Safety assessment in Child A cirrhotic patients treated with Ombitasvir/ Paritaprevir/Ritonavir and Dasabuvir with Ribavirin

E.D. Manea[1], I. Stefan[2,3], C. Olariu[4], O.C. Calina[1], R.E. Jipa[1], A. Hristea[1,4]

(1) "Prof. Dr. Matei Bals" National Institute for Infectious Diseases, Bucharest, Romania ; (2) "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania ; (3) 3 "Titu Maiorescu" University, Bucharest, Romania ; (4)4 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania .

Abstract

Background : **In our country, the national program for hepatitis C virus treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir was approved for patients with stage four of liver fibrosis and stage three associated with specific comorbidities. Our aim was to analyze the characteristics associated with the presence of adverse events in patients receiving this antiviral regimen, with ribavirin in cirrhotic patients.**

Methods : **We prospectively studied a cohort of adults with hepatitis C virus infection with Child A cirrhosis, treated for 12 weeks with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin, which have been followed in an infectious diseases tertiary-care hospital.**

Results : **We included 137 adult patients diagnosed with compensated cirrhosis, hepatitis C virus genotype 1b infected, 82 (60%) previously treated. We recorded 201 adverse events in 98 (71.5%) patients, with a median number of events per patient of one. The intensity of adverse events was classified as mild, moderate and severe in 50%, 36% and 14% of cases, respectively. Forty-five (22%) episodes required medical intervention. The most frequently reported adverse events were pruritus 34(35%), asthenia 22(22%) and insomnia 15(15%). The presence of severe adverse events was associated with the presence of comorbidities (p = 0.01, OR : 9.5, 95% CI : 1.2-74.3) and with the presence of associated medication (p = 0.02, OR : 3.9, 95% CI : 1.08-14.2). At the end of current treatment, 136 (99.2%) patients had undetectable viral load.**

Conclusion : **We found a high number of adverse events, but most of them were mild or moderate and only one quarter of them required medical intervention. Only severe adverse events were associated with comorbidities and associated medication.** (Acta Gastroenterol. belg., **2018**, 81, **9-13**).

Key words : adverse events, hepatitis C virus, cirrhosis, ombitasvir/ paritaprevir/ritonavir and dasabuvir.

Introduction

The interferon-free combination of paritaprevir/ ritonavir-ombitasvir and dasabuvir (OBV/PTV/r/DSV) with or without ribavirin is indicated for the treatment of chronic hepatitis C in both treatment-naïve and experienced patients, with genotype one and four infections. In our country, the national program for hepatitis C virus (HCV) treatment with OBV/PTV/r/ DSV, with or without ribavirin was approved only for patients with stage four liver fibrosis and stage three associated with type one diabetes mellitus, autoimmune diseases and severe depression. Although the OBV/ PTV/r/DSV regimen has demonstrated a high level of efficacy in clinical trials, to date, there are limited data regarding its safety and tolerance in patients with compensated cirrhosis, in real clinical practice. Our aim was to analyze the characteristics associated with the presence of adverse events in HCV genotype one infected patients with compensated cirrhosis, receiving OBV/PTV/r/DSV with ribavirin, for 12 weeks.

Methods

We performed an observational study of a prospective adults cohort with HCV infection with stage four liver fibrosis (Child A cirrhosis), treated for 12 weeks with OBV/PTV/r (25/150/100 mg once daily) and DSV (250 mg twice daily), with ribavirin (1000 mg/day in patients weighing <75 kg or 1200 mg/day in those weighing >75 kg), between December 2015 and January 2017, in a tertiary-care hospital. The viral genotype was determined before starting the treatment and all the patients were infected with genotype 1b. In Romania 98% of patients are infected with this genotype (1).

The inclusion criteria were : age over 18 years, confirmed diagnosis of HCV infection (detectable viral load, any value), F4 fibrosis, stage Child A, negative hepatitis B surface antigen, negative HIV serology and abdominal ultrasound without evidence of nodules suggesting hepatocellular carcinoma. We excluded patients diagnosed with Child B and Child C cirrhosis, with a lower than four stage of fibrosis, pregnant women and patients with suspicion of hepatocellular carcinoma (based on the high value of alpha fetoprotein level and suggestive modifications on imaging). All patients signed an informed consent before the inclusion in the study. Hospital ethics committee approved the study.
Hepatic fibrosis was assessed at baseline by the same method in all patients (Fibromax, BioPredictive test, with the values between 0.745 and 1 corresponding to

Correspondence to : Adriana Hristea, National Institute of Infectious Diseases "Prof Dr Matei Bals", no 1 Calistrat Grozovici street, sect 2, 021105, Bucharest, Romania. Phone : +40213186100 ext 5204. Mobile phone : +40723562370. Fax : +40213186090.
E-mail: adriana_hristea@yahoo.com

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stage four of liver fibrosis). All patients were classified according to the Charlson comorbidity index. The patients were evaluated monthly during the treatment, at the end of therapy and at 12 weeks after the end of therapy. We analyzed the incidence of adverse events, according to presence of comorbidities and/or associated medication, age, presence of esophageal varices, baseline values of albumin, platelet and alpha fetoprotein and also according to criteria cited by EASL guidelines as markers associated with a higher relapse rate: alpha fetoprotein level ≥ 20 ng/ml and platelet count < $90x10^9$/L (2). We defined the adverse event as 1) mild if the patient reported a transient discomfort (<48 hours), with no medical intervention required, 2) moderate if the adverse event implied moderate limitation in activity without or with minimal therapy required and 3) severe if the adverse event implied marked limitation in activity, with medical intervention required and possible hospitalization. We monitored the patients for adverse events from initiation of treatment until 30 days following the end of antiviral treatment.The data collected were analysed using the statistical analysis software package SPSS 23.0 (IBM SPSS, Chicago, IL, USA). Differences between groups were analyzed using the Mann-Whitney U test for continuous variables and the chi-square test for dichotomous variables.

Results

We included 137 adult patients diagnosed with compensated cirrhosis, HCV genotype 1b infected. The median viral load at the moment of treatment initiation was 998.000 IU/mL. Seventy-four (54%) patients were male and the median age was 63 years, with inter-quartile range (IQR) of 57-69 years. The baseline biochemical characteristics of the patients are shown in Table 1.

All patients were evaluated at baseline for liver fibrosis with Fibromax (Biopredictive test) and all of them had stage four of liver fibrosis, with a median value of 0.9 (IQR : 0.84-0.93). Fifty-one patients (37%) were also evaluated with Fibroscan, with a median value of 22.9 kPa (IQR: 18.3-36.2 kPa).

Eighty-two (60%) patients were previously treated for HCV infection : 77 (94%) patients with pegylated interferon alpha and ribavirin, one (1%) patient with interferon only, one (1%) patient with the triple regimen (pegylated interferon, ribavirin and telaprevir/boceprevir) and three (4%) patients were exposed to multiple antiviral regimens. Forty-seven (57%) treatment-experienced patients were non-responders and 35 (43%) were relapsers following the previous treatment. At the end of the treatment with OBV/PTV/r/DSV and ribavirin, 136 (99.2%) patients had undetectable viral load and had sustained virologic response. The median Charlson comorbidity index was 3 (IQR : 3-4). Ninety-five (69%) patients had another disease diagnosed before starting antiviral treatment. The most frequent comorbidities were cardiovascular diseases in 49 (52%) patients and diabetes mellitus in 37 (39%) patients, followed by chronic renal disease, chronic respiratory pathology and psychiatric pathology (each one in less than 5% of patients). The main cardiovascular conditions were arterial hypertension, in 47 (34%) patients and ischemic heart disease, in 11 (8%) patients, followed by atrial fibrillation (4 patients), congestive heart failure (2 patients) and history of a major cardiac event (myocardial infarction in one patient and stroke in one patient). Nineteen (20%) patients had multiple comorbidities. Eighty-four (61%) patients also received other medication during antiviral treatment and 22 (16%) patients received more than three different drug classes, but without major potential drug-drug interactions. The concomitant medication recorded was: angiotensin converting enzyme inhibitors in 23 (17%) patients, angiotensin receptor blockers in 12 (9%) patients, beta blockers in 27 (20%) patients, calcium channel blockers in 13 (9%) patients, thiazide-like diuretics in 20 (15%) patients, loop diuretics in 6 (4%) patients, aldosterone antagonists in 5 (4%) patients, oral antidiabetics in 13 (9%) patients, insuline in 13 (9%) patients, antiagreggants in 10 (7%) patients, oral anticoagulants in 5 (4%) patients, statins in 2 (1%) patients, digitalis medication in 1 (0.7%) patient, levothyrozine in 9 (7%) patients, antidepressants (selective serotonin reuptake inhibitors) in 3 (2%) patients, anxiolytics in 1 (0.7%) patient and dopamine agonists in 1 (0.7%) patient.

An upper gastrointestinal endoscopy was performed in 88 (64%) patients and 33 (38%) of them had esophageal varices.

All patients underwent abdominal ultrasound at baseline. Sixteen (12%) patients had splenomegaly over 12 mm diameter. The median portal vein diameter was 11 mm (IQR : 11-13 mm) and the median retro-pancreatic splenic vein diameter was 6 mm (IQR : 5-7 mm). Neither ascitis nor liver masses were found at the baseline ultrasound evaluation. A contrast-enhanced computed tomography was performed in 24 (18%) patients presenting elevated alpha fetoprotein (over 50 ng/ml) and there were no signs of hepatocellular carcinoma.

We recorded a number of 201 adverse events in 98 (71.5%) patients. The median number of adverse events

Table 1. – **Patient baseline biochemical characteristics**

Variables	Median (IQR*)
Alanin aminotransferase (UI/L)	101 (72-147)
Bilirubin (mg/dL)	1 (0.8-1.3)
INR**	1.09 (1.03-1.18)
Albumin (g/L)	4.2 (3.9-4.5)
Haemoglobin (g/dL)	14.5 (13.5-15.5)
Platelets (cells/dL)	133.000 (101.000-176.000)
Creatinine (mg/dL)	0.8 (0.7-0.9)
Sodium (mEq/L)	142 (140-143)
Potassium (mEq/L)	4.4 (4.2-4.8)
Alpha fetoprotein (ng/mL)	11.1 (6.47-25.06)

* interquartile range. **international normalized ratio

per patient was one (IQR: 0-2), with 40 (41%) patients with one adverse event, 24 (25%) two adverse events, 19 (19%) three adverse events and 15 (15%) with more than three adverse events. The intensity of adverse events was classified as mild in 50% of cases, moderate in 36% of cases and severe in 14% of cases. Forty-five (22%) episodes required medical intervention. Only one patient interrupted the treatment after two weeks due to an unrelated reason (newly diagnosed pancreatic cancer, without liver involvement). The adverse events rapidly resolved in 163 (78%) episodes. In 45 (22%) cases the adverse event persisted during the antiviral treatment, but only 31% of them persisted after the end of treatment.

The reported adverse events were pruritus in 34 (35%) patients, asthenia in 22 (22%) patients, insomnia in 15 (15%) patients, fatigue in 13 (13%) patients, nausea in 12 (12%) patients, headache in 12 (12%) patients, arthralgias and myalgias in nine (9%) patients, rash in six (6%) patients, diarrhea in five (5%) patients, abdominal pain in four (4%) patients, cardiac arrhythmia in three (3%) patients – ventricular extrasystoles, syncope due to severe bradycardia and ventricular bigeminy, ascites in two (2%) patients, peripheral edema in two (2%) patients and mononeuritis of the abducens nerve in one (1%) patient. The most frequently seen laboratory abnormalities were hyperbilirubinemia and anemia each in 25 (26%) patients, followed by acute renal insufficiency in four (4%) patients – the maximal value of creatinine being 2.6 mg/dL (creatinine cleareance 26 mL/min/1.73m^2), hyperkalemia in three (3%) patients – the maximal value recorded in one patient, 8.3 mEq/L, hyponatremia in two (2%) – the minimal value being 115 mEq/L and abnormal pancreatic tests in two (2%)

Table 2. – **Patient baseline characteristics according to the presence of adverse events**

	Patients with adverse events N=98 N(%) or Median(IQR)	**Patients without adverse events N=39 N(%) or Median(IQR)**	**p OR (95% CI)**
Male sex	52 (53)	22 (56)	0.7 0.8 (0.4-1.8)
Age (years)	64 (57-69)	62 (57-70)	0.8
RNA-HCV	1.024.304 (410.500-1.949.589)	928.000 (229.136-1.870.000)	0.8
Comorbidities	68 (69)	27 (69)	0.9 1 (0.4-2.2)
Co-medication	62 (63)	22 (56)	0.4 1.3 (0.6-2.8)
Angiotensin converting enzyme inhibitors	20 (20)	3 (8)	0.07 3.07 (0.8-11.02)
Angiotensin receptor blockers	7 (7)	5 (13)	0.2 0.5 (0.1-1.7)
Beta blockers	19 (19)	8 (21)	0.8 0.9 (0.3-2.3)
Calcium channel blockers	10 (10)	3 (8)	0.6 1.3 (0.3-5.2)
Thiazid-like diuretics	16 (16)	4 (10)	0.3 1.7 (0.5-5.4)
Oral antidiabetics	10 (10)	3 (8)	0.6 1.3 (0.3-5.2)
Insuline	10 (10)	3 (8)	0.6 1.3 (0.3-5.2)
Antiagreggants	6 (6)	4 (10)	0.4 0.5 (0.1-2.1)
Levothyrozine	7 (7)	2 (5)	0.6 1.4 (0.2-7.1)
Co-medication with more than three different drug classes	17 (17)	5 (13)	0.5 1.4 (0.4-4.1)
Median Charlson comorbidity index	3 (3-4)	3 (3-4)	0.5
Esophageal varices*	25 (26)	8 (12)	0.7 0.8 (0.3-2.4)
Albumin value, g/L	4.2 (3.8-4.5)	4.2 (3.9-4.4)	0.7
Platelet count, cells/dL	132.000 (99.000-184.000)	134.000 (107.000-169.000)	0.4
Alpha fetoprotein level, ng/mL	11.05 (7-28)	11.6 (5.67-22.9)	0.3
Platelet count less than 90.000/dL	18 (18)	5 (13)	0.4 1.5 (0.5-4.4)
Alpha fetoprotein level over 20ng/mL	22 (22)	8 (21)	0.7 1.2 (0.4-3.1)

* 88 patients were evaluated

patients – the maximal value of lipase being 603 UI/L. In patients with hyperbilirubinemia, the median bilirubin value was 2.7 mg/dL (IQR : 2.35-3.25) at four weeks of treatment, while the median bilirubin value at the moment of treatment initiation was 1.2 mg/dL (IQR : 0.95-1.65). Eleven patients had a value of bilirubin over 3 mg/dL and the maximal value of bilirubin recorded was 6.3 mg/dL. In patients with anemia, the median haemoglobin value was 10.3 g/dL (IQR : 9.9-11.6) at four weeks of treatment, with a median haemoglobin of 13.5 g/dL (IQR : 12.75-14.2) at the beginning of treatment. Haemoglobin less than 10 g/dL was recorded in eight patients and the minimal haemoglobin found during treatment was 8.4 g/dL.

The main adverse events classified as severe were: anemia (in five patients), nausea and vomiting requiring hospitalization and intravenous re-equilibration (in five patients), severe diarrhea (in two patients), acute renal insufficiency (in three patients), severe hyperkalemia (in two patients) and cardiac arrhythmia (in three patients).

In Table 2 are the variables that were examined for association with the adverse events. Furthermore, we analyzed potential factors associated with severe adverse events and we found that the severe adverse events were associated with the presence of comorbidities in 18 (19%) cases versus the absence of comorbidities in one (1%) case, p = 0.01 (OR : 9.5, 95% CI : 1.2-74.3) and with the presence of associated medication in 16 (19%) cases versus the absence of associated medication in three (6%) cases, p = 0.02 (OR : 3.9, 95% CI : 1.08-14.2). We also analyzed the concomitant medication classified as specific drug classes and we found that severe adverse events were associated with the use of beta blockers in eight (42%) cases versus 19 (16%) cases without use of beta blockers, p = 0.008 (OR : 3.7, 95% CI : 1.3-10.6) and with the use of angiotensin receptor blockers in four (21%) cases versus eight (7%) cases without the use of angiotensin receptor blockers, p = 0.04 (OR : 3.6, 95% CI : 0.9-13.6). Six (32%) patients with severe adverse events received as a concomitant medication more than three different drug classes versus 16 (14%) patients with fewer co medication or none, p = 0.04 (OR : 2.9, 95% CI : 0.9-8.8).

Discussion

Our study evaluated the safety of the antiviral regimen with OBV/PTV/r/DSV, with ribavirin, in the 12 weeks administration, under routine clinical practice in patients infected with genotype 1b HCV with Child A cirrhosis. We intended to identify the factors associated with adverse events in this population. We noted a high rate of virologic response at the end of the treatment (99.2%). The study cohort included elderly patients (median age over 60 years), most of them with comorbidities (69%). We recorded at least one adverse event in 71.5% of patients.

The proportion of adverse events reported in our study was similar with the rate of adverse events reported in non-cirrhotic patients in the clinical trial PEARL-II (79.1% in 91 non-cirrhotic patients) (3). Moreover, real-world data from the AMBER study showed a similar proportion of 76.9% adverse events in 119 patients with stage four liver fibrosis, receiving OBV/PTV/r/DSV with ribavirin, as opposed to a proportion of 58.5% adverse events in the group of patients receiving the antiviral regimen without ribavirin (4).

Other studies reported a higher rate of adverse events. The clinical trial TURQUOISE-II, including 208 patients with compensated cirrhosis and receiving the combined regimen with ribavirin, reported a rate of 91.8% adverse events (5). Also, a recently published study, with real-life data from 86 patients of which 80.2% were cirrhotic, reported a rate of 96.5% adverse events (6).

In contrast, an overall rate of 45% adverse events was reported in a real-world study from the German Hepatitis C Registry including 389 patients, of which 52% had stage four of liver fibrosis (7).

In all these studies the majority of reported adverse events were of mild intensity, which is consistent with our findings. The majority of the adverse events in our study were of mild intensity (50%) and only 22% required medical intervention. Our proportion of 14% severe adverse events was higher than the proportions reported by other studies, in which the severity varied from 2.2% (the clinical trial PEARL-II), 2.3% (the German Hepatitis C Registry), 2.6% (AMBER study) and 6.2% (TURQUOISE-II) to 12.8% (Esther Chamorro-de-Vega et al) (3-7). All these studies emphasized the association of a higher number of adverse events with the administration of ribavirin. In our study, neither antiviral treatment nor ribavirin has been discontinued because of adverse events.

The most common adverse events reported in our study were similar to those reported in the clinical trials and other real-life studies, with pruritus, asthenia, insomnia, headache and nausea being the most frequently reported. One patient developed severe diplopia due to a mononeuritis of the abducens nerve, during the first month of therapy. The patient had been previously diagnosed with arterial hypertension and type two diabetes mellitus, but both conditions were well controlled with specific treatment. The patient was treated with tapering doses of corticosteroids and the diplopia slowly improved, with complete resolution at four months after the end of antiviral treatment. Furthermore, another patient had a syncope between week four and week eight of antiviral treatment, due to severe bradycardia (ventricular rate less than 50 beats/minute). The patient was receiving concomitant therapy with propranolol, 40mg three times per day, as prophylaxis for bleeding secondary to esophageal varices and we suspected potential drug-drug interactions. After this episode we reduced the doses of propranolol and the ventricular rate remained within normal range until the end of the antiviral treatment.

Another patient, diagnosed with atrial fibrillation on oral anticoagulant treatment, developed ventricular bigeminy after the first two weeks of therapy, requiring very close monitoring of cardiac activity during the whole antiviral therapy.

Regarding the laboratory abnormalities, anemia and hyperbilirubinemia prevailed, both of mild intensity, which is consistent with the existing data. Unlike previously mentioned studies, we found a few cases of hyperkalemia (one of them with severe hyperkalemia of 8.3 mEq/L, leading to serious cardiac arrhythmia and without other apparent cause for hyperkalemia), moderate hyponatremia and moderate pancreatic reaction.

We did not find any association between the presence of adverse events and the patients' baseline characteristics : age, presence of comorbidities, associated medication, esophageal varices, albumin value, platelet count and alpha protein level. Nevertheless, the severe adverse events had a statistically significant association with the presence of comorbidities and associated medication.

The main contribution of our study was investigating potential factors associated with adverse events and the safety of OBV/PTV/r/DSV in combination with ribavirin in a large number of cirrhotic patients, while most of the studies have focused on efficacy. The limitation was that we analyzed exclusively patients with stage four liver fibrosis, treated with ribavirin, because of the national program criteria which only allowed the inclusion of a few patients with stage three liver fibrosis, so we could not assess the potential influence of fibrosis staging and ribavirin on the rate of adverse events.

Conclusion

In conclusion, we found a high number of adverse events, but most of them were mild or moderate and only one quarter of them required medical intervention. Only severe adverse events were associated with comorbidities and associated medication, especially with co administration of beta blockers, angiotensin receptor blockers and combination of more than three different drug classes Our findings suggest the need to monitor closely these patients. Since we reported unusual adverse events, which have not been mentioned in previous studies, further surveillance is necessary to identify all kinds of adverse events related to treatment.

Conflict of interest

The authors have nothing to disclose.

References

1. PETRUZZIELLO A., MARIGLIANO S., LOQUERCIO G., CACCIAPUOTI C. Hepatitis C virus (HCV) genotypes distribution: an epidemiological up-date in Europe. *Infect. Agent. Cancer*, 2016, **11** : 53.
2. EASL Recommendations on Treatment of Hepatitis C 2016. *J. Hepatol.*, (2016), http://dx.doi.org/10.1016/j. jhep.2016.09.001.
3. ANDREONE P., COLOMBO M.G., ENEJOSA J.V., KOKSAL I., FERENCI P., MAIERON A. *et al*. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir achieves 97% and 100% sustained virologic response with or without Ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology*, 2014, **147** : 359-365.
4. FLISIAK R., JANCZEWSKA E., WAWRZYNOWICZ-SYCZEWSKA M., JAROSZEWICZ J., ZAREBSKA-MICHALUK D., NAZZAL K. *et al*. Efficacy and safety of Paritaprevir/r/Ombitasvir/Dasabuvir ± Ribavirin in GT1 HCV infected patients treated in real life settings (AMBER study: interim analysis) AMBER-GT1 : summary. *Aliment. Pharmacol. Ther.*, 2016, **44** : 946-956.
5. POORDAD F., HEZODE C., TRINH R., KOWDLEY K.V., ZEUZEM S., AGARWAL K. *et al*. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *N. Engl. J. Med.*, 2014, **370** : 1973-82.
6. CHAMORRO-DE-VEGA E., GIMENEZ-MANZORRO A., RODRIGUEZ-GONZALEZ C.G., ESCUDERO-VILAPLANA V., BORRELL R.C., IBANEZ-GARCIA S. *et al*. Effectiveness and Safety of Ombitasvir/ Paritaprevir/Ritonavir and Dasabuvir. With or Without Ribavirin for HCV Genotype 1 Infection for 12 Weeks Under Routine Clinical Practice. *Ann. Pharmacother.*, 2016, **50** (11) : 901-908.
7. HINRICHSEN H., WEDEMEYER H., CHRISTENSEN S., SARRAZIN C.M., BAUMGARTEN A., MAUSS S. *et al*. Real-world safety and effectiveness of Ombitasvir/ Paritaprevir/R with Dasabuvir and/or Ribavirin in the German Hepatitis C Registry. *J. Hepatol.*, 2016, **64** : 159-S182.