OH&RM ONE HEALTH & RISK MANAGEMENT

VOL. 1, ISSUE 1
2020

ARTICOLE DE CERCETARE – НАУЧНЫЕ СТАТЬИ – RESEARCH ARTICLES – ARTICLES DE RECHERCHE

MEDICAL SCIENCES

OPEN ACCESS

THE EFFICACY OF DIRECT-ACTING ANTIVIRAL THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

Irina RUSU[1], Liliana HODOROGEA[2], Tiberiu HOLBAN[1]

[1]Department of Infectious Tropical Diseases and Medical Parasitology, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2]*Toma Ciorba* Clinical Hospital of Infectious Diseases

Corresponding author: Irina Russu, e-mail: irina.rusu@usmf.md

DOI: 10.5281/zenodo.3700945 UDC: 616.36-002.2-085.281.8

Key words: *chronic HCV, treatment, sofosbuvir, ledipasvir, daclatasvir.*

Introduction*. Viral hepatitis C (HCV) is a significant global health problem. The risk of developing chronic HCV is up to 80% of patients, of whom 10-20% can develop liver cirrhosis or hepatocellular carcinoma which can lead to death. Treatment with direct-acting antiviral agents (DAAs) contributes to a sustained virological response (SVR) in 97-99% of cases.*
Material and methods. *The study was conducted on 206 patients with chronic HCV who underwent two generic antiviral agent therapies: group I (103) – Sofosbuvir 400 mg + Ledipasvir 80 mg, whereas group II (103) – Sofosbuvir 400 mg + Daclatasvir 60 mg orally, once a day, for 12 weeks. The assessment of hepatitis C virus RNA and genotype, as well as the degree of hepatic fibrosis by Fibroscan, biochemical and complete blood count (CBC) indices were carried out.*
Results. *The study results showed high efficacy of the generic DAAs treatment in patients with chronic HCV over 12 weeks. The SVR rate made up 90.3% in Sofosbuvir + Ledipasvir therapy and 86.4% – in Sofosbuvir + Daclatasvir. Similar treatment response was recorded in naive patients and those who previously underwent unsuccessful treatment with Pegylated Interferon and Ribavirin. The DAAs treatment showed the following minor adverse reactions: asthenia, headache, sleep* disorder, *and nausea, which did not require treatment discontinuation.*
Conclusions. *The 12-week course of DAAs therapy exhibited high SVR rate in both chronic HCV naive patients and those previously treated with Pegylated Interferon and Ribavirin.*

Cuvinte cheie: *HVC cronică, tratament, sofosbuvir, ledipasvir, daclatasvir.*

EFICACITATEA TRATAMENTULUI CU PREPARATE ANTIVIRALE CU ACȚIUNE DIRECTĂ LA PACIENȚII CU HEPATITĂ VIRALĂ C CRONICĂ
Introducere. *Hepatita virală C (HVC) este o maladie cu un impact semnificativ la nivel mondial. Riscul de cronicizare a HVC este de până la 80% dintre pacienții diagnosticați cu această maladie iar 10-20% dintre aceștea dezvoltă ciroza hepatică, carcinomul hepatocelular sau poate surveni decesul. Tratamentul cu preparatele antivirale, cu acțiune directă (PAAD) contribuie la obținerea răspunsului virusologic susținut (RVS) în 97-99% de cazuri morbide.*
Material și metode. *Studiul științific a inclus 206 de pacienți cu HVC cronică, care au primit două scheme de preparate antivirale generice: I lot (103) – Sofosbuvir, 400 mg + Ledipasvir, 80 mg, însă cei din lotul II (103) – Sofosbuvir, 400 mg + Daclatasvir, 60 mg per os, o dată în zi, timp de 12 săptămâni. Au fost evaluate ARN-VHC, genotipul virusului C, gradul de fibroză hepatică prin Fibroscan, indicii biochimici și hemoleucograma.*
Rezultate. *Rezultatele studiului au demonstrat randamentul ridicat al tratamentului cu PAAD, efectuat pe parcursul a 12 săptămâni pacienților cu HVC cronică. Rata RVS a fost de 90,3% – în cazul tratamentului cu Sofosbuvir + Ledipasvir și 86,4% – cu Sofosbuvir + Daclatasvir. Răspunsul la tratament a fost similar la pacienții naivi și la cei tratați anterior cu Interferon pegilat și Ribavirină* – fără succes. Tratamentul antiviral cu PAAD a înregistrat reacții adverse minore*: astenie, cefalee, dereglarea somnului, grețuri, care nu au pretins întreruperea tratamentului.*
Concluzii. *Tratamentul cu PAAD, administrat timp de 12 săptămâni, a atins RVS ridicat atât la pacienții cu HVC cronică naivi, cât și cei tratați anterior cu PEG-INF și Ribavirină.*

INTRODUCTION

Viral hepatitis C is a significant global health problem. According to the World Health Organization data, 71 million people with hepatitis C virus are estimated worldwide, accounting for 1.2% of the world population. Approximately 399 000 people die annually from HCV-related complications, which include cirrhosis, hepatocellular carcinoma and liver failure (1). Annually, 3-4 million new cases of HCV occur, including 1300-1400 cases in the Republic of Moldova. The prevalence of HCV infection considerably ranges from a very low level (0.05-0.1%) in the UK and Scandinavian countries, to the highest level in Asia and Egypt (>5-10%) (2, 3). The HCV incidence in the Republic of Moldova was estimated at 4.5-5.0% in the overall population with the prevalence of genotype 1b, accounting for 98% (4, 5). People aged between 30-49 are predominantly affected, men being more common than women. The risk of chronic HCV infection is very high. Untreated acute hepatitis C can develop into a chronic form in up to 80% of people, of whom 10-20% develop liver cirrhosis over 20 years, followed by decompensated liver disease, hepatocellular carcinoma and even death (6). Once the onset of chronic infection occurs, the rate of spontaneous recovery is significantly reduced. Chronic HCV in most patients develops asymptomatically or nonspecifically, as long as no cirrhosis is present (7, 8, 9). As a result, HVC is often diagnosed accidentally or remains undiagnosed. It has been estimated that only 30-50% of HCV people are aware of their disease. Therefore, the lack of an effective vaccine, that would contribute to a decrease in HCV morbidity rate and subsequent consequences, requires the development of early diagnostic measures and treatment in order to eradicate the infection. Once HCV is identified, the assessment of the therapeutic success is possible by dosing the amount of RNA-HCV and the sustained virologic response. Over time, the SVR rate increased from 5-20% in interferon monotherapy, to 40-50% in combined IFN + Ribavirin treatment. Currently, the SVR rate accounts for 95-100% in cases treated with DAAs (10). The major advantage in the treatment of chronic HVC is the opportunity to administer DAAs – NS3/4A protease inhibitors, NS5B polymerases and NS5A replication complex.

These drugs require oral short-term administration, having a high SVR rate and minimal side effects. The purpose of antiviral treatment is to definitely eliminate the virus and get negative RNA-HCV at a 6-month interval after treatment completion by obtaining a SVR. The literature data confirm that over 99% of patients who have obtained a SVR remain HCV-negative over 4-5 years after the treatment was discontinued, with no signs of hepatitis. The long-term SVR showed a 75% reduction of hepatocellular carcinoma cases, decompensated and compensated cirrhosis and death over the next 15 years (11). It has recently been shown that patients with SVR have a similar quality-of-life status as the overall population (7), whereas those with compensated and decompensated cirrhosis do not require liver transplant (9, 12).

MATERIAL AND METHODS

The purpose of the research: to study the effectiveness of Interferon-free treatment in patients with chronic HCV infection.

The research objectives: to assess the efficacy of the DAAs therapy: Sofosbuvir + Ledipasvir and Sofosbuvir + Daclatasvir in patients with chronic HCV infection. To study the evolution of clinical, biochemical, virological and paraclinical indices in patients with chronic HCV infection both at the beginning and end of treatment, as well as over 24 weeks after treatment. To analyze the adverse reactions and complications that can occur after the DAAs treatment.

The research hypothesis: the emergence of new therapeutic opportunities allows each patient diagnosed with chronic HCV infection to receive antiviral treatment. DAAs have shown a higher efficacy and tolerability, as well as shorter treatment duration compared to interferon therapy. A combination of at least two of the three major classes of drugs results in SVR≥95% in just 8-12 weeks of treatment. Patients who were treated for HCV infection exhibited a better quality of life, as well as a reduced risk of developing liver cirrhosis, hepatocellular carcinoma and death related to liver and extrahepatic diseases.

The study was conducted on 206 adult patients with chronic HCV who initiated DAAs treatment within the PHMI *Toma Ciorba* Clinical Hospital of Infectious Diseases during 2017-2018.

The inclusion criteria were as follows: patients ≥18 years of age, with chronic HCV confirmed by anti-HCV, anti-HCV IgM, RNA-HCV>25 IU/mL, with F0-F3 fibrosis of all genotypes, naive patients

or patients subjected to a previous unsuccessful antiviral treatment.

The exclusion criteria were as follows: pregnant and nursing patients, HIV-HBV-HVD co-infection, liver cirrhosis, F4 fibrosis, hepatocellular carcinoma or other malignancies.

The patients included in the study were randomly divided into two groups of 103 patients each. The study groups were comparable in terms of age and gender. The degree of liver fibrosis was assessed via Fibroscan. Patients with F0, F1, F2 and F3 fibrosis were selected. Chronic HCV patients were initially diagnosed by detecting anti-HCV via the immuno-enzymatic assay and confirmed by ARN-HCV testing. Serum levels of ARN-HCV were determined by real-time polymerase chain reaction (PCR) with a low detection limit <25 IU/mL. Prior to treatment initiation, the HCV genotype was assessed (1a, 1b, 2, 3 and 4). Anamnestic, epidemiological, clinical, biochemical, serological and molecular biology data were collected in all patients at the beginning, over 4 and 12 weeks of treatment, as well as over 24 weeks after the antiviral treatment completion.

The 1st group included 103 patients treated with Twinvir (Sofosbuvir 400 mg/Ledipasvir 90 mg), (manufacturer: Incepta Pharmaceuticals, Bangladesh), one pill orally, once daily, for 12 weeks.

The 2nd group included 103 patients, undergoing treatment with Nucleobuvir (Sofosbuvir 400 mg) – one pill, and Daclavirdin (Daclatasvir 60 mg) – one pill orally (manufacturer: EVAPHARMA, Egypt), for 12 weeks.

All patients signed an informed consent. The study protocol was positively endorsed by the Research Ethics Committee of *Nicolae Testemitanu* SUMPh (meeting no. 75 of 26.04.2017).

RESULTS

Of the 206 patients with chronic HCV included in the study, there were 104 (50.5%) men and 102 (49.5%) women. There were patients aged between 20-79 years old, mean age 50.13±1.28 years. Patients aged 41-50 years – 55 (26.7%) were the most affected, as well as patients aged 51-60 years – 63 (30.6%). There were 19 (9.2%) patients aged 20-30, 33 (16%) patients aged 31-40 years, 30 (14.5%) patients aged 61-70 years, and 6 (2.9%) patients aged 71-80 years. More than half of the patients had concomitant digestive diseases or extrahepatic manifestations. The results were similar in both research groups. Most patients were naive, whereas 14 (13.6%) patients from group I and 11 (10.7%) patients from group II previously administered antivirals with Interferon, Ribavirin, Boceprevir or Telaprevir, but unsuccessfully. Of the total number of patients, 174 (84.4%) were infected with genotype 1. Of them, 170 cases were detected with 1b GT, 2 patients with GT 1a and mixed GT (1a+1b) each, 2 (1%) patients – genotype 2, 10 (4.9%) patients – genotype 3, of whom 6 – genotype 3a and 2 patients had mixed genotypes (3a+ 3b) and (3a+1b) each, one patient (0.5%) – genotype 4+1b. The only diagnostic tests available in the Republic of Moldova were for genotypes 1-4. Genotypes 5, 6 and 7 have remained unidentified. Therefore, 19 (9.2%) patients with detectable quantitative HCV RNA have not been assessed for genotype (tab. 1).

FibroScan elastometry assessment or elastography detected minor F0-F1 fibrosis in 70 (34%) patients, moderate fibrosis (F2) in 55 (26.7%) cases and advanced fibrosis (F3) in 81 (39.3%) cases. Patients of group I more frequently exhibited minor fibrosis – in 52 (50.5%) cases, and group II had predominantly advanced fibrosis in 58 (56.3%) cases. At the beginning of antiviral treatment, the level of HCV viremia ranged from 2 168 to 64 402 936 copies/mL (mean value – 6 413 266 ± 776 462 copies/mL) and did not differ significantly in both groups (tab. 1).

At least one gastrointestinal disease, such as chronic pancreatitis, chronic cholecystitis or chronic gastroduodenopathy was found in 64 (62.1%) patients from group I and in 60 (58.2%) patients from group II.

Concomitant chronic hepatitis C virus infection with diabetes were found in 62 (30.1%) patients, with hypertensive disease – in 63 (30.6%), ischemic heart disease – in 27 (13.1%), autoimmune thyroiditis – 18 (8.7%), and vasculitis – 20 (9.7%), which could be extrahepatic manifestations of HCV, due to unknown disease onset (tab. 2).

Patients with extrahepatic manifestations were older (55.86±0.97 years) than those without manifestations (45.08±1.07 years) ($p<0.001$). Patients without extrahepatic manifestations exhibited a short-term disease from the time of detection (9.52±0.58 years), compared to those who had extrahepatic manifestations (11.54±

0.63 years), (p<0.05). There were no contraindications for DAAs, compared to Interferon treatment, in 9 (8.73%) patients from group I and in 6 (5.82%) patients from group II, who exhibited extrahepatic manifestations, as well as cancer remission.

Table 1. General characteristics of chronic HCV patient groups at the initiation of antiviral treatment.

Indices	Lot SOF+LDV (n=103)	Lot SOF+DCV (n=103)	OR 95% CI, P
Age, years	50.03±1.29	50.24±1.28	>0.05
Males, n/(%)	51 (49.5)	53 (51.4)	0.93 (0.54-1.60), >0.05
Females, n/(%)	52 (50.5)	50 (48.6)	0.78 (0.63-1.87), >0.05
Gastrointestinal comorbidities, n/(%)	64 (62.1)	60 (58.2)	1.18 (0.67-2.06), >0.05
Extrahepatic manifestations, n/(%)	56 (54.3)	60 (58.21)	0.85 (0.49-1.48), >0.05
Previous antiviral treatment, n/(%)	14 (13.6)	11 (10.7)	1.32(0.57-3.05), >0.05
Genotype, n/(%)			
1b	98 (95.1)	72 (69.9)	8.43 (3.13-22.76), <0.001
2	1 (0.97)	1 (0.97)	
3	0	10 (9.7)	
4	0	1 (0.97)	
Mixed	0	4 (3.88)	
Unidentified	4 (3.88)	15 (14.5)	0.24 (0.08-0.74), <0.05
Fibrosis staging, n/(%)			
F0-F1	52 (50.5)	18 (17.5)	4.81 (2.54-9.12), <0.001
F2	28 (27.2)	27 (26.2)	1.05 (0.57-1.94), >0.05
F3	23 (22.3)	58 (56.3)	0.22 (0.12-0.41), <0.001
ARN-VHC, copies /mL, mean value	6.231.148± 745.259	6.595.385± 1.450.617	>0.05

Table 2. Comorbidities of patients with chronic HCV at the initiation of antiviral treatment.

Comorbidities	Lot SOF+LDV (n=103)	Lot SOF+DCV (n=103)	OR 95% CI, P
Chronic pancreatitis, n/(%)	23 (22.33)	26 (25.24)	1.17 (0.61-2.23), >0.05
Chronic cholecystitis, n/(%)	31 (30.09)	26 (25.24)	0.78 (0.42-1.44), >0.05
Chronic gastroduodenopathy, n/(%)	26 (25.24)	25 (24.27)	0.95 (0.50-1.78), >0.05
Diabetes mellitus, n/(%)	32 (31.06)	30 (29.12)	0.91 (0.50-1.65), >0.05
Hypertensive disease, n/(%)	22 (21.35)	41 (39.8)	2.43 (1.32-4.50), <0.01
Cardiomyopathy, n/(%)	17 (16.5)	10 (9.7)	0.54 (0.24-1.25), >0.05
Tumors, n/(%)	9 (8.73)	6 (5.82)	0.65 (0.22-1.88), >0.05
Obesity, n/(%)	11 (10.68)	13 (12.62)	1.21 (0.51-2.83), >0.05
Autoimmune thyroiditis, n/(%)	9 (8.73)	9 (8.73)	1.0 (0.38-2.63), >0.05
Vasculitis, n/(%)	9 (8.73)	11 (10.68)	1.25 (0.49-3.15), >0.05

The DAAs treatment showed a good biochemical response even from the first month of treatment. There was a significant ALAT decrease in both groups, thus over 4 weeks of treatment, the mean ALAT values showed decreasing rate of 3.47 times in group I and 2.81 times in group II, which reached the normal indices and maintained during the treatment and after its completion (p<0.001) (fig. 1).

Virologic response over 12 weeks after the treatment was recorded in 95 (92.2%) patients treated with SOF+LDV; in 90 (87.4%) patients with SOF+DCV, RNA-HCV it was undetectable. Virologic failure at the end of treatment was recorded in 8 (7.8%) patients from group I and in 13 (12.6%) from group II.

Over 24 weeks after antiviral treatment completion, undetectable RNA-HCV was maintained in 93 (90.3%) patients in group I and 89 (86.4%) in group II. Although the SVR_{24} rate in patients who administered SOF+LDV treatment was higher than in those with SOF+DCV, there was not any statistically significant difference OR=0.68, 95% CI (0.20-1.61), p=0.39 (fig. 2).

Table 3. Mean values of biochemical indices at the initiation of antiviral treatment.

Biochemical parameters	Lot SOF+LDV (n=103)	Lot SOF+DCV (n=103)	P
Thymol test, U	4.78±0.28	6.0±0.31	<0.01
Total bilirubin, µmol/L	16.54±0.93	15.98±0.73	>0.05
ALAT, IU/L	108.23±12.2	118.8±14.78	>0.05
ASAT, IU/L	81.8±8.44	90.38±7.49	>0.05
Alkaline phosphatase, IU/L	206.17±9.18	183.94±8.68	>0.05
GGT, UI/L	67.03±5.72	76.63±8.24	>0.05
Glucose, mmol/L	5.96±0.18	6.05±0.19	>0.05
Amylase, IU/L	89.44±4.83	99.14±5.25	>0.05
Prothrombin time index, %	88.56±0.65	86.27±0.65	<0.05

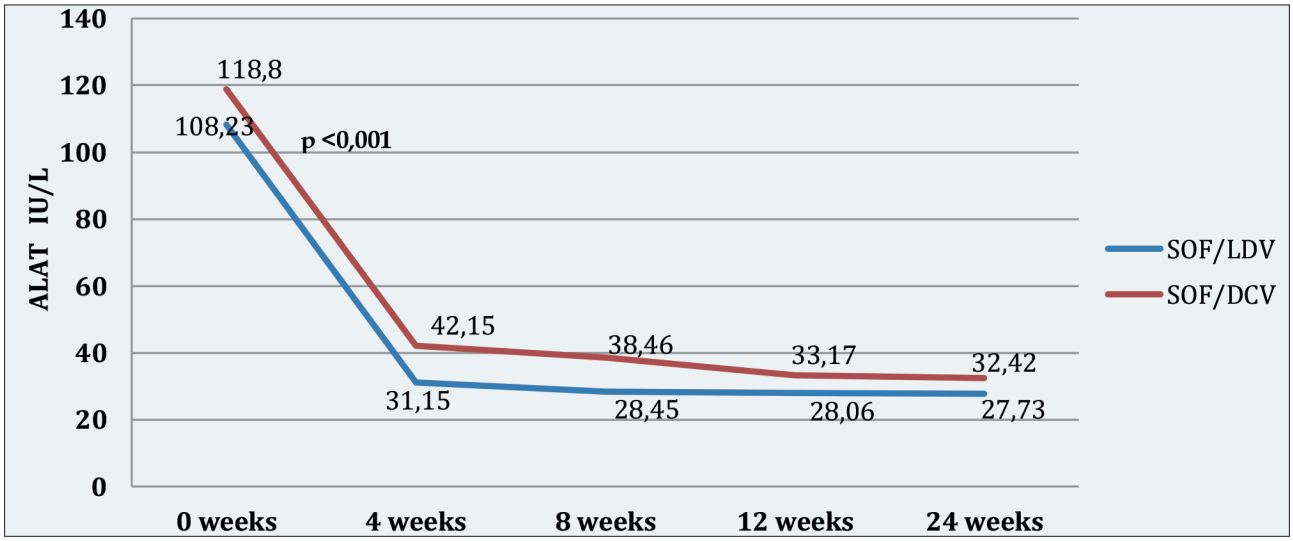

Figure 1. Dynamics of ALAT activity in patients with chronic HCV treated with DAAs.

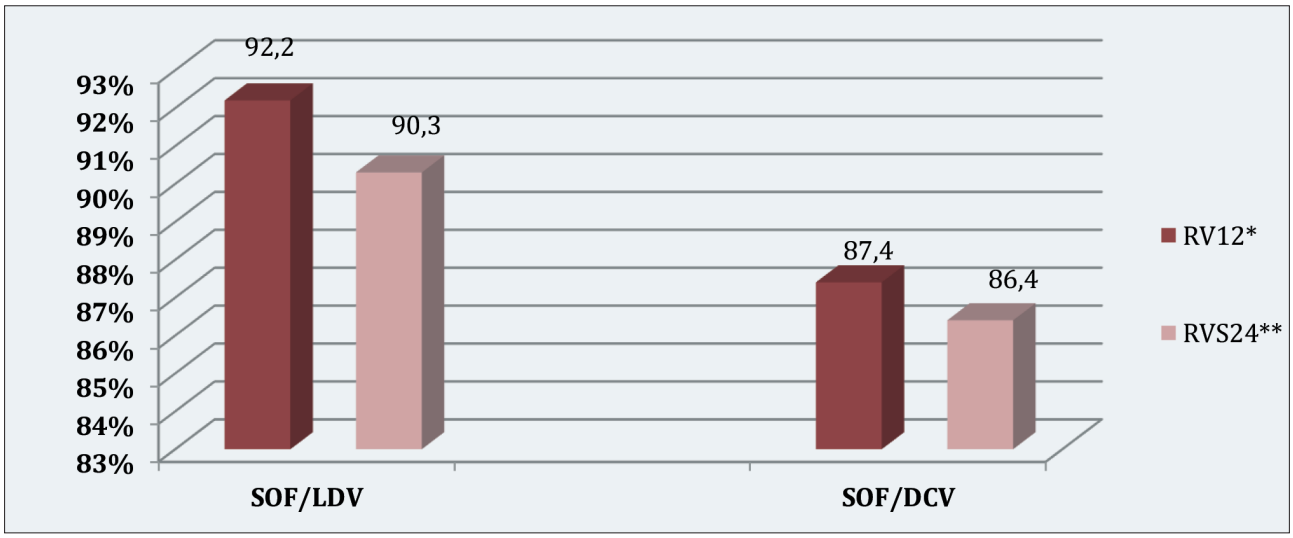

Figure 2. Virologic response in chronic Hepatitis C patients.

* VR12 – virologic response at the end of treatment

** SVR_{24} – sustained virologic response over 24 weeks after treatment

The analysis of the SVR-related predictive factors in DAAs treatment (tab. 4, tab. 5), revealed that SVR was mostly found in patients with high cytolytic activity compared to those who had serum aminotransferase level within normal range. Young patients showed a more frequent SVR than those over 60, although the differences were not statistically significant. At the same time, patients with SVR showed a higher initial level of ALAT (117.75±10.69 IU/L), compared to those in whom virologic failure was recorded (79.68±11.88 IU/L), ($p<0.05$). The obtained data help to conclude that age, gender, level of viremia, liver fibrosis stage and genotype are not predictive factors of SVR in DAAs treatment.

Table 4. SVR-related predictive factors for Sofosbuvir+Ledipasvir treatment.

Factors	SVR n=93	Total n=103	%	95% CI	P
Age					
≤40 years	22	24	91.6	1.0	
41-60 years	51	56	91.1	0.93 (0.17-5.15)	0.93
≥60 years	20	23	86.9	0.61 (0.09-4.01)	0.60
Gender					
Males	48	51	94.1	1.0	
Females	45	52	86.5	0.40 (0.10-1.65)	0.21
ALAT					
Normal range	18	22	81.8	1.0	
> normal range	75	81	92.6	2.78 (0.71-10.89)	0.14
ARN-VHC					
< 1 mln copies/mL	13	13	100	1.0	
1-5 mln copies/mL	43	50	86.0	0.21 (0.01-4.01)	0.30
>5 mln copies/ mL	37	40	92.5	0.40 (0.02-8.20)	0.55
Fibrosis stage					
0-1	49	52	94.2	1.0	
2-3	44	51	86.3	0.38 (0.09-1.58)	0.19
Genotype					
1	88	98	89.8	1.0	
2,3,4	1	1	100	0.36 (0.01-9.31)	0.53
Unidentified	4	4	100	1.06 (0.05-21.25)	0.97

Table 5. SVR-related predictive factors for Sofosbuvir+Daclatasvir treatment.

Factors	SVR n=89	Total n=103	%	95% CI	P
Age					
≤40 years	24	27	88.9	1.0	
41-60 years	47	53	88.7	0.98 (0.23-4.26)	0.98
≥60 years	18	23	78.3	0.45 (0.09-2.13)	0.31
Gender					
Males	46	53	86.8	1.0	
Females	43	50	86	0.93 (0.30-2.88)	0.91
ALAT					
Normal range	14	18	77.8	1.0	
> normal range	75	85	88.2	2.14 (0.59-7.8)	0.25
ARN-VHC					
< 1 mln copies/mL	22	24	91.7	1.0	
1-5 mln copies/mL	33	39	84.6	0.50 (0.09-2.70)	0.42
>5 mln copies/ mL	34	40	85	0.52 (0.10-2.79)	0.44
Fibrosis Stage					
0-1	15	18	83.3	1.0	
2-3	74	85	87	1.35 (0.33-5.41)	0.68
Genotype					
1	60	71	84.5	1,0	
2, 3, 4	17	17	100	6.65 (0.37-118.64)	0.20
Unidentified	2	15	80	0.73 (0.17-3.03)	0.66

Treatment failure was established in 24 (11.6%) patients. Of them, there were 14 women (58.3%) and 10 men (41.7%). There were 19 (79.2%) patients over 40 years and those with an average (F2) and advanced (F3) fibrosis level 18 (75%) were more likely to fail the treatment. The ARN-HCV viremia level was similar in patients who had SVR and those with virologic failure. The SVR rate was similar in naive patients and those previously treated with antivirals, that was 160 (88.4%) and 22 (88%) cases, respectively.

The DAAs therapy was well tolerated by patients from both groups, whereas 27 (13.1%) patients experienced minor adverse reactions like asthenia, headache, nausea, insomnia, hypertensive crisis, which were quickly compensated without suspending the treatment (tab. 6).

Table 6. Adverse reactions to antiviral treatment in patients with chronic HCV.

Indices	SOF/LDV	SOF/DCV	OR 95% CI, P
	I	II	
	N=103	N=103	
Asthenia, n (%)	4 (3.9)	5 (4.9)	0.79 (0.21-3.04), p= 0.73
Headache, n (%)	4 (3.9)	3 (2.9)	1.35 (0.29-6.17), p= 0.70
Nausea, n (%)	2 (1.9)	4 (3.9)	0.49 (0.09-2.73), p=0.42
Insomnia, n (%)	3 (2.9)	2 (1.9)	1.51 (0.24-9.26), p=0.65
Hypertensive seizures, n (%)	0	1 (0.97)	0.33 (0.01-8.20), p=0.50

DISCUSSIONS

The implementation of the National Program of combating viral hepatitis B, C and D over 2017 and 2021 has as an overall purpose to further reduce the morbidity rate of acute and chronic hepatitis B, C and D viral infections and cirrhosis, as well as minimize their socioeconomic consequences. Access to modern DAAs schemes leads to the disappearance of HCV RNA over four weeks after treatment initiation, as well as to virus elimination in about 90% of cases. Reactivation of HCV over 24 weeks after DAAs treatment completion is rare, although reinfection should not be excluded. About 99% of patients who exhibited SVR had a negative ARN-HCV after treatment, thus the progression of liver cirrhosis and hepatocellular carcinoma being stopped (8, 9). Our study results have proved a high efficacy of generic antiviral agents administered over 12 weeks in patients with chronic HCV, thus a sustained virologic response was recorded over 24 weeks after treatment in 90.3% of patients undergoing Sofosbuvir + Ledipasvir and 86.4% patients receiving Sofosbuvir+Daclatasvir. The treatment was effective in both naïve patients and those who underwent a previous unsuccessful treatment with PEG-INF, RBV, Boceprevir or Telaprevir.

CONCLUSIONS

1. The generic direct-acting antiviral agents showed a high efficacy, having a sustained virologic response in approximately 90% of patients treated with both treatment schemes.

2. The sustained virologic response was similar in both naïve patients and in those who underwent a previous unsuccessful antiviral treatment.

3. Generic antiviral agents have been well tolerated by most patients, whereas minor side effects did not require treatment discontinuation.

CONFLICT OF INTERESTS

The authors do not declare any conflict of interest.

REFERENCES

1. World Health Organization. Global Hepatitis Report 2017. Available from: http://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf?sequence=1 [Accessed 10th January 2019].

2. Pântea V. *Hepatitele virale acute şi cronice (etiologie, epidemiologie, patogenie, tablou clinic, diagnostic şi profilaxie).* Chişinău: 2014.
3. World Health Organization. Global Hepatitis Report 2016. Available from: https://www.who.int/hiv/pub/arv/ global-AIDS -update-2016_en.pdf [Accessed 27th December 2018].
4. Agenţia Naţională pentru Sănătate Publică. *Notă informativă cu privire la realizarea Programului Naţional de combatere a hepatitelor virale B, C şi D pentru anii 2017-2021*. 2017. p.5-6. Available from: https://msmps.gov.md/ro/content/nota-informativa-cu-privire-la-realizarea-programului-national-de-combatere-hepatitelor [Accessed 10th January 2019].
5. European Association for the Study of the Liver. *Recommendations on Treatment of Hepatitis C 2018*. Available from: http://www.easl.eu/medias/cpg/HEPC-2018/Full-report.pdf [Accessed 10th January 2019].
6. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology*. 2009; 136:138-148.
7. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. *Recommendations for Testing, Managing, and Treating Hepatitis C*. 2016. Available from: https://www.hcvguidelines.org/ [Accessed 10th January 2019].
8. Chhatwal J, Wang X, Ayer T, et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. *Hepatology.* 2016; 64:1442-1450.
9. Asselah T, Boyer N, Saadoun D, et all. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. *Liver Int.* 2016; 36:47-57.
10. Ahmed OA, Kaisar HH, Badawi R, et al. Efficacy and safety of sofosbuvir-ledipasvir for treatment of a cohort of Egyptian patients with chronic hepatitis C genotype 4 infection. *Infect Drug Resist*. 2018; 11:295-298.
11. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. *Hepatology – A clinical textbook.* 7th Edition 2016.
12. Săndulescu O, Streinu-Cercel A, Stoica A, et al. Regression of liver fibrosis following sustained virological response in patients with chronic HCV infection and cirrhosis. *BMC Infectious Diseases.* 2016; 16(602):46-47.

Date of receipt of the manuscript: 03/02/2020
Date of acceptance for publication: 29/02/2020

Irina RUSU, ORCID 0000-0002-2759-3171
Liliana HODOROGEA, ORCID 0000-0003-4795-9852
Tiberiu HOLBAN, ORCID 0000-0003-0923-3129