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Extended panel of biomarkers for long term monitoring of effectiveness of 3 direct antiviral regimen in HCV genotype 1b infection: results from a Romanian infectious disease hospital

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Abstract

***Background**: Hepatitis C virus can be eradicated with antiviral therapy, thus reducing the risk of disease progression and death associated with the final stage of liver disease. **Methods**: 241 patients received PrOD+RBV for 12 weeks. Clinical and laboratory data were assessed at baseline, week 4, 8, 12 (end of treatment, EOT), and 12 weeks after therapy (sustained virological response, SVR). Subsequently, biological and virological measurements were performed at least 48 weeks after obtaining SVR12 in responder patients. **Results**: Per protocol SVR12 rate was 97,6%. Severe adverse events were reported in 3 patients (1.24%) and led to treatment discontinuation (liver decompensation). One 58-year-old patient who completed the treatment died before SVR evaluation due to acute mesenteric ischemia (not related to antiviral therapy). Baseline total bilirubin above 2 mg/dl can be considered a predictive factor for non-response to PrOD+RBV treatment (p = 0.004). Of the 30 patients evaluated at least 48 weeks after SVR no one presented relapses, with no statistically significant differences in biological parameters changes and no adverse events were noted during the 48-week follow up period. **Conclusion**: Our study revealed the high effectiveness and good safety profile of PrOD +RBV in patients with genotype-1b HCV compensated cirrhosis (Child Pugh A) which were maintained during a 48-week period after treatment finalization.*

***Keywords:** hepatitis C virus, compensated cirrhosis, direct-acting antiviral agents*

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Introduction

Patients with chronic hepatitis C virus (HCV) infection are at increased risk for progressive liver fibrosis, cirrhosis, hepatocellular carcinoma, and decompensated liver disease [1]. Currently, hepatitis C virus can be eradicated with antiviral therapy, thus reducing the risk of disease progression and death associated with the final stage of liver disease. Since the first publication of the use of interferon therapy for hepatitis C, there has been a continuous improvement in treatment options, including dual interferon plus ribavirin therapy, followed by peginterferon, and the first generation of direct acting antivirals agents (DAAs) acting as protease inhibitors and used in combination with interferon and ribavirin [2].

In recent years, basic research on HCV has led to the discovery and development of the newest DAAs that are directed against several molecular targets which overcome the limitations of the previous treatments and offered an important benefit in "hard-to-treat" patients [3].

Therefore, starting with 2013-2014, therapeutic strategies for HCV have significantly changed since the infection can now be cured safely and effectively by the newest generation of DAAs.

Unfortunately, within European countries, Romania has the highest death rate from liver disease related to HCV infection [4]. In the first national program conducted between 2015-2016, the Romanian National Insurance House established the eligibility criteria for 5000 HCV patients to receive the interferon-free treatment. The interferon-free therapy approved in the protocol was PrOD regimen consisting in paritaprevir (PTV)+ombitasvir (OBV)+ritonavir (R)+dasabuvir (DSV) and was administered in combination with ribavirin (RBV). This therapeutic regimen has been available in all European countries since it was approved by European Medicines Agency since 2015 [5, 6].

Methods

The aims of our study were to evaluate the real-world effectiveness and safety of DAAs in HCV genotype 1b infected patients, hospitalized in the Clinical Hospital of Infectious Diseases "Sf. Parascheva" Iasi between 2015-2016. The second objective was to perform a follow-up analysis of effectiveness (by certifying the persistence of virus clearance by using molecular biology techniques) and safety of PrOD+RBV regimen in a prospective interventional short-term study in a subgroup of 30 patients who achieved sustained virologic response (SVR) after the interferon-free treatment.

Ethics

The study was carried out according to the Declaration of Helsinki 2008 and the International Ethical Guidelines. All 30 patients selected for the follow-up evaluation signed an informed consent approved by the UMF "Grigore T. Popa" Iasi Ethics Committee. Also, the study was approved by the Ethics Committee of the Infectious Diseases Hospital "Sf. Parascheva" Iasi.

Patients and treatment

Patients included under the Romanian National Health Insurance House (NHIH) reimbursement program on interferon-free treatment between December 2015-July 2016 were prospectively enrolled in a regional registry of antiviral therapy. Eligible patients were included according to the criteria established by the Romanian NHIH protocol [7], as follows: treatment naive or experienced patients aged over 18 years with HCV genotype 1 infection, compensated cirrhosis score Child-Pugh A and advanced fibrosis (F4) by Fibromax Biopredictive.

Exclusion criteria were decompensated liver cirrhosis, severe chronic kidney disease, malignant neoplastic disease, and co-infection with human immunodeficiency virus (HIV). Alcohol abuse

or withdrawal less than 3 months, concomitant treatments known to interact with PrOD agents (e.g. CYP3A4, CYP2C9 inhibitors, etc.) were also excluded.

The PrOD regimen consisted of daily administration of OBV 12.5 mg and PTV 75 mg boosted with R 100 mg (as single dose), and DSV 250 mg given twice daily. The dose of RBV was 1000-1200 mg/day according to body weight, but the doses were adjusted depending on hemoglobin level. Treatment administration was in accordance with the approved Summary of Product Characteristics [5, 6].

Patient evaluation

Clinical data related to gender, age, treatment history, and comorbidities were collected at baseline. According to protocol laboratory data included HCV-RNA level, determination of genotype and subgenotype, liver function tests (aspartate and alanine aminotransferases, total bilirubin, gama-glutamyl transpeptidase, albumin and international normalized ratio [INR]), HBsAg, anti-HIV antibodies, serum creatinine, hemoglobin, platelets, leukocytes, neutrophils, alpha-fetoprotein and abdominal ultrasound. Serum HCV-RNA levels were measured with the Cepheid GeneXpert system (Cepheid, Sunnyvale, CA) with a lower limit of quantification and detection of 15 IU/mL. The degree of liver fibrosis was evaluated based on Fibromax test.

Liver enzymes and quantitative viral load for virus C were re-evaluated at the end of treatment (EOT) and SVR_{12} (12 weeks after EOT). Biological dynamics was also evaluated during the treatment [7].

Subsequently, biological and virologic measurements were performed at least 48 weeks after obtaining SVR_{12} in responder patients.

Outcomes

Effectiveness of therapy was assessed by the percentage of patients achieving SVR_{12} (defined as HCV-RNA below the limit of detection 12 weeks after the EOT). According to the protocol, therapeutic failure was defined as detectable HCV-RNA on EOT. Relapse was considered detectable HCV-RNA at SVR_{12} in patients with undetectable viremia on EOT. Presence of ascites, digestive hemorrhage, jaundice, Child-Pugh score B or C, and encephalopathy had defined liver decompensation.

In the follow-up monitorization, effectiveness was evaluated based on maintenance of SVR.

Safety and tolerability assessment included only the severe adverse events and laboratory data analysis. The severity of adverse events was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (2018). The relation with the administered medication was also assessed. The hematological side effects (hemoglobin or platelet count), and liver toxicity (any abnormal ALT, AST, and bilirubin levels during treatment) were of special interest.

Statistical analysis

Continuous variables were reported as a mean ± standard deviation, while categorical variables were reported as frequencies and percentages.

The measures of effectiveness (HCV-RNA) and biological parameters of interest at the end of study were compared with those at baseline by Wilcoxon matched pairs test. The parameters measured more than twice were compared by non-parametric Kruskal-Wallis test. A correlation between baseline characteristics and rate of response (SVR rate) was made using t-student test.

Safety evaluation was based on the incidence and type of adverse events.

Results

Patients characteristics

A total of 241 patients with HCV genotype 1b

liver cirrhosis (genotyping was performed for all patients, and they were all genotype 1b), naive and treatment experienced, were eligible for PrOD treatment. The baseline characteristics of these patients are described in Table I.

Of the 241 patients included in the national program, most of them were females (52.7%).The mean ±SD age of the patients was 58.23±8.75 years, and only 25.72% were aged ≥65 years.

Although some patients had initial total bilirubin elevations (4 above 2 mg/dL) the abdominal ultrasound did not show the presence of cholelithiasis or biliary obstruction in any of them.

Efficacy of PrOD treatment

Of the total study group, 235 patients (97.6%) achieved SVR_{12}. Of the 2.4% cases who did not achieve SVR, 1 patient (0.4%) showed detectable viremia at EOT (virologic failure) and another patient had undetectable viremia on EOT, but detectable at 12 weeks after treatment completion (relapse). Also, 3 patients (1.2%) prematurely discontinued treatment due to side effects, and one patient died between EOT and SVR (unrelated to antiviral therapy).

Data analysis in patients who achieved SVR_{12} revealed that baseline had not significantly in-

Table I. Baseline demographical, clinical and laboratory characteristics (N=241 patients)

Characteristics	N = 241
Sex, Female, n (%)	127 (52.7)
Age, years, mean (range)	58.23 (33-82)
≥65 years, n (%)	62 (25.72)
Baseline HCV-RNA, IU/mL, mean (SD)	1,039,954 (161,012)
Creatinine, (mg/dl), mean (SD), n = 237	0.87 (0.28)
Hemoglobin level, g/dl, mean (SD), n = 241	14.45 (1.55)
ALT, IU/L, mean (SD), n = 241	129.84 (77.48)
AST, IU/L, mean (SD), n = 241	106.33 (55.85)
Bilirubin, mg/dl, mean (SD), n = 241	0.898 (0.375)
>2 mg/dl, n (%)	4 (1.66)
GGT, IU/L, mean (SD), n = 241	114.96 (96.99)
Albumin, %, mean (SD), n = 241	47.02 (5.92)
Alpha-Fetoprotein, %, mean (SD), n = 241	19.61 (34.2)
Platelets, /mm³, mean (range), n = 241	135290.5 (56311.4)
<70.000/mm³, n (%)	24 (9.96)
INR, mean (range), n = 241	1.28 (0.98 – 4.07)
AgHBs, n (%)	3 (1.24)
HCV antiviral treatment history, n (%)	
Naive	91 (37.76)
Non-responder	75 (31.12)
Partial responders	21 (8.71)
Relapser	44 (18.26)
Discontinued due to side effects	10 (4.15)
Comorbidities, n (%)	
Diabetes mellitus	34 (14.11)
Cardiovascular disease	60 (24.9)
Psychiatric disorders (depression)	10 (4.15)

AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamaglutamyl transpeptidase; INR: international normalized ratio; SD: standard deviation

fluenced the SVR rate, except baseline total bilirubin above 2 mg/dl, which can be considered a predictive factor for non-response to PrOD+R-BV treatment (p=0.004) (Table II).

The differences in biological parameters between baseline and different time points during antiviral therapy are summarized in Table III. The antiviral therapy significantly modified the biological parameters.

Safety

One 58-year-old patient who completed the treatment died before SVR evaluation due to acute mesenteric ischemia, an adverse event evaluated as not related to antiviral therapy. Severe adverse events were reported in 3 patients (1.24%) and led to treatment discontinuation (liver decompensation).

Post-baseline laboratory abnormalities were infrequent and without clinical significance. None of them was life threatening (Table IV).

Follow-up assessment

All patients received (mail and phone call) invitations to be re-evaluated after at least 48 weeks after achieving SVR. The results from the thirty

Table II. RVS rates according to the patients' characteristics

Parameters	SVR	nonSVR.	p
Gender			0.483
Male	98.2%	1.8%	
Female	98.9%	3.1%	
Age, years	58.20±8,81	59.3±5.77	*0.755
< 65 ani	97.2%	2.8%	0.591
≥ 65 ani	98.4%	1.6%	
HCV antiviral treatment history			0.537
Naive	96.7%	3.3%	
Experienced	98.0%	2.0%	
HCV-RNA, UI/mL	1.050.816±106.152	614.494±219.504	*0.513
< 6 mil	97.5%	2.5%	0.696
≥ 6 mil	100.0%	0.0%	
Platelets, n/mm³	135.604±56.576	123.000±47.155	*0.589
< 50.000	100.0%	0.0%	0.716
50.000-100.000	96.7%	3.3%	
100.000-150.000	96.6%	3.4%	
Total bilirubin, mg/dl	0.90±0.37	0.92±0.56	*0.876
< 2	97.6%	2.1%	**0.004**
≥ 2	75.0%	25.0%	
Alpha-Fetoprotein, mg/dl	19.82±14.60	11.42±5.77	*0.554
< 20	100.0%	0.%	0.591
≥ 20	96.7%	3.3%	
Diabetes mellitus			0.227
Yes	94.1%	5.9%	
No	98.1%	1.9%	
Cardiovascular disease			0.180
Yes	95.0%	5.0%	
No	98.7%	1.7%	

* t-Student test

Table III. Mean laboratory parameters changes between baseline and at SVR

Variable	Baseline	Week 4	Week 8	Week 12 (EOT)	Week 24 (SVR)	P value
Hemoglobin (g/dL)	14.45	12.65	12.42	12.31	14.54	<0.0001
WBC (/mm³)	5721.08	6997.29	6469.62	6257.71	6305.14	<0.0001
Platelets (/mm3)	135290.5	180087.5	177435.3	176805.1	151086.4	0.003
ALT (IU/L)	131.53	36.83	31.19	27.83	35.17	<0.0001
AST (IU/L)	109.4	35.01	32.6	30.77	34.62	<0.0001
Total bilirubin (mg/dL)	0.90	1.62	1.52	1.24	1.06	0.003

AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cells

Table IV. Proportion of patients with treatment-emergent AEs and laboratory abnormalities.

Adverse event	PrOD+RBV N = 241
AE leading to treatment discontinuation	3 (1.24)
Hemoglobin decreased	
Grade 2 (<10-8 g/dl)	27 (11.2)
Grade 3 (<8-6.5 g/dl)	4 (1.65)
Total bilirubin increased	
Grade 2 (>1.5-3 x ULN)	98 (40.66)
Grade 3 (>3-10 x ULN)	20 (8.29)
Alanine aminotransferase increased	
Grade 3 (>5-20 x ULN)	5 (2.07)
Aspartate aminotransferase increased	
Grade 3 (>5-20 x ULN)	2 (0.82)

Values are n (%). **ULN**: upper limit of normal.

patients who responded to our calls are presented in Table V. None of the 30 patients evaluated presented relapses. The biological parameters noted at SVR_{12} were maintained during the next period, with no statistically significant differences except for a significant improvement of AST (Table VI). There were no adverse events noted during the 48-week follow-up period.

Table V. Laboratory parameters at baseline and 48 weeks after SVR

Variable	SVR_{12} N=30	48 weeks after SVR_{12}
Baseline HCV-RNA, IU/mL, mean	859576.83	<15
Creatinine, (mg/dl), mean (SD), n = 29	0.88 (0.15)	0.94 (0.15)
Hemoglobin level, g/dl, mean (SD), n = 30	14.32 (1.56)	14.48 (1.44)
ALT, IU/L, mean (SD), n = 30	111.63 (46.7)	36.6 (38.67)
AST, IU/L, mean (SD), n = 30	98.27 (42.86)	30.5 (10.3)
Bilirubin, mg/dl, mean (SD), n = 30	0.98 (0.36)	1.03 (0.42)
>2mg/dl, n (%)	0	1 (3.33)
GGT, IU/L, mean (SD), n = 30	101.7 (69.03)	45.69 (22.52)
Platelets, /mm³, mean (range), n = 30	105933.3 (33000 – 214000)	140600 (69000 - 227000)
<70.000/mm³, n (%)	5 (16.67)	1 (3.33)
HCV-RNA > 48 weeks after SVR, < 15 IU/ mL, n (%)	30 (100)	30 (100)

Table VI. Mean laboratory parameters changes between SVR12 and 48 weeks post-SVR

Variable	Week 24 (SVR)	Week 48 Post-SVR	P value
Hemoglobin (g/dL)	14.32	14.48	0.76
WBC (/mm³)	5978.15	6552	0.190
Platelets (/mm3)	131592.59	140600	0.250
ALT (IU/L)	34.7	36.6	0.57
AST (IU/L)	36.04	30.5	0.009
Total bilirubin (mg/dL)	1.07	1.03	0.749

AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC: white blood cells

Discussion

Romania belongs to medium level endemicity for viral hepatitis (except for HEV) and 3.3% of people live with HCV [8], 99% of them, infected with 1b genotype [9, 10]. Starting from this context, Romanian public health authorities initiated a national program to reduce this high HCV rate, and regional studies have been carried out in recent years on this topic.

Our cohort study consisted of 241 patients with chronic infection with VHC genotype 1b and compensated liver cirrhosis (Child-Pugh A) admitted to the Infectious Disease Hospital Iasi during 2015-2016.

A slightly higher prevalence of chronic HCV infection in female (52.1%) was found, in accordance with our national epidemiological data. In an epidemiological study on 2851 adult patients on the prevalence of viral hepatitis in Romania, Voiculescu *et al*. (2010) noted a significantly higher prevalence in women than in men [11]. These data suggest a different gender distribution in Romania compared to other European countries, as ECDC (2016) reported an almost double incidence of HCV infection in males compared to females [12].

A wide range distribution of age was noted in our study, with the highest incidence in 60-69 year-old patients, as claimed by previous literature data [11, 13]. These data suggest that the prevalence of HCV in the Romanian youth population, born after 1990, is under than 1.5%, and there may be a tendency for the prevalence to decline in the following years [14].

The emergence of second-generation DAAs has changed the paradigm for the treatment of chronic HCV infection with RVS rates of over 90%, regardless of the presence of cirrhosis, the lack of response to previous therapies, and the different host-related factors [15]. According to the approved Romanian therapeutic protocol, only patients with advanced fibrosis (F4) were eligible for the interferon-free therapy, namely PrOD+RBV. According to the protocol, effectiveness was assessed on EOT and 12 weeks after the treatment. In the phase III TURQUOISE-II study, naïve and experienced cirrhotic patients with HCV genotype 1 infection (Child-Pugh A) treated with PrOD+RBV for 12 weeks reported SVR_{12} rates of 91.8% (98.5% in patients with genotype 1b) [16]. Based on these results, the PrOD+RBV regimen for 12 weeks is recommended for cirrhotic patients with HCV genotype 1 infection [17].

In our study, treatment with PrOD+RBV for 12 weeks resulted in a high percentage of patients achieving SVR_{12}, similar to the results obtained in clinical trials. The SVR rate after 12 weeks post-treatment was 97.6% in our study, comparable with the previous phase III clinical studies [16].

In this study, we also evaluated influences of interferon-free therapy on some biochemical and hematological parameters. Significant changes

were observed during and after treatment completion. Thus, a significant improvement of evolution of functional liver tests (ALT, AST) was observed during the 12 weeks of treatment compared with the baseline. This is confirmed by both Phase III clinical studies and real world studies [17, 18, 19]. The total bilirubin level increased significantly during the 12 weeks of treatment, with a peak in week 4, but returned to normal after 12 weeks following treatment completion. Increases in bilirubin concentrations are consistent with those described in previous safety studies and were related to inhibition of bilirubin transporter proteins (OATP1B1 and OATP1B3) by paritaprevir and concomitant RBV-induced hemolysis [18, 20].

Treatment of HCV genotype-1 patients with PrOD+RBV for 12 weeks was associated with a low virologic failure (0.4%) similar to those found in other clinical trials. In a meta-analysis of 3115 patients with HCV genotype 1 infection who received treatment with PrOD±RBV, the SVR rate in the 12-week treated group was 97% and the rates of virologic failure and relapse were 0.08% and 1.5% respectively. These results were maintained regardless of the subgroup analyses performed, including viral subgenotypes, the presence of cirrhosis, or the failure of the previous treatment. Adverse effects were mild to moderate and occurred in 70-90% of the groups treated with different regimens, while severe adverse effects or leading to premature discontinuation of treatment were rare [15]. Time of relapses was not studied in phase III clinical trials. However, available data are contradictory. Relapses after PrOD treatment occurred before week 4 post-treatment, as found in phase II AVIATOR study [21]. On the other hand, Calleja *et al.* (2017) noted later relapses associated with this interferon-free regimen and suggested the need of a long term follow-up evaluation [22]. In this context, we conducted a follow-up monitoring of 48-week period after SVR. None of the patients evaluated had relapsed. Moreover, all biochemical parameters investigated were maintained at levels similar to those obtained at SVR_{12}. TOPAZ-I is the first multicenter trial to evaluate long term (5 years) efficacy and safety of PrOD±RBV in adults with genotype 1 chronic HCV infection. The first interim analysis revealed a high efficacy based on SVR12 rate and liver stiffness remained stable in patients without cirrhosis, while decreases were observed in patients with cirrhosis [23].

PrOD+RBV regimen was well tolerated in patients enrolled in our study. One case of death related to patients' comorbidities (cardiovascular, diabetes mellitus) was reported. Three patients withdrew from the study due to adverse events (liver decompensation). A low incidence of adverse events was also noted in other clinical studies. Calleja *et al.* (2017) reported severe adverse events in 84 patients (5.4%), and 1.8% of patients discontinued the treatment prematurely. The occurrence of adverse effects has been linked to advanced fibrosis and age [20]. Preda *et al.* (2018) also found a decreased rate of liver decompensation related to DAAs in genotype-1b HCV compensated cirrhosis [24]. In our study, we did not note any adverse events during the follow-up of 48-week period of evaluation of the subgroup of 30 patients.

An important limitation of our small sized study is the lack of safety data for the studied group, regarding the clinical adverse events during the 12 weeks, as well as after the completion of the treatment. No data regarding the patients' compliance could be collected. The number of the patients with long-term follow-up is small; no antiviral resistance profile could be evaluated in patients who failed the treatment, even if several studies show that treatment failure is due to the mutations harbored by HCV resistance associated variants (RAVs) selected during therapy [25].

In **conclusion**, our study revealed the high effectiveness and good safety profile of PrOD+RBV in patients with genotype-1b HCV compensated cirrhosis (Child-Pugh A) which were maintained during a 48-week period after treatment finalization. Future follow-up studies are necessary to confirm long-term virologic response, recommendation that is based on clinical trial results, and is also important to continue post-SVR surveillance for hepatocellular carcinoma (HCC) in cirrhotic patients who have achieved SVR.

Abbreviations

HCV: hepatitis C virus
DAAs: direct-acting antiviral agents
SVR: sustained virologic response
PEG-IFN: peginterferon
RBV: ribavirin
PrOD: paritaprevir/ritonavir, ombitasvir and dasabuvir
UMF: University of Medicine and Farmacy
NHIH: National Health Insurance House
HIV: human immunodeficiency virus
OBV: ombitasvir
PTV: paritaprevir
R: ritonavir
DSV: dasabuvir
INR: international normalized ratio
EOT: end of treatment
CTCAE: Common Terminology Criteria for Adverse Events
ALT: alanine aminotransferases
AST: aspartate aminotransferases
HBV: hepatitis B virus
GGT: gama-glutamyl transpeptidase
SD: standard deviation
WBC: white blood cells
AE: adverse event
ULN: upper limit of normal
HEV: hepatitis E virus
ECDC: European Centre for Disease Prevention and Control.

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Authors’ contributions:

I.A.H.A. - study concept and design; acquisition and centralization of data;
M.C.L., C.D.M., A.V., A.B., M.E.H. - provided a significant number of patients who were analyzed and were, also responsible for patients selection, treatment monitorization and evaluation according to Romanian NHIH protocol;
A.B. - performed the ARN extraction in the laboratory and interpreted the results;
A.M.C., I.M.H. - medical writing and statistical analysis;
L.S.I. - study concept and design; material support and study supervision.
All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Conflicts of interest

There are no conflicts of interests.

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