REVIEW ARTICLE

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Efficacy and safety of Ombitasvir/Paritaprevir/Ritonavir+ Dasabuvir and Ribavirin in patients with compensated HCV cirrhosis

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Abstract: *Background and aim: Ombitasvir/Paritaprevir/Ritonavir+Dasabuvir in association with ribavirin was the only interferon-free regimen available in 2015 in Romania for compensated HCV cirrhosis. The aim of our study is to reveal our experience with interferon-free therapy in compensated HCV cirrhosis.*

Materials and methods: We conducted a multicenter prospective study including 90 patients with compensated (Child-Pugh A) HCV cirrhosis treated with Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir and Ribavirin regimen for twelve weeks. The HCV infection was diagnosed using clinical, biological, and FibroMax tests. Each patient had follow-up visits at four, eight, twelve and twenty-four weeks after the initiation of the treatment.

Results: 44 (49% of) patients were female and 46 (51 % of) were male. The mean age of patients in the study was 61 years old. All the patients had HCV genotype 1b infection. 22 patients were naive and 68 had previous antiviral therapies based on pegylated IFN-α and ribavirin. At the initiation of treatment 64 (71%) of patients had cytolysis, 38 (42%) had thrombocytopenia, 19 (21%) patients had hyperbilirubinemia and 11 (12%) patients had anemia. It was noticed a decreasing of cytolysis, only 10% of 64 patients still having cytolysis after four weeks of treatment. One patient (1%) died after four weeks of treatment by complications of cirrhosis. 89 (99%) of patients had a virologic response (VR) at the end of treatment (EOT) and sustained virologic response (SVR) twelve weeks after the last dose administration.

Conclusion: The most common side effect among the patients in the study group was anemia (47% cases). Cytolysis disappeared after four weeks of treatment in 61% of patients. The interferon-free combination treatment was safe and highly effective in compensated HCV cirrhosis.

Keywords: *interferon-free regimen, HCV cirrhosis, anemia, Ombitasvir/Paritaprevir/ Ritonavir+Dasabuvir*

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INTRODUCTION

The World Health Organizations estimates that there are 150 million people infected with hepatitis C virus [1].

Hepatitis C virus (HCV) affects individuals worldwide with a high degree of morbidity and mortality. Chronic HCV can lead to cirrhosis, hepatocellular carcinoma, the need for transplantation and death. The annual incidence of hepatocarcinoma in patients with HCV

cirrhosis is between 1% to 7% [2, 3, 4, 5]. Genotype -1 is the most common HCV genotype from all the 7 genotypes [6]. Genotype-1b is the most prevalent HCV subtype in Europe, Central America, the Middle, and Asia [7].

Therapy with pegylated interferon and ribavirin for 12 weeks to 72 weeks was associated with low SVR (only 60% of them achieved sustained virologic response) and with adverse events [8, 9]. It can be a challenge for patients with cirrhosis to achieve SVR.

Sustained virologic response is defined as undetectable HCV-RNA at 12 weeks, after the end of treatment (EOT) and it is associated with improved survival and reduced risk of HCC development in patients with cirrhosis [10,11,12].

New IFN-free direct- acting antiviral (DAA) therapies have greatly improved SVR rates in patients with cirrhosis [13, 14, 15, 16, 17]. In most regimens for maximizing the SVR rates in patients with cirrhosis, it was required the addition of ribavirin [18, 19].

The available DAA are classified according to the viral target protein as NS3/4A protease inhibitor, NS5B polymerase inhibitors (including non-nucleoside and nucleoside inhibitors) and NS5A inhibitors [20].

Direct-acting antiviral agents were approved for the first time in 2011 for the treatment of hepatitis C. Although the addition of the NS3/4A protease inhibitors boceprevir, telaprevir or simeprevir to pegylated interferon and ribavirin regimens increased SVR rates in patients with genotype-1 infection efficacy rates have remained low in patients with cirrhosis [21, 22, 23, 24, 25].

The regimen containing ombitasvir/paritaprevir/ ritonavir and dasabuvir with or without ribavirin was approved by the European Medicine Agency and/or the Federal Drug Administration for the treatment of patients without and with cirrhosis Child-Pugh-Turcotte class A.

Ombitasvir (OBV) is an NS5A inhibitor co-formulated with NS3/4A protease inhibitor paritaprevir (PTV), and the pharmacokinetic enhancer ritonavir which increases peak through drug allowing for once daily PTV dosing exposure [26,27]. Dasabuvir is a non-nucleoside NS5B polymerase inhibitor. This 3-DAA regimen with or without ribavirin (RBV) is approved in many countries to treat HCV genotype-1 infection.

Most of prospective phase II and III trials included only a few patients with cirrhosis.

The regimen Ombitasvir/paritaprevir/ritonavir and dasabuvir were evaluated in two studies in patients with compensated HCV cirrhosis. One study- TURQUOISE II trial, an open-label phase III trial evaluated the 3D regimen with ribavirin for 12 weeks vs 24 weeks in patients with compensated HCV cirrhosis. The other study – TURQUOISE III phase III b, open-label study evidenced if it could be achieved a good SVR without ribavirin at 3D regimen in 60 patients with compensated HCV cirrhosis. Ombitasvir/ paritaprevir/ritonavir + dasabuvir with ribavirin became available in Romania for compensated HCV cirrhosis from November 2015 to November 2017 as the only interferon-free regimen.

We reported the results of a prospective study designed to asses the efficacy and safety of the regimen ombitasvir/paritaprevir/ritonavir+dasabuvir with ribavirin in patients with compensated HCV cirrhosis genotype-1b, with or without experienced pegIFN/RBV.[28, 29, 30].

PATIENTS AND METHODS

Study Patients

We conducted a multicenter prospective study including 90 patients with compensated (Child-Pugh A) HCV cirrhosis treated with Ombitasvir/Paritaprevir/ Ritonavir+Dasabuvir and Ribavirin regimen for 12 weeks. Patients were diagnosed by clinical, biological, and FibroMax tests.

Patients 18 years or older were eligible for the therapy if they had HCV genotype-1b infection for at least 6 months prior to screening, an HCV RNA > 15 UI/ml. Cirrhosis had to be documented by liver biopsy (Metavir score >3) or FibroMax (available within 3 months before therapy) and a Child-Pugh Turcotte score 5 or 6.

We included in the treatment-naive patients or those with prior exposure to PegIFN/RBV based therapy.

Decompensated cirrhosis and hepatocarcinoma were exclusion criteria.

Each patient had follow-up visits at four, eight, twelve and 24 weeks after treatment initiation. Biological tests included: hemoglobin, ALT, AST, platelets, total bilirubin, serum albumin, INR. We defined anemia as Hb<12 g/dl in women and Hb< 13 g/dl in men. Cytolysis was defined as values of ALT or AST > at least 2 times upper limit of normal. Hyperbilirubinemia was defined as a level of bilirubin > than 1.2 mg/dl. HCV RNA level in blood was evaluated at baseline, end of treatment (EOT) and 12 weeks after EOT. Undetectable HCV RNA was defined as a viral load <15 UI/ml, assessment by PCR. Virological response (VR) was defined as undetectable HCV RNA at EOT and sustained virologic response (SRV) as undetectable HCV RNA at 12 weeks after EOT.

Study design

All patients received the therapy for 12 weeks. Co-formulated OBV/PTV/r was administered once daily (25/150/100 mg) and DSV 250 mg twice daily. Patients were followed up at four, eight, twelve, and twenty-four weeks after treatment initiation.

Written informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Efficacy, safety and pharmacokinetic assessments

Plasma samples were collected at screening and at each study visit and HCV RNA levels were determined processed by real-time polymerase chain reaction using the COBAS TaqMan HCV version 2.0 (Roche Molecular Diagnostics). Efficacy was assessed by the percentage of patients with SVR12, defined as an HCV RNA below the lower limit of quantitation of 25 UI/ml and a lower limit of detection of 15 UI/ml after the last dose of study drug.

The primary efficacy endpoint was SVR12 (HCV RNA level <25 UI/ml 12 weeks after the last dose of study drug. The rates of SVR 4 weeks after the end of treatment (SVR4) and rapid virologic response (RVR; HCV RNA level <25 UI/ml) were also determined.

Treatment adverse events were collected from the start of study drug administration until 30 days after the last dose. Laboratory tests and clinical parameters were assessed during the study. The severity of the adverse events and their relationship with treatment were evaluated by the investigator.

Statistical Analysis

Number and percentage of patients in different categories are reported. Categorical variables included in the analysis were: sex, the previous treatment regimen. Continuous variables included were: age, cytolysis, thrombocytopenia, anemia, hyperbilirubinemia.

Results

Baseline Patient Demographics and Characteristics.

We screened patients from November 2015 to August 2016 at five sites in Bucharest. 90 patients were enrolled and received the study drug. The majority of patients had prior treatment experience with PegIFN/RBV. 22 patients were treatment-naive and 68 patients had experienced Peg/IFN/RBV.

Demographics and clinical characteristics are presented in Table 1 and Table 2.

Table 1. Baseline demographic characteristics

Parameter	**Patients** (n=90) n/%
Age (years)	65
Female gender	44 (49)
Male gender	46 (51)
Treatment naïve	22 (24)
Treatment experienced	58 (76)

Table 2. Baseline clinical characteristics

Parameter	**Patients** (n=90) n/%
Cytolysis	64 (71)
Anemia	11 (12)
Hyperbilirubinemia	19 (21)
Thrombocytopenia	38 (42)

Efficacy Outcomes

89-99% of patients completed 12 weeks of treatment with ombitasvir/paritaprevir/ritonavir, dasabuvir and ribavirin. After 12 weeks of treatment, 99% of patients achieved SVR 12 (89/90, 95% CI, 80%-99.9%) (Table 3). One patient died after four weeks of treatment.

Another patient (female, 60 years old, known with diabetes mellitus) gave up ribavirin after four weeks of treatment because of severe anemia (level of hemoglobin was 6 g/dl). We hadn't any virologic failure.

Table 3. Efficacy and safety of DAA regimen

Parameter	**Patients** (n=90) n/%
SVR	89 (99)
Anemia	42 (47)
Death	1 (1)

Improvement in laboratory assessments

At baseline 71 % (64) of patients had cytolysis and 42 % (38) had thrombocytopenia (Table 4).

Only 10% (9) of patients had cytolysis at the end of treatment. Thrombocytopenia was improved at the end of treatment, thus it was seen at only 26% of patients.

Table 4. Characteristics of patients at the end of treatment

Parameter	**Patients** (n=90) n/%
Cytolysis	9 (10)
Anemia	2 (47)
Hyperbilirubinemia	6 (40)
Thrombocytopenia	3 (26)

Safety outcomes

Most of the patients had adverse events and one patient died after four weeks of treatment. Anemia was the most frequent adverse event. At baseline only 12% of patients had anemia, but at the end of treatment the number of patients who developed anemia was increasing up to 47%. Another laboratory abnormality was hyperbilirubinemia. At the beginning of the treatment, only 21% of patients presented a high level of bilirubin. At the end of treatment, hyperbilirubinemia was seen in 40% of patients. One patient developed severe anemia (hemoglobin level was 6 g/dl) after four weeks of treatment and thus ribavirin was stopped.

DISCUSSION

Patients with HCV infection and cirrhosis are at the highest risk for hepatocarcinoma, decompensation and, mortality. In this study treatment with OBV/PTV/r, DSV and RBV had the SVR 12 rate of 99% in HCV genotype-1b infected patients with compensated cirrhosis. Treatment was well tolerated with a low rate of severe AE.

The most side effect among the patients in the study group was anemia in 47% cases. Cytolysis disappeared after four weeks of treatment at 61 % of patients. 89 of 99 patients (99%) had sustained virologic response at twelve weeks. One patient died after four weeks of treatment (1%). The treatment was safe and effective in compensated HCV cirrhosis.

In conclusion the 12 week 3-DAA regimen of OBV/PTV/r, DSV and RBV achieved the SVR 12 rate of 99% experienced and naive treatment patients with compensated cirrhosis HCV genotype-1b.

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