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A Real-World Study to Compare the Safety and Efficacy of Paritaprevir/Ombitasvir/Ritonavir and Dasabuvir, with or without Ribavirin, in 587 Patients with Chronic Hepatitis C at the Fundeni Clinical Institute, Bucharest, Romania

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Background: In the European Union, a tablet with fixed doses of ombitasvir, paritaprevir, and ritonavir combined with dasabuvir is an authorized treatment for patients with chronic hepatitis C virus (HCV) infection. Ribavirin is a broad-spectrum antiviral used in several treatment regimens for patients with HCV infection. This real-world study aimed to compare the safety and efficacy of ombitasvir, paritaprevir, and ritonavir combined with dasabuvir, with or without ribavirin, in 587 patients with chronic hepatitis C attending the Fundeni Clinical Institute, Bucharest, Romania.

Material/Methods: This is an observational prospective study including 315 patients with F4 degree of fibrosis and compensated cirrhosis, 185 patients with F3 fibrosis, and 83 patients with F2 fibrosis. Liver fibrosis was evaluated by liver biopsy or Fibromax. Efficacy was defined as undetectable HCV-RNA at 12 weeks after the end of treatment. In terms of safety, we monitored the development of adverse reactions, liver cytolysis, cholestasis, and hematologic disorders.

Results: Of the 587 patients, 2 patients with B-cell lymphoma died during therapy. In total, 3/585 patients (0.51%) did not achieve sustained virologic response. Common adverse effects were nausea and asthenia (especially in patients with other medical treatments; P=0.03 and P=0.04, respectively) and anemia in patients who received ribavirin (P<0.01). None of the patients discontinued antiviral treatment. Patients with kidney transplant or end-stage kidney disease did not receive or discontinued ribavirin.

Conclusions: Ombitasvir, paritaprevir, and ritonavir combined with dasabuvir, with or without ribavirin had an efficacy rate of over 99% in HCV genotype 1b infection. We report no serious adverse reactions.

Keywords: Anemia • Hepatitis, Chronic • Liver Transplantation

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Background

Chronic hepatitis C virus (HCV) represents an important public health issue, with more than 180 million people infected worldwide [1]. Curing HCV infection has proven efficient in reducing the rate of complications and the progression of cirrhosis [2,3]. Patients who achieve sustained virologic response (SVR) during chronic hepatitis stage have shown a reduction in liver fibrosis, normal liver enzymes, and similar survival with non-infected patients. The benefits of antiviral treatment are less obvious in patients with severe liver disease; however, patients with compensated cirrhosis present slowly decreasing levels of liver fibrosis and have similar life expectancy rates as non-infected patients [4]. Furthermore, antiviral treatment has a positive impact on the outcome of patients with HCV-associated comorbidities, such as lymphoma and cryoglobulinemia, and also type 2 diabetes and atherosclerosis [5].

Cure in HCV hepatitis is defined as undetectable HCV RNA at 12 (SVR12) or 24 (SVR24) weeks after the end of antiviral therapy, with a concordance of these 2 responses and further viremia detection of over 99% [6]. While past therapies were based on interferon and ribavirin, with a duration of at least 24 weeks, [7], current international guidelines recommend all oral antiviral therapies for all HCV genotypes [8,9]. According to the first EASL guidelines, by including direct-acting antiviral agents, patients with all types of HVC genotypes and all degrees of liver fibrosis should benefit from interferon-free treatment of variable duration and composition [3]. In the European Union, a tablet with fixed doses of ombitasvir, paritaprevir, and ritonavir combined with dasabuvir (OMB/PTV/r+DSV) is an authorized treatment for patients with chronic hepatitis C virus (HCV) infection [10]. These antivirals target several proteins of the HCV virus: ombitasrvir inhibits non-structural protein 5A, paritaprevir inhibits the non-structural protein 3-4A serine protease, ritonavir is a protease inhibitor used to amplify the effects of paritaprevir, while dasabuvir inhibits the non-structural protein 5B polymerase [10]. Ribavirin is a broad-spectrum antiviral used in several treatment regimens for patients with HCV infection [11].

We will be referring to treatment options for genotype 1b HCV, as this is the prevalent strain in Romania [1]. At the time of our trial (2015-2017) the therapeutic options included sofosbuvir/ledipasvir±ribavirin (RBV), sofosbuvir/veltapasvir±RBV, OMB/PTV/r+DSV±RBV, grazoprevir/elbasvir±RBV, and sofosbuvir+daclatasvir±RBV [3]. The national therapeutic protocol in our country indicates the use of OMB/PTV/r+DSV in F2 liver fibrosis associated with HCV-related comorbidities and F3 liver fibrosis, OMB/PTV/r+DSV±RBV in patients with compensated cirrhosis and relapse after liver transplantation, and sofosbuvir/ledipasvir±RBV in patients with decompensated cirrhosis.

The criterion standard for evaluating the degree of liver fibrosis is liver biopsy, with inherent bleeding and infectious possible complications. New noninvasive methods, such as elastography (Fibroscan) or serum determinations of biological parameters (Fibromax) are used on a large scale to classify patients as having chronic hepatitis, with F0-F2 degree of fibrosis, advanced fibrosis (F3) and cirrhosis (F4) [12]. Because of the national treatment protocol, only liver biopsy and Fibromax were accepted as means of evaluating liver fibrosis for antiviral therapy.

Treatment with OMB/PTV/r+DSV has been associated with high levels of efficacy in real-life studies. For instance, a retrospective study showed a 95% SVR rate (39/41 patients); in this trial, the 2 nonresponsive patients had discontinued antiviral therapy due to acute renal failure, deemed by the investigators as nonrelated to the direct-acting antiviral agents [13]. Another large retrospective trial found an SVR rate of 97% in 5726 patients in Poland [14].

Therefore, this real-world study aimed to compare the safety and efficacy of OMB/PTV/r+DSV±RBV in 381 patients with chronic hepatitis C who were treated at the Fundeni Clinical Institute, Bucharest, Romania.

Material and Methods

The study was approved by the institutional board of Fundeni Clinical Institute as an observational prospective study (approval no. 3425/2015), and informed consent was obtained from all patients before the beginning of the therapy. The consent included requirements for monthly clinical and biologic evaluation as well as for agreement to participate in the scientific and teaching activities of the department.

This is an observational prospective study that included patients admitted to our clinic between December 2015 and December 2017 who were eligible for all oral antiviral treatment, according to the criteria established by the National HCV Healthcare Program [15]. Thus, liver fibrosis was evaluated by liver biopsy or Fibromax, and patients were classified as: F2 (moderate fibrosis), F3 (advanced fibrosis), or F4 (cirrhosis). Patients with an F2 degree of fibrosis and HCV-related comorbidities (lymphoma, cryoglobulinemia) received OMB/PTV/r+DSV for 12 weeks. Patients with an F3 degree of fibrosis received OMB/PTV/r+DSV for 12 weeks, regardless of comorbidities. Patients with F4 degree of fibrosis and chirrhosis class Child A received OMB/PTV/r+DSV with or without RBV for 12 weeks. Patients with HCV relapse after liver transplantation were given OMB/PTV/r+DSV with or without RBV for 24 weeks, regardless of the degree of fibrosis. Patients with HCV infection before or after kidney transplantation received OMB/PTV/r+DSV±RBV for 12 weeks, regardless of the degree of liver fibrosis.

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The degree of fibrosis was evaluated by liver biopsy or Fibromax at the initiation of therapy.

HCV RNA was determined using the Roche COBAS Ampliprep TNAI/TaqMan 48 RUO Assay for HCV RNA Quantification for HCV in human serum or ethylenediamine tetraacetic acid plasma samples at the beginning of the therapy, at the end of the therapy, and 12 weeks after the end of therapy.

Patients were evaluated monthly and were questioned about the onset of new symptoms and progression of comorbidities.

Periodic evaluations of liver function (liver enzymes, billirubin, gama-glutamyl transpeptidase, alkaline phosphatase), kidney function (serum urea, creatinine, proteinuria), and blood count were performed at week 0, week 4, week 8, week 12, week 24, and week 36. Furthermore, in patients with diabetes mellitus, glycosylated hemoglobin was evaluated at 3 months, and in patients with thyroid disease (possibly secondary to HCV infection), serum levels of TSH and fF4 were determined monthly. Patients with positive serum cryoglobulins were evaluated by monthly serum determination and proteinuria.

Strict monitoring of tacrolinemia was required in patients with liver transplantation.

Patients with HCV-associated lymphoma were also monitored by serum levels of lactate dehydrogenase and peripheral blood smear.

Results

Baseline Characteristics

A total of 587 patients were included in this study. The mean age in the study population was 62.1+/- 24.8 years (between 24 and 93 years). Distribution according to sex revealed a female predominance, without a significant age difference between men and women. A predominance of F4 fibrosis could be noticed. Further detailed baseline characteristics are presented in **Table 1**.

Table 1. Baseline characteristics of the study group.

Mean age	62.1±24.8 years
Sex ratio	Males: 194 (33.04%) Females: 263 (66.95%)
Mean HCV RNA	1 067 865±253.151 IU/mL
F2 fibrosis	83 patients among which – 43 patients with cryoglobulinemia – 8 patients with lymphoma – 29 patients with end-stage kidney disease – 3 patient after kidney transplantation
F3 fibrosis	185 patients among which – 11 patients with cryoglobulinemia – 3 patients with lymphoma
F4 fibrosis	315 patients among which – 7 patients with cryoglobulinemia – 5 patients with lymphoma
HCV relapse after liver transplantation	4 patients
Mean ALT levels	65.5±18.4 IU/mL
Mean bilirubin levels	1.2±0.4 mg/dL
Mean hemoglobin	12.7±2.8 g/dL

HCV – hepatitis C virus; ALT – alanine aminotranspherase.

Efficacy

We noticed that 4 patients presented detectable HCV RNA at the end of treatment (0.68%), 2 of them with an increase in viremia from baseline characteristic and 1 with HCV RNA at the limit of detectability (20 IU/mL). Twelve weeks after the end of treatment, only 3 patients had detectable HCV RNA; therefore, a cure of HCV infection was obtained in 99.48% of patients (582/585). The 3 non-responder patients were women with F4 fibrosis evaluated by Fibromax, high levels of transaminases (ALT 146 IU/mL, 88 IU/mL, and 92 IU/mL, respectively), and without significant comorbidities. One of the patients was a previous non-responder to antiviral therapy with peg-interferon and ribavirin, while the others were therapeutically naïve. All patients with liver transplantation achieved sustained virologic response.

Notably, antiviral treatment decreased the levels of proteinuria in patients with cryoglobulinemia (P=0.02, 95% CI odds ratio 1.14-1.56). Furthermore, proteinuria was dramatically decreased after the first month of therapy in a patient with systemic lupus erythematosus and class 4 lupus nephritis (from 4.3 g/24 h to 1.4 g/24 h); the decrease continued throughout the duration of therapy, reaching 0.6 g/24 h at the end of therapy and 0. 5g/24 h at SVR.

Safety

We recorded 2 deaths during antiviral treatment: 2 patients with F4 fibrosis and B-cell lymphoma, with serious hematologic decompensation. Both patients had begun treatment outside lymphoma remission: 1 patient without response to ibrutinib and risk of hepatic decompensation if attempted to treat with rituximab and 1 patient without prior hematologic diagnostic or treatment. After the initiation of antiviral treatment

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Table 2. Common adverse reactions in the study groups.

	Total group (N=587 patients)	Without ribavirin (n=343 patients)	With ribavirin (n=245 patients)	Chi-square
Asthenia	178 patients (30.32%)	56 patients (16.37%)	112 patients (49.79%)	-0.52
Nausea	213 patients (36.28%)	98 patients (28.57%)	115 patients (46.93%)	-0.47
Headaches	132 patients (22.48%)	43 patients (12.53%)	89 patients (36.32%)	-0.33

Table 3. Biologic abnormalities during direct-acting antiviral agent therapy in patients with and without ribavirin.

	Total group (N=587 patients)	With ribavirin (n=245 patients)	Without ribavirin (n=343 patients)	Chi-square
Anemia	293 patients (49.91%)	245 patients (100.0%)	38 patients (11.07%)	-0.82
Liver cytolysis	46 patients (7.83%)	28 patients (11.42%)	18 patients (5.24%)	-0.41
Cholestasis	37 patients (6.30%)	15 patients (6.12%)	12 patients (3.49%)	-0.23

(after 2 days and 2 months, respectively), both patients presented extensive abdominal and thoracic adenopathies with severe alteration in clinical status. Treatment with cyclophosphamide, vincristine, and prednisone for diffuse large B-cell non-Hodgkin lymphoma and dexametasone for small B-cell marginal zone non-Hodgkin lymphoma was attempted, without response. The other patients with lymphoma had registered remission for at least 6 months prior to the initiation of therapy, and both had an F2 degree of liver fibrosis.

Ribavirin was administered with weight-adjusted doses in 245 patients: 210 F4 patients, 31 F2 patients with end-stage kidney disease, and 4 patients after liver transplant. Common adverse effects of the antiviral treatment included asthenia, nausea, headaches. None of the patients had serious adverse events and none discontinued therapy because of adverse effects. All adverse effects were significantly more common in patients receiving ribavirin (asthenia, nausea, and headaches had *P* values of 0.02, 0.03, and 0.03, respectively; **Table 2**).

Furthermore, these adverse reactions were significantly more common in patients with diabetes mellitus (asthenia *P*=0.002, 95% CI risk ratio [RR] 1.5-1.8; nausea *P*=0.001, 95% CI RR 1.6-2.5; and headaches *P*=0.03, 95% CI RR 1.4-1.8) and arterial hypertension (asthenia *P*=0.001, 95% CI RR 1.9-2.6; nausea *P*=0.02, 95% CI RR 1.3-1.9; and headaches *P*=0.001, 95% CI RR 2.2-2.7).

The most frequent hematologic side effect was anemia (49.91%), noted especially in patients with F4 fibrosis who received ribavirin (n=210/210; *P*<0.01) but also in the patients with F2 fibrosis and end-stage kidney disease (**Table 3**). Hemoglobin values returned to normal after discontinuation of ribavirin. A total of 58 patients required 1 or 2 doses of erythropoietin to restore hemoglobin levels. Further abnormalities noted more frequently in patients who received ribavirin were cytolysis (*P*=0.04) and cholestasis (*P*=0.1). Transitory increase in liver enzymes (up to 3-fold normal values) were noticed in 7.83% of patients and resumed after the first 8 weeks without requiring medical intervention. Also, 6.30% of the patients presented slightly elevated levels of serum bilirubin (up to 2.1 mg/dL) in the first 4 weeks of treatment and were given ursodeoxycholic acid, with normalization of bilirubin levels at week 8.

Immune suppression with tacrolimus following liver or kidney transplant was particularly challenging in the setting of antiviral treatment. Dose reduction of tacrolimus to 0.5 mg/week was necessary in all patients, the day before beginning antiviral therapy. In 2 cases, patients overlapped their regular dose of 1.5 mg/day of tacrolimus with the antiviral treatment in the first day of therapy, and the result was an increase in tacrolinemia of up to 30 ng/mL. None of these patients presented kidney failure or neurologic symptoms; serum levels of tacrolimus decreased slowly during the first 3 weeks of therapy and, afterward, suppression could be reintroduced at the reduced dosage without further complications, but with weekly monitoring.

Discussion

In our study, we found that HCV genotype 1b-infected patients achieved SVR in 99% of cases after treatment with OMB/PTV/r+DSV±RBV. The high rates of SVR were not influenced by the degree of fibrosis or previous antiviral therapies. There were several minor adverse events related to treatment, and

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we found that these correlated significantly with the association of ribavirin.

Several studies have reported the high efficacy of OMB/PTV/r+DSV±RBV in achieving SVR in patients with chronic hepatitis or compensated cirrhosis [16-19]. The reported rates vary from 99.5% with ribavirin and 99.0% without ribavirin to 93.5%, 96.0%, and 100% according to the type of response to previous interferon therapy (non-responders, partial responders, and relapsers). Furthermore, there seems to be a negligible difference between SVR rates after antiviral treatment with or without ribavirin [20]. An international study performed on patients with and without cirrhosis who received antiviral treatment without ribavirin found SVR rates of 90.0% to 95.2% in patients without cirrhosis (treatment naïve or non-responders) and of 96.2% to 97.9% in patients with cirrhosis. Our findings are consistent with these findings, with a very high rate of SVR (99.37% combined rate for patients with or without cirrhosis) independent of discontinuation of ribavirin.

Although several studies have shown improvement of hematologic malignancies after interferon- based treatment of HVC [21,22], experience of all oral antiviral treatment in the setting of HCV-associated lymphoma is limited, mostly due to its novelty. Two case reports [23,24] have found that treatment with sofosbuvir and ribavirin (12 weeks) is useful in marginal zone lymphoma. A recent study including 32 patients with HCV-associated diffuse large B-cell lymphoma proved the safety and efficacy of direct-acting antivirals (including OMB/PTV/r+DSV in 2 cases) either after or during first-line immunochemotherapy [25]. We report a 50% survival rate in patients with HCV-associated lymphoma and antiviral therapy. In this case, selection of patients is essential, and we strongly argue for antiviral treatment as early as possible in the evolution of liver disease in association with lymphoma. Although the scarcity of data makes this statistically unprovable, we support the fact that immunochemotherapy should be considered before antiviral therapy and that antiviral agents should be started when remission is obtained.

Most studies report minor adverse reactions to OMB/PTV/r+DSV [20,26] and statistically lower rates compared to treatment with peg-interferon, ribavirin, and a first generation non-structural protein 3/4A protease inhibitor (reactions considered were anemia, pruritus, rash, nausea, and asthenia). To the best of our knowledge, no study has related the incidence of minor adverse reactions to the presence of comorbidities. We have found that patients with diabetes mellitus and/or arterial hypertension are more prone to asthenia, nausea, and headaches. Notably, all these reactions are hard to quantify and have a strong personal impact; therefore, their appearance should not constitute a reason for altering antiviral therapy.

Minor disturbances in liver enzymes and hemoglobin levels have been reported [20,27] even without adding ribavirin in the therapeutic regimen, without correlation to the degree of fibrosis or prior response to antiviral therapy. Our data are consistent with those from studies including ribavirin. We report higher rates of increased liver enzymes or bilirubin (7.83% and 6.3%, respectively) compared with literature data (1.7% and 2.4%, respectively).

Relapse of HCV infection after liver transplantation is a rule, and these patients present a more rapid evolution toward cirrhosis and liver failure [28,29], and therefore these patients benefit from antiviral therapy as soon as possible. OMB/PTV/r+DSV+RBV has high efficiency in these patients (SVR obtained in 33 of 34 patients), with a 17% rate of anemia [30]. Careful monitoring of immune suppression is the criterion standard in this case [31] owing to the fact that OMB/PTV/r+DSV increases the concentration of tacrolimus and decreases elimination.

An important aspect of HCV hepatitis is its association with mixed cryoglobulinemia and antiviral therapy, which should also be considered from the perspective of improving signs and symptoms of renal involvement (cryoglobulinemia-associated glomerulonephritis). Sofosbuvir-based therapeutic regimens have proven efficient in reducing proteinuria and serum creatinine in these patients [32]. One case report [33] has described the effect of OMB/PTV/r+DSV on reducing neurologic symptoms of cryoglobulinemia and lowering serum levels of cryoglobulins below detectability. Recently, a detailed article on extrahepatic manifestations in HCV hepatitis cites a reduction of cryoglobulin levels in 5 of 12 cases [34]. We have found a significant reduction in serum levels of cryoglobulins as well as a reduction in proteinuria.

Ultimately, the main goal of all oral antiviral therapy is the reduction of complications due to evolving liver disease [35]. The most recent EASL guidelines recommend using pan-genotipic therapeutic regimens, although in genotype 1, there may be an additional benefit from using genotype-specific direct-acting antiviral agents [36-38]. Ribavirin is currently reserved for patients with decompensated cirrhosis, regardless of genotype. However, as our study confirms, administering ribavirin requires careful monitoring, as patients often develop adverse clinical and serologic reactions.

There were several limitations in this study. First, the study was conducted according to the National Treatment Protocol and a careful selection of patients was required; also, as this program was developed in the early days of direct-acting antiviral agents therapy, the criteria for inclusion was restrictive. Second, the methods of evaluating the presence of adverse events were subjective, based on the reports of the patients and no objective scores were used.

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Conclusions

OMB/PTV/r+DSV has shown high efficacy in inducing sustained virologic response and thus decreasing the risk of evolution toward cirrhosis and decompensated cirrhosis, with a real-life SVR rate of 99.48% in a large heterogenous group. Altogether, this therapeutic option is characterized by a small rate of serious adverse events and manageable minor adverse events. Association with direct-acting antiviral agents and ribavirin increases the risk of adverse events, especially in patients with advanced fibrosis.

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