treatment initiation, at 6 and 12 months after treatment.
4. Analysis of adverse reactions and complications during and after antiviral treatment in patients with HCV cirrhosis.
5. Elaboration of proposals on improvement of antiviral treatment algorithms in patients with cirrhosis, in order to obtain a sustained virologic response.

Scientific novelty and originality

For the first time in the Republic of Moldova, patients with HCV cirrhosis have the opportunity to undergo Interferon-free antiviral treatment. Therefore, it will be possible to evaluate the effectiveness of this treatment by monitoring clinical parameters, paraclinical and molecular biology tests in such patients. Adverse reactions, complications during and after completion of antiviral therapy will be evaluated to improve the quality of patients' lives and the definitive elimination of HCV infection.

Scientific problem solved

The efficacy of direct-acting antiviral agents in patients with cirrhosis of the liver with HCV at various stages has been evaluated. The development of hepatic fibrosis (acquired by Fibroscan) following antiviral therapy in this category of patients was assessed, as well as the response to treatment with sustained virologic response. The evolution of the disease after treatment was analyzed in order to decompensate cirrhosis or develop hepatocellular carcinoma. Adverse effects of antiviral therapy have also been identified and analysed.

Theoretical value

The results obtained have shown new clinical and paraclinical aspects of direct-acting antiviral treatment in patients with HCV cirrhosis in the Republic of Moldova depending on age, genotype, and, clinical staging and stage of fibrosis.

The applicative value of the work

1. The results obtained will allow the evaluation of the effectiveness of antiviral therapy in patients with different stages of cirrhosis by HCV and the subsequent elaboration of antiviral treatment regimens in order to obtain a sustained virologic response.
2. Making use of the results in medical practice through the implementation of the National Program for combating viral hepatitis B, C and D will contribute to the reduction of morbidity through cirrhosis of the liver with HCV and hepatocellular carcinoma.
3. The thesis materials will be published in the form of articles and theses in various collections and magazines, will be reported at scientific conferences, implemented in the practice of infectious doctors in the country as well, within the didactic process of the Departments of Infectious, tropical and medical parasitology and Infectious Diseases of the Faculty of Continuing Education of Physicians.

The volume and structure of the thesis. The thesis is written in Romanian, computer-based, composed of the following compartments: introduction, the review of literature (chapter 1), presentation of research materials and methods (chapter 2), and, presentation of personal research results (chapters 3, 4), general conclusions and practical recommendations and annexes. The thesis is exposed on 95 pages of basic text, includes 18 tables and 16 figures, 2 annexes, based on 203 bibliographic sources, of them 31 national sources and 172 foreign sources.

Key words: cirrhosis of the liver, hepatitis C virus, direct-acting antivirals, Ledipasvir, Daclatasvir, Sofosbuvir, Ribavirin.

THESIS CONTENT

The introduction includes the actuality and the scientific-practical significance of the approached topic and the situation in the researched field, are exposed the purpose and objectives of the research, the description and exposure of the scientific innovation and of the obtained results, and, which confirms the scientific aspect of the study and its importance for medicine.

1. HCV INFECTION AND ANTIVIRAL TREATMENT

In this chapter are presented recent literature data, including national and international bibliographic sources. The analysis of the bibliographic literature reflects new results on antiviral therapy in hepatic cirrhosis with hepatitis C virus. The prevalence of hepatic cirrhosis morbidity with HCV in our country is increasing from 229 cases in 2000 to 1960 cases in 2020 [8]. The literature data reveal that the Republic of Moldova ranks first in Europe in liver cirrhosis mortality [8; 9].

The emergence and approval of DAA in recent years has revolutionized antiviral therapy, especially for patients with cirrhosis of the liver. Although an SVR with antiviral DAA has been shown to induce regression of cirrhosis and reduce the risk of mortality in cirrhotic patients, the risk of developing complications remains significant [10; 11]. Therefore, patients with advanced and decompensated cirrhosis should be treated and monitored in experienced centres and the possibility of a liver transplant evaluated if necessary. Patients with decompensated cirrhosis and advanced liver fibrosis may have a greater benefit from antiviral therapy after a liver transplant [7; 12]. The current guideline recommendations support the use of SOF-based DAA regimens in combination with LDV, VEL or DCV, with or without RBV, for the treatment of HCV infection

in patients with cirrhosis. The majority of AEs are related to the administration of RBV, therefore dosage adjustment or cancellation of therapy with this preparation is required [15].

2. MATERIAL AND METHODS OF RESEARCH

2.1. General characteristic of the research

This research is a randomized comparative clinical trial. 144 Patients diagnosed with HCV liver cirrhosis hospitalised in the Clinical Hospital for Infectious Diseases "Toma Ciorba", between 2017-2021, were included for the study. Patients were divided into 2 batches according to treatment regimen followed: group L_0: 72 patients receiving Sofosbuvir (SOF) in combination with Ledipasvir (LDV)/Daclatasvir (DCV) plus Ribavirin (RBV) for 12 weeks and L_1 group: 72 patients receiving SOF in combination with LDV/DCV without RBV for 24 weeks. The subjects were selected based on the inclusion/exclusion criteria, and the inclusion of the persons in the study took place based on the informed agreement obtained after a verbal explanation and the offering of the loop about the essence, risks and benefits of the study.

2.2. Clinical and instrumental methods of diagnosis

The diagnosis of cirrhosis was established on the basis of clinical manifestations, paraclinical investigations (biochemical, molecular biology techniques, imaging) suggestive of advanced liver disease, and the extent of hepatic fibrosis was assessed by non-invasive methods (Fibroscan). The clinical parameters analyzed in the study were: demographic data (age, gender, background), anamnestic data (presence of risk factors: obesity, alcohol consumption, etc.), heredo-collateral history, history, documented chronic associated diseases, permanent treatments followed, antiviral treatment previously followed. The evaluation of the severity of cirrhosis in all patients included in the research was quantified using the Child-Pugh score. Biological parameters assessed: haemoleucogram: haemoglobin, erythrocytes, leukocytes, leukocyte formula, platelet count; serological tests: HCVsum; Ag Hbs , Ab anti HIV (exclusion criterion); molecular biology tests: HCV RNA, HCV genotyping; cytolytic syndrome tests: ALAT, ASAT; cholestasis syndrome tests: total bilirubin and its fractions, GGTP, AF; renal function assessment tests: urea, creatinine; blood glucose, serum amylase; hepatopriv syndrome: total protein, prothrombin time. The instrumental methods used were: fibroscan – for assessing the degree of hepatic fibrosis; abdominal ultrasound was performed to detect signs of liver disease, signs of portal hypertension and to assess the presence of hepatocarcinoma; superior digestive endoscopy for assessing and highlighting signs of portal hypertension, esophageal varices, hypertensive portal gastropathy; electrocardiogram for diagnosing rhythm disorders, organic disorders; computed tomography (without contrast)/nuclear magnetic resonance: to confirm or exclude tumor processes.

2.3. Methods used to analyse the results obtained

The data of the investigations were processed computerized by applying statistical-mathematical techniques. In the case of quantitative (continuous) quantities, the arithmetic mean, the standard deviation, the minimum and maximum values, the median were calculated. For the – ordinal and nominal qualitative sizes – were calculated absolute frequencies (number of occurrences) and relative frequencies expressed in percentages for a 95% confidence interval%. The significance of the indicators was determined by performing non-parametric tests (chi-square test, Wilcoxon test, U Mann-Witney test) and standard errors.

3. ASSESSMENT OF THE GENERAL CHARACTERISTICS OF THE STUDY POPULATION

3.1. Distribution by gender, age, background, genotype and duration of disease of patients with cirrhosis involved in the study

The average age of patients in the control group (L_0) was 59.3±7.8 years, varying between 36 years and 75 years and not significantly different from the age of patients in the research group (L_1) – 59,6±7,2 years, and, ranging from 35 to 80 years (t=0,240, p=0,8108). Of the total patients included in the study, in both batches, the most affected were people older than 55 years, representing 102 patients (70.8%) (p=0.001). Thus, in L_0, patients older than 55 years were 50 (69.4%) and 52 (72.2%) in L_1. The distribution by gender was as follows: women 59 (40.9%), men 85 (59%). Following the analysis, a difference was observed in the compared batches (p=0,0001), 41 female (56.9%) and 31 (43%) male (95% prevailed in L_0 CI= 31,9(15,921-45,6825), Chi-square – 15,045), and in L_1 predominated male 54 (75%) persons (95% CI= 32(16,0198-45,761), Chi-square – 15,134), and in L_1, women are 18 (25%). The duration of infection at the time of detection was between 1 and 39 years, on average being 11.04 ± 5.4 years in L_0 and 8.3 ± 5.7 years in L_1 (t=-2,918 p=0,0041).

Analyzing the distribution of patients by living environment, it was found that patients had an equal distribution (50%) (95% CI= 16.7(0.4000-31.8038), Chi-square – 3,988, which is, p=0,0458).

The genotype-based distribution of patients was as follows: 93.7% (135/144) patients had genotype 1, genotype 2 was identified in 1.3% (2/144) patients, patients, genotype 3 in 3.4 % (5/144) patients and unidentified in 1.3% (2/144) cases.

Table 3.1. **Characteristics of clinical manifestations in patients with HCV cirrhosis included in the study**

Clinical signs and syndromes	**L_0 n=72**	**L_1 n=72**	**95% CI, Chi- square, gl=1, p**
Sdr. asteno-vegetative,n(%)	67 (93%)	68 (94,4%)	1,4(-7,4305-10,3849), 0,119, p=0,7304
Sdr. dyspeptic, n(%)	46 (63,8%)	53 (73,6%)	9,8(-5,2987-24,3085), 1,597, p=0,2064
Sdr. jaundiced, n (%)	13 (18%)	9 (12,5%)	5,5(-6,4706-17,4150), 0,837, p=0,3603
Sdr. algic in the right hypochondrium n(%)	60 (83,3%)	62 (86,1%)	2,8(-9,1926-14,7621), 0,216, p=0,6419
Splenomegaly n (%)	64 (88,8%)	69 (95,8%)	7(-2,1567-16,7284), 2,465, p=0,1164
Splenectomy, n (%)	2 (2,7%)	0	2,7(-2,7342-9,4600), 1,957, p=0,1618

3.2. Assessment of patients in the study by Child-Pugh staging, degree of fibrosis and related diseases.

Following the targets, the patients in the study were assigned according to the Child-Pugh staging. The entire research group comprised 66 patients (45.8%) in class A, 71 patients (49.3%) in class B and 7 patients (4.8%) in class C. Analyzing the clinical manifestations in patients with cirrhosis of the liver included in the study, we attested the presence of astheno-vegetative syndrome in – 135 patients (93.7%), dyspeptic syndrome was present in 68.7% cases (99 patients), algic syndrome in the right hypochondrium – 84.7% (122 patients) and a high frequency of jaundice syndrome – 15.2% (22 patients), to which mechanical or haematological factors have been excluded (table 3.1). At the objective and ultrasound examination of the abdominal cavity splenomegaly was determined in 92.3% (133 patients), in 40 cases (27.7%) hypersplenism of various degrees, splenectomy supported 2 patients (1.3%) (table 3.1., 3.2).

Table 3.2. **Distribution of patients included in the study by decompensation level**

Clinical syndrome	**L_0 n=72**	**L_1 n=72**	**95% CI, Chi-square, gl=1, p**
Hypersplenism, n (%)			
light	10 (13,8%)	13 (18%)	4,2(-7,9542-16,2938), 0,472, p=0,4922
moderate	6 (8,3%)	7 (9,7%)	1,4(-8,5718-11,4453), 0,086, p=0,7699
severe	2 (5,5%)	2 (5,5%)	0(-8,5425-8,5425), 0, p=1
Ascites, n (%)			
minimum, n (%)	3 (4,1%)	2 (2,7%)	1,4(-5,8819-9,015), 0,213, p=0,6442
moderate, n (%)	3 (2,7%)	1 (1,3%)	1,4(-4,9280-8,2459), 0,358, p=0,5499
advanced, n (%)	0	1 (1,3%)	1,3(-3,8791-7,3141), 0,936, p=0,3334
Oesophageal varices, n (%)			
gr I	9 (12,5%)	9(12,5%)	0(-11,1906-11,1906), 0, p=1
gr II	14 (19,4%)	12 (16,6%)	2,8(-9,8790-15,4075), 0,190, p=0,6630
gr III	4 (5,5%)	3 (2%)	3,5(-3,7336-11,5092), 1,213, p=0,2707

Based on clinical data, paraclinical and imaging investigations, the degree of decompensation of hepatic cirrhosis with hepatitis C virus was evaluated in patients included in the study. Thus, ascites was recorded in 6.9% (10 patients), oesophageal varices were attested in 51 (35.4%) patients (table 3.2).

The degree of fibrosis was assessed by performing Fibroscan, selecting patients with F3 fibrosis (12.5-13.9 kPa) and F4 (>14 kPa). Thus, prior to initiation of DAA therapy, F3 stage (12.5 - 13.9 kPa) after the Metavir scale was recorded in 12 (8.3%) patients, patients, and stage F4 (>14 kPa) – 132 (91,6%) patients (p<0,001) (Figure 3.1).

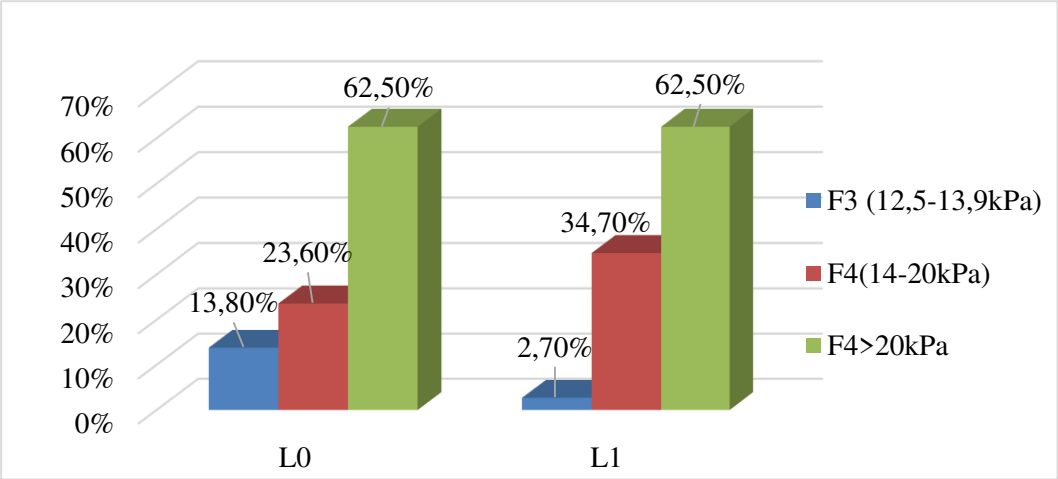

Figure 3.1. **Repartition of patients after the liver stiffness at initiation of DAA therapy**

At the same time, out of 91.6% (132/144) F4 fibrosis patients, 62.5% (90/144) advanced patients (F4>20 kPa): 45 (62.5%) of patients in each lot (p<0,001) (Figure 3.3). Thus, fibrosis between 14-20kPa had 42 (29.1%) patients: 17 (23.6%) in L_0, 25(34.7%) in L_1. The mean hepatic fibrosis at initiation of DAA therapy in L_0 was 29.6±13 kPa and 25.3 ±8.2 kPa for L_1.

Assessing the presence of extrahepatic manifestations, we detailed the spectrum of clinical manifestations, the incidence of which in the study group was: diabetes mellitus – 40(27.7%) patients, chronic kidney disease in 18(12.5%)cases, cases, seronegative arthritis in 2(1.3%) cases, thyroiditis in 2(1.3%), Raynaud's syndrome and vascular purpura in 1 patient (0.6%) (table 3.4).

Table 3.4. **Distribution of study patients by disease associated at initiation of DAA treatment**

Associated diseases	**L_0 n=72**	**L_1 n=72**	**95%CI, Chi-square, gl=1, p**
Hypertension, n (%)	32 (44,4%)	30 (41,6%)	2,8(-13,0656-18,4689), 0,114, p=0,7352
Obesity, n (%)	6 (8,3%)	5 (6,9%)	1,4(-8,0077-10,9174), 0,100, p=0,7521
Chronic gastroduodenopathies,n (%)	13 (18%)	8 (11,1%)	6,9(-4,8544-18,6200), 1,369, p=0,2420
Cholecystitis a/lithiazis, n (%)	49 (68%)	44 (61,1%)	6,9(-8,5842-21,9345), 0,744, p=0,3884
Extrahepatic manifestations			
diabetes mellitus, n (%)	19 (26,3%)	21 (29,1%)	2,8(-11,6916-17,1388), 0,140, p=0,7083
Chronic kidney diseases, n (%)	8 (11,1%)	10 (13,8%)	2,7 (-8,4533-13,8826), 0,239, p=0,6249
Other extrahepatic manifestations, n (%)	3 (4,1%)	3 (4,1%)	0 (-7,8391-7,8391), 0, p=1

4. ASSESSMENT OF THE EFFICACY OF DAA IN PATIENTS WITH HCV LIVER CIRRHOSIS

4.1. Dynamics of biochemical parameters in patients with HCV cirrhosis treated with different DAA regimens

The evaluation of cytolytic syndrome in patients with cirrhosis of the liver was carried out based on the determination of the activity of ALAT and ASAT, as well as the ratio of Ritis (ASAT/ALAT).

By performing the analysis of cytolysis markers in patients included in the study at the end of treatment, we established a decrease in the mean value of both ALAT: 27,0±7,4UI/l for L_0 and 27,8±7,0UI/L for/l L_1 (t=-0,666, p=0,5062) as well as ASAT: 32,4±10,0 IU/l L_0 and 29,2±7,0 IU/l L_1(t=-2,224, p= 0.0277), respectively, but without statistical significance (figure 4.1., 4.2.).

In both batches, normalisation of transaminases occurred as early as the second week of DAA treatment.

Higher ALT and ASAT values were determined in patients over 55 years of age compared to younger patients, although, the return of transaminases up to normal values towards the end of treatment was characteristic for patients in both batches, regardless of their age.

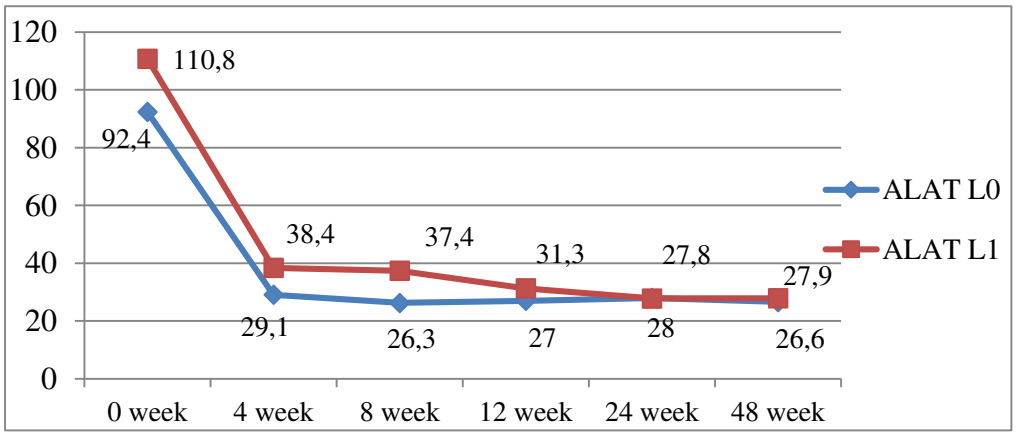

Figure 4.1. **Dynamics of ALT evolution in patients with cirrhosis receiving DAA treatment**

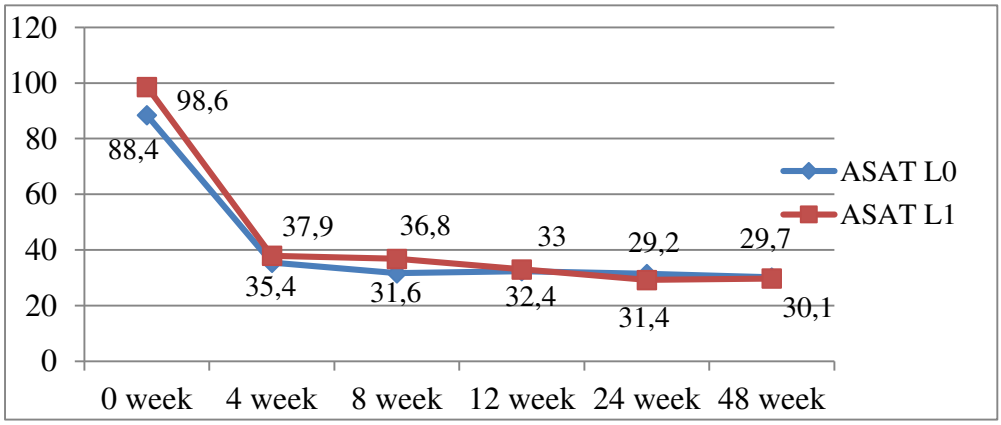

Figure 4.2. **Dynamics of ASAT evolution in patients with cirrhosis receiving DAA treatment**

Thus, after treatment, ALAT normal values in L_0 presented 95.8%(69) patients, ASAT – 93% (67) cases, and in L_1: ALAT – 94.4% (68) patients, ASAT – 91,6% (66) cases, showing statistical significance in both batches (p<0,0001). The combination of SOF and LDV/DCV with/without RBV obviously influenced hepatocytolysis syndrome in patients with cirrhosis, with the transaminase profile significantly improving at the end of treatment (over 91% patients had normal values in both batches) with biochemical response (p< 0.0001) (table 4.1).

To evaluate cholestatic syndrome in patients in the study, the following biochemical indicators were determined: bilirubin and its fractions and gamma-glutamyltranspeptidase (GGTP) (table 4.1).

Analyzing and comparing the mean total bilirubin at initiation and end of treatment, there is a greater decrease in L_1 (p<0,0001) compared to L_0 (p= 0,0585). We also found that the number of patients with normal total bilirubin values after treatment in L_1 is significantly higher 86.1%(62/72) cases(p=0.0012) compared to L_0 – 43% (31/72) patients (p=0,7342) (table 4.1).
GGTP values were decreasing after treatment in both groups thus, comparing the mean values dynamics in both batches up to and after treatment with DAA, there was a statistically significant improvement in both L_0 and L_1 patients (p < 0.0001) (table 4.1.). This also highlights the absence of toxic effect of DAA in patients with HCV cirrhosis.

Table 4.1 Assessment of cholestatic syndrome in HCV cirrhosis patients treated with DAA

Biochemical indices	**L_0 n=72**		**L_1 n=72**		**95%CI, P_0**	**95%CI,P_1**
	Initiation	**End**	**Initiation**	**End**		
GGTP*, N** (10-38U/l), n (%)	16 (22,2%)	47 (65,2%)	19 (26,3%)	45 (62,5%)	43(27,16-55,82) p<0,0001	36,2(20,12-49,72) p<0,0001
>N**, n (%)	56 (77,7%)	25 (34,7%)	53 (73,6%)	27 (37,5%)	43(27,16-55,82) p<0,0001	2,8(-12,63-18,05) p<0,0001
Total bilirubin, N** (5-21µmol/l), n (%)	29 (40,2%)	31 (43%)	45 (62,5%)	62 (86,1%)	2,8(-13-18.40) p= 0,7341	23,6(9,37-36,69 p=0,0012
>N**, n (%)	43 (59,7%)	41 (56,9%)	27 (37,5%)	10 (13,8%)	2,8(-13-18,41), p=0,7342	23,7 (9,49-36,77) p=0,0012

*gamma-glutamyl transpeptidase, ** normal

4.2. Dynamics of haematological parameters in patients with HCV cirrhosis treated with different DAA regimens

Haematological parameters allow highlighting and assessing inflammatory disorders in patients at the stage of cirrhosis, as well as the platelet changes present. The haematological parameters analysed during treatment were: white blood cell count, serum haemoglobin and platelet levels. The dynamics of the numeric values of the hematological indices (erythrocytes, leukocytes and platelets) in the complex, allow us to establish the presence of hypersplenism in the studied batches. The severity of liver disease is correlated with the degree of thrombocytopenia, hepatocellular lesions and hepatic fibrosis. Our study showed the beneficial influence of treatment on platelet count. Thus, the tendency to increase platelets was noted after the second month of treatment regardless of the followed schedule. The mean platelet count at the start of antiviral therapy was 105.1±40.4 x 10^9/l in L_0 ranging from 37-257 x 10^9/l to 115.0±47.9 x10^9/l for L_1,

respectively, varying between values 25-313 x 10^9/l (p=0,1822). After treatment, mean platelet count values increased: 123,0±42,3 x10^9/l in L_0 and 126,6±41,0 x10^9/l in L_1, respectively, but without statistical significance (p=0,6049) (table 4.2).

When completing antiviral therapy, 15(10.4%) patients maintained severe thrombocytopenia (52 – 69x10^9/l) (p<0.001) (Table 4.2). Comparing the dynamics of severe thrombocytopenia between batches up to and after antiviral treatment, there was a greater reduction in the number of patients after treatment in L_0 – 8.3% (6/72) cases (p0=0,0340), compared with L_1 – 12,5% (9/72) patients (p1=0,1256). After treatment, moderate thrombocytopenia remained in 69 (47.9%) patients: 39 (54.1%) in L_0, 30 (41.6%) in L_1. Normal platelet values (>120 x 10^9/l) at the initiation of antiviral therapy presented 45 (31.2%) patients and at the end of treatment – 60 (41.6%) patients (table 4.2).

To determine the risk of progression of thrombocytopenia in patients receiving DAA treatment without RBV reported in patients receiving the RBV regimen, statistical indices, were calculated, thus, starting from the fact that RR= 0,87, PR=0,7 and 95%=0,7(0,36-1,3) indicate the lack of connection between the RBV-free regimen and the progression of thrombocytopenia.

At the treatment initiation, leukopenia (1.8-3.9x10^9/l) was present in 63 (43.75%) patients: L_0 – 30 (41.6%) patients, L_1 – 33 (45.8%) (table 4.3).

Table 4.2. **Evolution of thrombocytopenia in patients treated with DAA**

Platelet values	**L_0 n=72**		**L_1 n=72**		**95%CI, P_0**	**95%CI, P_1**
	Initiation	**End**	**Initiation**	**End**		
severe (25-69 x 10^9/l)	15 (20,8%)	6 (8,3%)	16 (22,2%)	9 (12,5%)	12,5(0,85-24,11) p=0,0340	9,7(-2,81-22) p=0,1256
moderate (70-120x10^9/l)	38 (52,7%)	39 (54,1%)	30 (41,6%)	30 (41,6%)	1,4(-14,52-17,22) p=0,8667	0 (-15,71-15,71) p=1
N*(>125x10^9/l)	19 (26,3%)	27 (37,5%)	26 (36,1%)	33 (45,8%)	11,2(-3,98-25,7) p=0,1508	9,7(-6,2417-24,97) p=0,2382

Comparing the mean value of white blood cells in both batches after treatment was found to increase more in L_1 compared to L_0(p<0,0001). Analyzing the number of patients after DAA treatment in both batches that retained leukopenia, we found that their number decreased significantly in both batches. Thus, after treatment, leukopenia (2.7 – 3.9 x10^9/l) was preserved in 30 (20.8%) patients: L_0 – 19 (26.3%) patients, L_1– 11 (15.2%). Comparing the number of patients with normal leukocyte values in both batches until and after completion of antiviral treatment, a significant increase was noted in both batches.

At initiation of antiviral therapy in both batches, regardless of the regimen followed, there was an equal number of patients with Hg>120g/l (p>0.05) (table 4.3). Analyzing the haemoglobin levels in patients at the initiation of antiviral therapy, we found no statistically true differences in both groups, and after completion of antiviral therapy, the mean haemoglobin level in patients receiving RBV (L_0) at the end of treatment decreased more compared to the group receiving treatment with DAA without RBV (L_1) (p<0,0001).

Table 4.3. **Evolution of haematological parameters in DAA treated patients**

Haematological parameters	**L_0 n=72**		**L_1 n=72**		**95%CI, P_0**	**95%CI, P_1**
	Initiation	**End**	**Initiation**	**End**		
leukocytes						
leukopenia (1,8-3,9x10^9/l)	30 (41,6%)	19 (26,3%)	33 (45,8%)	11 (15,2%)	15,3(-0,15-29,79) p=0,0534	30,6(15,71-43,75) p=0,0001
N* (4-10,2 x 10^9/l)	42 (58,3%)	53 (73,6%)	39 (54,1%)	61 (84,7%)	15,3(-0,16-29,79) p=0,0535	30,6(15,69-43,76) p=0,0001
haemoglobin						
<109 g/l, n (%)	0	12 (16,6%)	5 (6,9%)	1 (1,3%)	16,6(8,07-26,83) p=0,0003	5,6(-1,58-13,96) p=0,0913
110-120 g/l, n(%)	16 (22,2%)	18 (25%)	11 (15,2%)	13 (18%)	2,8(-11,03-16,5) p=0,6934	2,8(-9,53-15,08) p=0,6528
>120 g/l, n (%)	56 (77,7%)	42 (58,3%)	56 (77,7%)	58 (80,5%)	19,4(4,15-33,46) P=0,0129	2,8(-10,51-16,01) P=0,6805

Patients initiating treatment with SOF and LDV/DCV in combination with RBV had Hb values greater than 110g/l at the start of antiviral therapy, the reason being anemia as a result of RBV administration. In order to determine the relative risk of anaemia by lowering Hb<120g/l in patients after treatment with SOF+LDV/DCV in relation to those treated with RBV, stastic indices were calculated: REE= 14/72=0,19; REC= 30/72= 0,41; RR = 0,19/0,41 = 0,46; RRR = 1-0,46= 0,54; RAR = |0,19-0,41| = 0,22; PEC = 30/42 = 0,71; PEE = 14/58 = 0,24; PR = 0,24/0,71 = 0,33; 95%CI = 0,3(0,15-0,71), NNT=4, p=0,004. Starting from the fact that RR=0,46, PR= 0,33 and 95% CI=0,3(0,15-0,71) are considered strong protection factors, and, the risk that patients treated with the DAA regimen without RBV develop anaemia is low (p=0,004) as opposed to those treated with DAA in combination with RBV.

4.3. Estimation of the action of DAA treatment on liver stiffness in patients with HCV cirrhosis

APRI and Fib-4 scores are considered markers of liver stiffness evaluation [13]. The mean APRI score at initiation of antiviral therapy was 2.6 ± 1.6 in L_0 and 2.6 ± 1.8 for L_1. The mean APRI score at 6 months after treatment decreased significantly in both batches. Thus, 6 months after treatment the average APRI score in L_0 was 0.6 ± 0.2, and in L_1 – 0.6 ± 0.3.

In our study, we correlated the APRI and Fibroscan scores at the start of antiviral therapy and 6 months after treatment, and we noted that at the start of antiviral therapy, the APRI score is in correlation with the Fibroscan values. However, by analysing the APRI at baseline and 6 months after treatment completion, a statistically significant decrease p <0.001 (table 4.4) is noted. Improvement in the APRI score after treatment with DAA is explained by normalization of liver

enzymes and increased platelet count) [14]. Similar results were noted for the Fib-4 score (table 4.4). If at the start of antiviral therapy 99(68.7%) patients had Fib-4 > 3.25, 6 months after treatment the number of patients with Fib-4 >3.25 reduced to 64 (44.4%) patients ($p < 0.001$) (table 4.4). However, Fib-4 was closely correlated with Fibroscan results for scores < 1.45 or > 3.25.

Table 4.4. **Dynamics of APRI and FIB-4 score at initiation and after antiviral treatment**

Score value	**L_0 (n = 72)**		**L_1 (n = 72)**		**95%CI,P_0**	**95%CI,P_1**
	Initiation	**6 months after treatment**	**Initiation**	**6 months after treatment**		
APRI						
< 1	13 (18%)	63 (87,5%)	20 (27,7%)	63 (87,5%)	69,5 (55,34-78,71) p< 0,0001	59,8 (45,01-70,5) p< 0,0001
1 – 2	24 (33,3%)	9 (12,5%)	24 (33,3%)	8 (11,1%)	20,8 (7,09-33,65) p=0,0031	22,2 (8,68-34,87) p=0,0014
> 2	35 (48,6%)	0	28 (38,8%)	1 (1,3%)	48,6 (36,32-59,91) p< 0,0001	37,5(25,47-49,09) p< 0,0001
Fib-4						
<1,45	4 (5,5%)	7 (9,7%)	4 (5,5%)	11 (15,2%)	4,2 (-5,07-13,81) p=0,3433	9,7 (-0,50-20,27) p= 0,0569
1,45–3,25	16 (22,2%)	26 (36,1%)	21 (29,1%)	36 (50%)	13,9 (-0,95-27,96) p=0,0674	20,9 (4,92-35,44) p=0,0106
>3,25	52 (72,2%)	39 (54,1%)	47 (65,2%)	25 (34,7%)	18,1 (2,34-32,65) p=0,0249	30,5(14,21-44,60) p= 0,0003

The results of our study showed an improvement in liver stiffness at the end of treatment and 6 months after DAA therapy with/without RBV (table 4.5). At initiation of F3 fibrosis therapy, 8.3% (12 /144) patients and F4 were present in 91.6% (132 /144) patients. At the end of treatment and 6 months after finishing therapy, F3 was recorded in 21.5% (31/144) and 31.9% (46/144) patients, and F4 in 78.4%, respectively% (113/144) patients and 68% (98 /144) patients, respectively. A decrease in the mean LSVwas also noted: from 29,5±13,1kPa in L_0 and 25,5±9,0 kPa in L_1, from, at 22,5±9,5kPa in L_0 and 21,1±7,7kPa in L_1 6 months after antiviral therapy. There were no significant associations between fibrosis regression and gender, patient age or regimen followed.

Table 4.5. **Evolution of liver stiffness at initiation and post-treatment in patients with liver cirrhosis included in the study**

Period	L_0 n=72				L_1 n=72			
	Average LSV kPa	F3 12,5-13,9kPa	F4 14-20kPa	F4 >20kPa	Average LSV kPa	F3 12,5-13,9kPa	F4 14-20kPa	F4 >20kPa
At initiation of treatment	29,5±13,1	10 (13,8%)	17 (23,6%)	45 (62,5%)	25,5±9,0	2 (92,7%)	25 (34,7%)	45 (62,5%)
At the end of treatment	25,1±10,0	15 (20,8%)	18 (25%)	39 954,1%)	22,7±8,5	16 (22,2%)	21 (29,1%)	35 (48,6%)
6 Months after treatment	22,5±9,5	25 (64,7%)	15 (20,8%)	32 (44,4%)	21,1±7,7	21 (29,1%)	21 (29,1%)	30 (41,6%)

4.4. Assessment of response to DAA treatment in HCV cirrhosis

Virologic response to DAA, with or without undetectable RBV and HCV RNA at the end of therapy, had 142 patients (98.6%), 6 months after DAA therapy was completed, SVR achieved 136 (94.4%) patients, 12 months after completion of antiviral therapy with DAA 134 (93.05%) patients had undetectable HCV RNA PCR (figure 4.3.).

Lack of response to treatment presented 10 (6.9%) patients: 2 (1.3%) patients (L_0) had HCV RNA positive PCR at end of treatment, and, at 6 months after completion of antiviral therapy 6 (4.1%)patients showed positive HCV RNA and 2 (1.3%) patients had HCV RNA PCR quantitatively positive 12 months after DAA treatment was completed (Figure 4.4). It was also found that 8/10 (80%) patients with treatment failure experienced an advanced degree of fibrosis (>20 kPa, which is, metavir scale) and significant thrombocytopenia (55 – 80 x 10^9/l). It was noted that of the 11 (7.6%) patients who had received prior standard antiviral combination therapy alpha-PEG –INF and RBV, 2 (18.1%)%) patients have also experienced failure in this therapy.

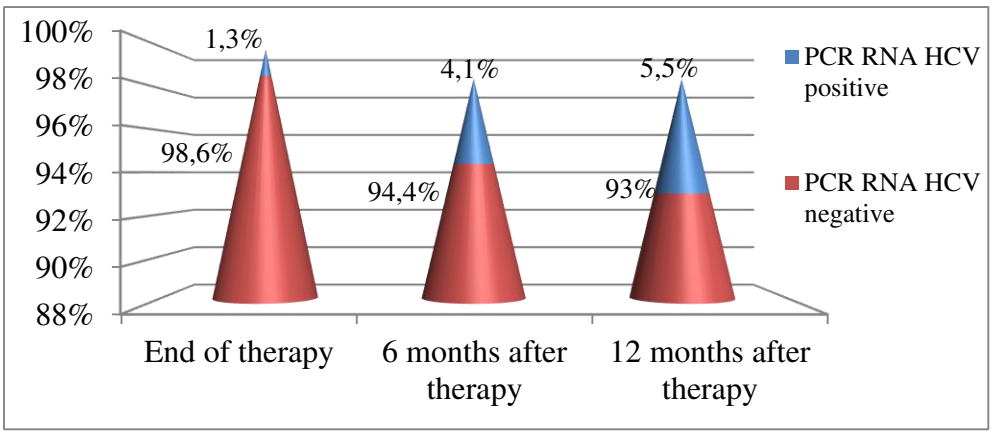

Figure 4.3. **Response to DAA treatment in HCV cirrhosis, %**

To determine the relative risk (RR) of treatment failure in patients on the SOF+LDV/DCV regimen compared to those treated with SOF+LDV/DCV+RBV, and, I calculated a number of statistical indices. Thus, we obtained the following results: REE= 4/72=0,05; REC= 6/72= 0,08; RR = 0,05/0,08 = 0,62; RRR = 1-0,62= 0,38; RAR = |0,05-0,08| =

0,03; PEC = 6/66 = 0,09; PEE = 4/68 = 0,05; PR = 0,05/0,09 = 0,65; 95%CI = 0,64(0,17-2,40), NNT= 36, p<0,001. The value of RR= 0,62, PR= 0,65 and 95% CI= 0,64(0,17-2,40), p<0,001 indicates a positive association between SOF+LDV/DCV treatment and SVR obtaining, being considered a moderate protection factor, and the risk that patients on the RBV-free regimen do not respond to treatment is small. After one month of treatment, the RBV dose was reduced by 200mg (1 tablet) in 14 (19.4%) patients and 8 (11.1%) in RBV treatment discontinued. Thus, the full dose of RBV by the end of treatment followed 36 (50%) patients.

Following completion of DAA therapy with/without RBV, 7 (4.8%) patients were diagnosed with HCC: 5 (6.9%) patients in L_0, 2 (2.7%) patients in L_1. Of them, treatment failure had 2 (2.7%) patients, both of whom were L_0. Thus, to assess the relative risk of developing CHC in patients treated with SOF+LDV/DCV without RBV, statistical indices were calculated: REE= 42/72=0,02; REC= 5/72= 0,06; RR = 0,02/0,06 = 0,33; RRR = 1-0,33= 0,67; RAR = |0,02-0,06| = 0,04; PEC = 5/67 = 0,07; PEE = 2/70 = 0,02; PR = 0,02/0,07 = 0,28; 95%CI = 0,39(0,07-2,04), NNT= 24, p<0,001. Considering that, RR=0,33, PR= 0,28 and CI 0,39(0,07-2,04), p<0,001, are considered strong protective factors, and the risk that patients treated with SOF+LDV/DCV for 24 weeks to develop HCC is small. After completion of antiviral therapy, 7(4.8%) deaths were recorded: 6 (85.7%) with HCC, 1 (14.2%) patient two months after finishing treatment, and, diagnosed with pancreatic head cancer.

4.6. Analysis of DAA therapy adverse events in patients with HCV cirrhosis included in the study

There are few studies describing the adverse effects (AE) associated with DAA therapy in patients with cirrhosis [10;15]. Overall, treatment was well tolerated in both batches. However, during treatment with DAA in combination with RBV a higher number of patients – 22 (30.5%) reported at least one minor adverse reaction (table 4.6).

Table 4.6. **Adverse events registered in patients throughout the study**

Adverse reactions	**L_0 n=72**	**L_1 n=72**	**RR_{0-1}**	**95% CI, p**
Fatigue, n(%)	22 (30,5%)	14 (19,4%)	0,63	0,54(0,25-1,18), p=0,12
Headache,n (%)	22 (30,5%)	7 (9,7%)	0,31	0,24(0,09-0,61), p<0,01
Nausea, n(%)	10 (13,8%)	4 (5,5%)	0,4	0,36(1,1-1,22), p=0,10
Vomiting, n(%)	4 (5,5%)	2 (2,7%)	0,5	0,48(0,09- 2,73), p=0,41
Diarrhoea, n(%)	2 (2,7%)	5 (6,9%)	2,5	2,61(0,5-13,92), p=0,26
Insomnia, n(%)	15 (20,8%)	7 (9,7%)	0,46	0,4(0,15-1,07), p=0,06
Eruptions, n(%)	0	2 (2,7%)	5	5,14(0,24-109), p=0,293
Dysrhythmia	6 (8,3%)	0	0,07	0,07(0,003-1,3), p=0,072
Anaemia, n(%)	12 (16,6%)	1 (1,3%)	0,08	0,07(0,01-0,55), p<0,001

Thus, patients in L_0 experienced more frequent adverse reactions compared to L_1 (table 4.7). The most commonly reported EAs in our study were: asthenia – 36 (25%), headache – 29 (20.1%)patients, insomnia – 22 (15.2%), nausea – 14 (9.7%), anaemia (9%), irritability (7.6%). EA such as: diarrhoea (4.8%), vomiting (4.1%), rhythm disturbances (4.1%), rash (1.3%) were low in frequency.

RBV-induced anemia may be moderate/severe, requiring dose adjustment or cancellation of therapy with this preparation. To estimate the relative risk of progression of anaemia with Hb values <109g/l in patients treated with SOF+LDV/DCV without RBV compared to patients who followed the DAA regimen associated with RBV, we calculated the statistical indices: REE= 1/72=0,01; REC= 12/72= 0,16; RR = 0,01/0,16 = 0,06; RRR = 1-0,06= 0,94; RAR = |0,01-0,16| = 0,15; PEC = 12/60 = 0,2; PEE = 1/71 = 0,01; PR = 0,01/0,2 = 0,05; 95%CI = 0,07(0,01-0,55), NNT=6, p<0,001.

Thus, starting from the fact that RR= 0,06, PR= 0,05, CI 0,07(0,01-0,55), p<0,001, are considered strong protective factors, the risk that in patients treated with SOF+LDV/DCV for 24 weeks to progress anemia is very small compared to those treated with SOF+LDV/DCV and RBV. Major adverse reactions, which would require discontinuation of DAA, have not been recorded and the EA present did not affect the response to antiviral therapy.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

General conclusions

1. Following the analysis we found that the average age of patients with viral cirrhosis C in the study was 59.6±7.2 years, male sex constituted 59% (85/144) patients, and, 63.8% (92/144) cases had HCV infection duration less than 10 years from the time of detection, previous antiviral treatment experience had 12.5%(18/144) patients, and, genotype 1 was present in 93.7% (135/144) cases.
2. When initiating SOF+LDV/DCV therapy with/without RBV, in patients with viral cirrhosis C, F3 stage fibrosis was recorded in 8.3% (12/144) patients, F4 in 91.6% (132/144) patients, after the Child Pugh staging, patients in stages B and C constituted 54.1% (78/144) cases, extrahepatic manifestations caused by HCV infection pezentat 44.4%(64/72) patients.
3. Sustained virologic response to SOF+LDV/DCV with/without RBV was achieved in 93.05% of patients and lack of response to treatment was recorded in 6.9% patients, 80% of them showing an advanced degree of fibrosis (>20 kPa, Metavir) and significant thrombocytopenia (55 – 80 x 10^9/l).
4. The results of our study showed an improvement in both liver fibrosis values (appreciated by fibroscan) and APRI and Fib-4 scores at the end of treatment and 6 months after SOF+ therapyLDV/DCV with/without RBV, with no significant association between fibrosis regression and gender, patient age or regimen followed.
5. The combination between SOF+LDV/DCV with/without RBV obviously influenced hepatocytolysis syndrome, thus more than 91% of patients had normal end-of-treatment transaminases in both batchesDupă terapia cu SOF+LDV/DCV cu/fără RBV, 7(4,8%) patients were diagnosed with HCC, 6 died every 2-16 months, 1 death – head cancer of the pancreas.
6. Treatment with SOF+LDV/DCV with/without RBV has beneficially influenced the evolution of haematological parameters in both batches, regardless of the scheme

followed, and patients in the stages of Child-Pugh B and C experienced a slower increase in platelet count.

7. Treatment was overall well tolerated without the need to discontinue SOF+LDV/DCV and most adverse reactions were experienced by patients receiving combination therapy with RBV(L_0), respectively, therefore, dose adjustment and/or cancellation of therapy with this preparation was necessary in 36 (50%) patients.

Practical recommendations

1. The combination of SOF +LDV/DCV with or without RBV is effective in the treatment of cirrhosis of the liver with HCV with a high rate of SVR, and, it is therefore recommended as a first-line antiviral treatment in patients with viral hepatitis C cirrhosis.
2. Combinations with DAA without IFN are the best and reasonable option for patients with advanced cirrhosis, with the advantages of: possibility of oral administration, short duration of treatment, and, high SVR and minimal side effects, decreased liver stiffness (fibrosis) even without SVR, improved liver function
3. Before deciding on a particular DAA regimen, several factors that could influence this therapy should be considered: HCV genotyping, severity of liver disease, and, presence of comorbidities and extrahepatic manifestations, co-infections (HBV-HCV, HIV-HCV), potential drug-drug interactions, analysis of renal function (estimated glomerular filtration rate), presence of contraindications.
4. Patients with relapse or no response after previous DAA treatments may be associated with resistance to treatment, so resistance is recommended to select an effective DAA combination.
5. Treatment of chronic HCV infection is a priority for patients with severe hepatic fibrosis and cirrhosis because of the increased risk of decompensation and development of HCC.
6. RBV-induced anemia may be moderate/severe, requiring dose adjustment or cancellation of therapy with this preparation, and patients with decompensated cirrhosis, RBV is suggested to be administered at an initial dose of 600 mg/day and increased according to patient tolerability
7. The chance of achieving SVR with DAA in patients with compensated cirrhosis (Child-Pugh A) is comparable to non-cirrhotic patients, but still, there is a risk of acute decompensation and hepatic failure during and after treatment, therefore patients with advanced and decompensated cirrhosis should be treated and monitored in centres with experience in the field, and if necessary, the possibility of a liver transplant should be evaluated.
8. Chronic HCV infection can also induce systemic disorders such as diabetes and chronic kidney disease, therefore, these patients require anti-HCV investigation to detect new cases of HCV infection and to initiate antiviral therapy.

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  - ✓ **national**

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22. **Avricenco M.** Non-invasive evaluation of liver fibrosis as a result of direct-acting antiviral treatment in viral cirrhosis C: the experience of a center. *The 37th Balkan Medical Week"The perspectives of Balkan Medicine in post COVID-19 era"*. Chișinău, 7-9 June 2023.

- **Participation with posters in scientific fora:**

Avricenco M., Rusu I., Holban T. Effect of Direct Acting Antivirals with/without Ribavirin on hematological parameters in cirrhosis with HCV. *19-th edition of The Scientific days of the National Institute for Infectious Diseases "Prof.Dr. Matei Balş"*. Bucharest, Romania, 14-17 September 2023.

ABBREVIATIONS

Ab	Antibodies
AE	Adverse effects
AF	Alkaline phosphatase
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
DNA	Deoxyribonucleic acid
HCC	Hepatocellular carcinoma
GGT	Gamma-glutamyltransferase
HIV	Human Immunodeficiency Virus
IFN	Interferon
LDV	Ledipasvir
LF	Liver fibrosis
LSV	Liver stiffness value
RBV	Ribavirin
RH	Liver stiffness
RNA	Ribonucleic acid
SVR	Sustained virologic response
SOF	Sofosbuvir
VHB	Viral hepatitis B
VHC	Viral hepatitis C
VHD	Viral hepatitis D

ADNOTARE

Avricenco Mariana. Eficacitatea terapeutică a preparatelor antivirale cu acțiune directă la pacienții cu ciroză hepatică prin virus hepatitic C.

Teză de doctor în științe medicale, Chișinău, 2023

Volumul și structura tezei: introducere, 4 capitole, sinteza rezultatelor obținute, concluzii și recomandări, bibliografie din 203 surse, 18 tabele, 16 figuri, 2 anexe, expuse pe 95 pagini. **Rezultatele cercetării** au fost publicate în 15 de lucrări științifice.

Cuvinte-cheie: ciroza hepatică, virus hepatitic C, antivirale cu acțiune directă, Ledipasvir, Daclatasvir, Sofosbuvir, Ribavirin.

Domeniul de cercetare: boli infecțioase, hepatologie

Scopul cercetării: Aprecierea eficacităţii tratamentului antiviral cu preparate antivirale cu acțiune directă la pacienţii cu ciroză hepatică (prin evaluarea parametrilor clinici, biochimici, imagistici și virusologici), pentru optimizarea supravegherii și implementării schemelor eficiente de tratament.

Obiectivele cercetării. Evaluarea datelor clinice, indicilor biochimici, virusologici și altor parametri paraclinici la bolnavii cu ciroză hepatică cu virus hepatitic C la inițierea tratamentului antiviral. Aprecierea eficienței schemelor de tratament antiviral: Sofosbuvir și Daclatasvir/Ledipasvir cu Ribavirin și Sofosbuvir și Daclatasvir/Ledipasvir fără Ribavirin la pacienții cu ciroză hepatică prin VHC prin evaluarea indicilor biochimici, hematologici și virusologici la 1,3, 6, 12 luni de la inițierea tratamentului antiviral. Evaluarea fibrozei hepatice apreciată prin Fibroscan la inițierea tratamentului și la 6,12 luni după tratament. Analiza reacțiilor adverse și a complicațiilor în timpul și după tratament antiviral la bolnavii cu ciroză prin HVC. Elaborarea propunerilor privind perfecționarea algoritmelor de tratament antiviral la pacienții cu ciroză pentru obţinerea unui răspuns virusologic susţinut.

Noutatea ştiinţifică: pentru prima dată în Republica Moldova, pacienții cu ciroză hepatică prin VHC au posibilitatea de a urma tratament antiviral Interferon-free. Astfel, fiind posibilă aprecierea eficienței tratamentului și monitorizarea parametrilor clinici, paraclinici și virusologici la acești pacienţi pentru a ameliora calitatea vieții pacienților și eliminarea definitivă a virusului hepatitic C.

Direcţii noi de cercetare: a fost evaluată eficacitatea terapiei cu preperate antivirale cu acține directă la pacienții cu ciroza hepatică cu VHC în diferite stadii evolutive, a fost apreciată evoluția fibrozei hepatice după terapia antivirală la această categorie de pacienți, a fost analizată evoluția maladiei după tratament, în vederea decompensării sau dezvoltării carcinomului hepatocelular.

Valoarea teoretică şi aplicativă: Valorificarea rezultatelor în practica medicală prin realizarea Programului Național de combatere a hepatitelor virale B, C și D pentru anii 2017-2021 va contribui la diminuarea morbidității cirozei hepatice prin HVC și carcinomului hepatocelular.

Implementarea rezultatelor ştiinţifice: materialele tezei au fost publicate sub formă de articole în diferite culegeri şi reviste, au fost raportate la diferite conferinţe ştiinţifice, au fost implementate în practica medicilor infecţioniști din întreaga republică, în procesul didactic al Catedrelor de Boli infecţioase, tropicale şi parazitologie medicală.

АННОТАЦИЯ

Авриченко Марьяна. Терапевтическая эффективность противовирусных препаратов прямого действия у больных циррозом печени, вызванным вирусом гепатита С.

Диссертация на соискание научной степени кандидата медицинских наук, Кишинев, 2023.

Объем и структура диссертации: введение, 4 главы, обобщение полученных результатов, выводы и рекомендации, библиография из 203 источников, 18 таблицы, 16 рисунков, 2 приложения, размещенные на 95 страницах.

Результаты исследования опубликованы в 15 научных статьях.

Ключевые слова: цирроз печени, вирус гепатита С, противовирусные препараты прямого действия, Ледипасвир, Даклатасвир, Софосбувир, Рибавирин.

Область исследования: инфекционные болезни, гепатология.

Цель исследования: Оценка эффективности противовирусного лечения противовирусными препаратами прямого действия у больных циррозом печени (путем оценки клинических, биохимических, вирусологических показателей и методов визуализации печени), для оптимизации наблюдения и реализации эффективных схем лечения.

Задачи исследования. Оценка клинических данных, биохимических, вирусологических показателей и других параклинических показателей у больных циррозом печени с вирусным гепатитом С (ВГС) в начале противовирусного лечения. Оценка эффективности схем противовирусного лечения: Софосбувир и Даклатасвир/Ледипасвир с Рибавирином и Софосбувир и Даклатасвир/Ледипасвир без Рибавирина у больных циррозом печени на фоне ВГС путем оценки биохимических, гематологических и вирусологических показателей через 1, 3, 6, 12 месяцев после начала лечения препаратами прямого действия. Оценка фиброза печени с помощью Fibroscan на исходном уровне и через 6,12 месяца после лечения. Анализ побочных реакций и осложнений во время и после противовирусного лечения у пациентов с циррозом печени вызванным ВГС. Разработка предложений по совершенствованию алгоритмов противовирусной терапии больных циррозом печени для получения устойчивого вирусологического ответа.

Научная новизна: впервые в Республике Молдова у пациентов с циррозом печени, вызванным ВГС, появилась возможность пройти безинтерфероновое противовирусное лечение. Таким образом, можно оценить эффективность лечения и контролировать клинические, параклинические и вирусологические показатели у этих больных с целью улучшения качества жизни больных и окончательной элиминации вируса гепатита С.

Новые направления исследований: роведена оценка эффективности терапии противовирусными препаратами прямого действия у больных циррозом печени с ВГС на разных стадиях эволюции, оценена эволюция фиброза печени после противовирусной терапии у данной категории больных, проанализирована эволюция заболевания после лечения, с целью компенсации или развития гепатоцеллюлярной карциномы.

Теоретическая и практическая значимость: Использование результатов в медицинской практике путем реализации Национальной программы по борьбе с вирусными гепатитами В, С и D на 2017-2021 годы будет способствовать снижению заболеваемости циррозом печени ВГС и гепатоцеллюлярной карциномой.

Внедрение научных результатов: материалы диссертации публиковались в виде статей в различных сборниках и журналах, докладывались на различных научных конференциях, внедрялись в практику врачей-инфекционистов всей республики, в учебно-методический процесс Кафедр инфекционных, тропических болезней и паразитологии.

ANNOTATION

Avricenco Mariana. Therapeutic efficacy of direct-acting antivirals in liver cirrhosis with hepatitis C virus.

The PhD thesis in medical sciences titled. Chisinau, 2023.

The volume and structure of the thesis: introduction, 4 chapters, the main conclusions and recommendations, bibliography of 203 sources, the main body of the text 95, 18 tables, 16 figures, 2 appendix.

The results were published in 15 scientific papers.

Keywords: liver cirrhosis, hepatitis C virus, direct-acting antivirals, Ledipasvir, Daclatasvir, Sofosbuvir, Ribavirin.

Field of the study: infection disease, hepatology.

Purpose of the thesis: Assessing the effectiveness of antiviral treatment with direct-acting antiviral preparations in patients with liver cirrhosis (by evaluating clinical, biochemical, imaging and virological parameters), to optimize the supervision and implementation of efficient treatment regimens.

The study objectives: Evaluation of clinical data, biochemical, virological indices and other paraclinical parameters in patients with liver cirrhosis with hepatitis C virus at the initiation of antiviral treatment. Assessment of the effectiveness of antiviral treatment regimens: Sofosbuvir and Daclatasvir/Ledipasvir with Ribavirin and Sofosbuvir and Daclatasvir/Ledipasvir without Ribavirin in patients with liver cirrhosis due to HCV by evaluating biochemical, hematological and virological indices at 1, 3, 6, 12 months after initiation of treatment antiviral. Fibroscan assessment of liver fibrosis at baseline and 6.12 months post-treatment. Analysis of adverse reactions and complications during and after antiviral treatment in patients with HVC cirrhosis. Elaboration of proposals regarding the improvement of antiviral treatment algorithms in patients with cirrhosis to obtain a sustained virological response.

Scientific novelty: for the first time in the Republic of Moldova, patients with liver cirrhosis due to HCV have the opportunity to undergo Interferon-free antiviral treatment. Thus, it is possible to assess the effectiveness of the treatment and monitor the clinical, paraclinical and virological parameters in these patients in order to improve the quality of life of the patients and the definitive elimination of the hepatitis C virus.

New research directions: the effectiveness of therapy with direct-acting antiviral preparations in patients with liver cirrhosis with HCV in different evolutionary stages was evaluated, the evolution of liver fibrosis after antiviral therapy in this category of patients was assessed, the evolution of the disease after treatment was analyzed, in order to compensate or the development of hepatocellular carcinoma.

Theoretical and applicative value: Capitalizing on the results in medical practice through the implementation of the National Program to combat viral hepatitis B, C and D for the years 2017-2021 will contribute to reducing the morbidity of liver cirrhosis through HCV and hepatocellular carcinoma.

Implementation of the scientific results: the thesis materials were published in the form of articles in various collections and magazines, were reported at various scientific conferences, were implemented in the practice of infectious disease doctors throughout the republic, in the didactic process of the Departments of Infectious, Tropical Diseases and Medical Parasitology.

AVRICENCO MARIANA

THERAPEUTIC EFFICACY OF DIRECT-ACTING ANTIVIRAL PREPARATIONS IN PATIENTS WITH HEPATIC CIRRHOSIS BY HEPATITIS C VIRUS

321.09 – INFECTIOUS, TROPICAL DISEASES AND MEDICAL PARASITOLOGY

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