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Real-life data on the efficacy and safety of ombitasvir/paritaprevir/ /ritonavir + dasabuvir + ribavirin in the patients with genotype 1 chronic hepatitis C virus infection in Serbia

Podaci iz realnog života o efikasnosti i bezbednosti ombitasvir/ /paritaprevir/ritonavir + dasabuvir + ribavirin režima kod bolesnika sa genop 1 hepas C virusnom infekcijom u Srbiji

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Abstract

Background/Aim. The era of direct-acting antiviral (DAA) regimen in the treatment of chronic hepatitis C virus (HCV) started in 2011. The aim of this study was to assess the antiviral efficacy and safety of DAA regimen, ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) + dasabuvir (DSV) + ribavirin (RBV), in patients with chronic HCV infection, genotype 1. **Methods.** The real-life data were collected. The study was multicentric and included seven infectious diseases and hepatology departments in Serbia. A total of 21 patients were enrolled in the OBV/PTV/r + DSV + RBV early access program, 20 of which were previously treated with pegylated interferon + RBV, while 1 was treatment-naive. All patients received the adequate doses of these antiviral drugs. RBV was not given to the patients with HCV genotype 1b infection according to the therapeutic protocol. For the majority of patient, the treatment duration lasted for 12 weeks. For the patients with liver cirrhosis, who were infected with HCV genotype 1a, the duration of treatment was 24 weeks. Viremia was assessed at four points in time: at baseline, 4 weeks after the treatment beginning (rapid viral response, RVR), 12 or 24 weeks after the treatment beginning (end of treatment response – ETR) and 12 weeks after the end of treatment (sustained viral response – SVR). SVR, as a confirmation of the absence of HCV was considered as endpoint of successful treatment. **Results.** Complete RVR, ETR and SVR were achieved in 64.71%, 85.71% and 95.24% of the patients, respectively. Only 3 patients had mild adverse effects which did not required dose reduction. **Conclusion.** The treatment of the patients with a chronic HCV infection with OBV/PTV/r + DSV + RBV resulted in excellent antiviral activity and tolerability.

Key words:
antiviral agents; drug therapy, combination; hepatitis c, chronic; ritonavir; sulfonamides.

Apstrakt

Uvod/Cilj. Era direktno delujućeg antivirusnog (DAA) režima lečenja bolesnika sa hroničnom hepatitis C virusnom (HCV) infekcijom započela je 2011. godine. Cilj rada bio je ispitivanje efikasnosti i bezbednosti DAA režima ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r) + dasabuvir (DSV) + ribavirin (RBV), kod bolesnika sa genotip 1 HCV infekci-

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jom u Srbiji. **Metode.** U multicentričnu studiju je bilo uključeno sedam centara u Srbiji. Prikupljeni su podaci iz realnog života. U rani pristupni program OBV/PTV/r + DSV + RBV bio je uključen 21 bolesnik od kojih jedan nije prethodno lečen, dok je ostalih 20 prethodno lečeno pegilovanim interferonom i RBV. Svi bolesnici su dobijali odgovarajuće doze lekova. Bolesnici sa HCV genotipom 1b nisu dobijali RBV u skladu sa terapijskim protokolom. Za većinu bolesnika trajanje terapije je iznosilo 12 nedelja. Za četvoro bolesnika sa cirozom i HCV genotipom 1a trajanje terapije je iznosilo 24 nedelje. Viremija je određivana četiri puta: pre početka terapije, 4 nedelje posle početka terapije (rapidni virusološko odgovor – RVR), 12 ili 24 nedelje nakon početka terapije (kraj terapije – ETR) i 12 nedelja nakon završetka terapije (stabilan virusološki odgovor – SVR). Postignut SVR kao potvrda odsustva virusne RNK u serumu, smatran je završnicom uspešnog lečenja. **Rezultati.** Kompletan RVR, ETR i SVR postignut je kod 64,71%, 85,71%, i 95,24% bolesnika sukcesivno. Samo 3 bolesnika imali su blage neželjene efekte koji nisu zahtevali korekciju doze lekova. **Zaključak.** Lečenje bolesnika sa hroničnom HCV infekcijom sa OBV/PTV/r + DSV + RBV pokazalo je odličnu antivirusnu aktivnost i podnošljivost.

Ključne reči:
antivirotici; lečenje, kombinovano; hepatitis c, hronični; ritonavir; sulfonamidi.

Introduction

Hepatitis C virus (HCV) was identified as one of the non-A-non-B hepatitis virus in 1989 [1]. It was estimated that it causes a chronic viral hepatitis in circa 71 million people throughout the world [2]. This disease that emulates the epidemiology of HIV/AIDS is also a risk factor in the development of hepatic cancer, since up to a third of the patients with chronic hepatitis C infection develop liver cirrhosis [3]. The prevalence of hepatitis C infection is highest in the Eastern Mediterranean basin (2.3%) and in Europe (1.5%), while in the rest of the world it amounts 0.5%–1% [4]. Some local data from the Balkans give an estimated prevalence of only 0.25% [5] and a relatively recent study in Serbia reports a seroprevalence of 0.19% among blood donors [6] and 1.13% in the general population [7]. Incidence of hepatitis C infections is 1.75 million, or 23.7 new infections per 100,000 people [4]. A total of seven HCV genotypes have been identified so far, with genotypes 1 and 3 responsible for 46.2% and 30% of all HCV infections, respectively. Genotype 4 is most prevalent in Africa and Middle East, where it can account for as much as 90% of all cases, such as in Egypt [8]. HCV genotype 1b is the most prevalent one in Serbia [6].

After the introduction of recombinant interferons (rIFN) in 1991 and pegylated interferons (PEG-IFN) in 2001, the combination of the latters with ribavirin (RBV) became a standard treatment, with the sustained viral response (SVR) of 44%–51% for genotype 1 and 70% for genotypes 2 and 3. Indeed, in a recent Serbian study this combination assured a total SVR of 70.5% [9]. Unfortunatelly, this combination is still the standard of care in Serbia. The era of direct-acting antivirals (DAAs) in the treatment of HCV started in 2011, when telaprevir (TVR) and boceprevir (BOC), as the first generation, were approved [1]. Our own study with BOC + PEG-IFN + RBV in the genotype 1-infected chronic HVC patients with advanced fibrosis assured the overall SVR of only 55% [10].

The low percentage of obtained SVRs and numerous adverse effects of the interferon-based regimens prompted the development of new therapeutic schemes, including the second generation of DAAs, such as the combination of ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) + dasabuvir (SV). The results of phase 3 trials and real-world data with this type of treatment were excellent, with obtained SVRs of more than 93% [11, 12]. Moreover, this therapeutic regimen without ribavirin assured in the TURQUOISE-III phase IIIb open-label clinical study the 100% SVR in the HCV subgenotype 1b-infected cirrhotic patients [13].

The aim of this study was to evaluate the efficacy and safety of OBV/PTV/r + DSV therapeutic regimen in the patients with a chronic HCV infection in Serbia included in the early access program.

Methods

This prospective, multicentric, real-life clinical study was performed at seven infectology and hepatology departments of five Serbian university clinics in Belgrade, Novi Sad, Niš and Kragujevac.

The diagnostic and treatment approach to these patients was inspired by the Polish real-life (AMBER) study [14, 15]. A total of 21 male and female patients were included in this study. They had a chronic HCV infection, caused by genotype 1, and majority of them were previously treated (nonresponders or relapsers). The anatomical status of their livers was assessed by elastography (fibrosis scores F0-F4), while the hepatic functional status was assessed by the values of bilirubin, albumin, international normalized ratio (INR), alanine-aminotransferase (ALT), aspartate aminotransferase (AST) and presence of encephalopathy and ascites. Based on these parameters, the Child-Pugh score was calculated in order to assess the existence of liver dysfunction. Some additional parameters were also estimated: hemoglobin, red blood cell (RBC), white blood cell (WBC), platelet (PTL) counts and alpha-fetoprotein (AFP) concentrations.

All patients in this study received the dose of OBV/PTV/r 12.5 mg/75 mg/5 mg, two tablets as a morning dose and DSV 250 mg dose of 500 mg/day divided into two doses. The dose of RBV, administered in 200 mg tablets, was 1,000 mg/day for the patients weighing < 75 kg or 1,200 mg/day for the patients weighing > 75 kg divided into two doses. It was planned to reduce the dose of RBV in the patients who developed severe adverse effects, or laboratory abnormalities, such as anemia. RBV was given to all patients except to those with HCV genotype 1b. For the majority of patient the treatment duration was 12 weeks. The duration of the treatment was extended to 24 weeks in the high-risk patients, i.e., patients with liver cirrhosis who were infected with HCV genotype 1a.

Viremia was assessed at baseline, 4 weeks after beginning of treatment (rapid viral response – RVR), 12 or 24 weeks after beginning of treatment (the end of treatment response – ETR), and 12 weeks after the end of treatment (SVR). A number of replications of viral RNA was expressed in IU/mL. The HCV levels were obtained by the quantitative polymerase chain reaction (PCR) assay. The viral RNA detection limit was ≥ 12 IU/mL.

Descriptive statistics such as the calculation of mean values and their standard deviations (SD) were used.

Results

A total of 21 patients with the HCV infection were included in this study. Twenty of them were previously treated with PEG-IFN and RBV, while 1 was treatment-naive. Among previously treated patients, 18 paients were null-responders and 2 patients were relapsers (Table 1).

All 21 patients were infected with genotype 1. In 11 of them subgenotyping was not performed, 1 patient had a combined genotype 1a and 1b infection, 1 had a genotype 1a, while 8 were infected with genotype 1b. Out of 21 patients, 9 (42.85%) had fibrosis stages F3/F4, which are considered difficult to treat. Initial viremia varied over the large range of values (152×10^3–527×10^6 IU/mL) with the median of 1.17×10^6 IU/mL. The liver function in these patients was well preserved with the Child-Pugh score class A for 18 patients, with 3 patients without the Child-Pugh score. All the biochemical and hematological parameters were within the normal range of values (Table 1).

Table 1

Baseline demographic and clinical characteristics of patients with chronic hepatitis C treated with OBV/PTV/r + DSV + RBV

Parameters	Values (n = 21)
Age (years), mean ± SD	41.70 ± 11.59
Gender, n (%)	21 (100)
male	13 (61.91)
female	8 (38.09)
BMI (kg/m^2), mean ± SD	25.43 ± 3.82
Treatment history, n (%)	21 (100)
naive	1 (4.76)
relapser	2 (9.52)
null-responder	18 (85.71)
Fibrosis stage, n (%)	21 (100)
F0	6 (28.57)
F1	5 (23.81)
F3	7 (33.33)
F4	2 (9.52)
unknown	1 (4.76)
HCV genotype, n (%)	21 (100)
1a	1 (4.76)
1b	8 (38.09)
1a+1b	1 (4.76)
1 (subgenotype not available)	11 (52.38)
HCV RNA level (× 106 IU/mL), mean ± SD	55.80 ± 15.30
Child-Pugh score A, n (%)	18 (85.71)
Albumin (g/L), mean ± SD	43.03 ± 5.60
Bilirubin (μmol/L), mean ± SD	13.57 ± 5.22
INR	1.06 ± 0.12
Creatinine, (μmol/L), mean ± SD	72.19 ± 15.87
ALT (IU/L), mean ± SD	83.42 ± 58.60
AST (IU/L), mean ± SD	79.11 ± 70.46
Hemoglobin (g/L), mean ± SD	151.68 ± 19.94
RBC (× 10^6/L), mean ± SD	5.710 ± 0.47
WBC (× 10^3/L), mean ± SD	6.58 ± 2.62
PLT (× 10^3/L), mean ± SD	204.84 ± 51.32
AFP (ng/mL), mean ± SD	16.31 ± 34.40

BMI – body mass index; HCV – hepatitis C virus; RNA – ribonucleic acid; INR – international normalized ratio; ALT – alanine aminotransferase; AST – aspartate aminotransferase; RBC – red blood cells; WBC – white blood cells; PLT – platelets; AFP – alpha-fetoprotein; OBV – ombitasvir; PTV – partiaprevir; r – ritoravir; DSV – dasabuvir; RBV – ribavirin.

Note: Normal range of biochemical parameters – albumin: 34–55 g/L; bilirubin 0–20.5 μmol/L; INR: 2–3; creatinine 59–104 μmol/L; ALT 0–41 U/L; AST 0–37 U/L; RBC – 4.34–5.72 × 10^6/L; WBC 3.40–9.70 × 10^3/L; PLT 158–424 × 10^3/L; AFP < 20 ng/mL.

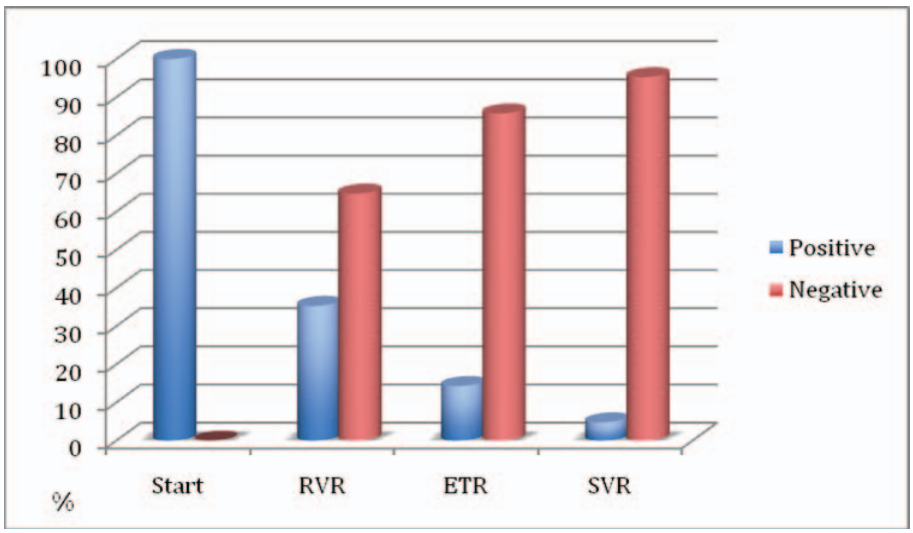

Fig. 1 – Results of the PCR testing during the treatment with OBV/PTV/r + DSV + RBV.

Start – before commencement of treatment; RVR – rapid viral response after 4 weeks of treatment; ETR – end of therapy response after 12 or 24 weeks of treatment; SVR – sustained viral response 12 weeks after the end of treatment; PCR – polymerase chain reaction; OBV – ombitasvir; PTV – paritaprevir; R – ritoravir; DSV – dasabuvir; RBV – ribavirin.

The four-week RVR data were available in 17 patients. In 11 (64%) patients, HCV could not be found, 5 patients had low viral concentration (15–623 IU/mL) and only 1 patient had a significant viral load (99.000 IU/mL). ETR was estimated after 12 weeks of therapy in 18 patients and after 24 weeks of therapy in 3 high-risk patients. Complete ETR was achieved in 18 patients, in the rest of them the viral load was 12×10^3, 192×10^3 and 1.24×10^6. Full SVR, estimated 12 weeks after the end of the treatment, was achieved in 20 patients, while only 1 had a significant viremia of 902×10^3 IU/mL (Figure 1).

The used DAAs were well-tolerated and no adverse events were recorded in 18 (85.71%) patients. The remaining 3 (14.29%) patients had adverse events. Two patients had hyperbilirubinemia and one had anemia, asthenia, fatigue, headache, insomnia and pruritus. These side effects were mild and therefore the therapy did not have to be stopped, nor the reduction of RBV dose was needed. The life-threatening treatment emergent serious adverse event (SAE) was not recorded.

Table 2

Concomitant medication in five patients

Concomitant medication	Numbers per patient
Nebivolol	1
Propylthiouracil	1
Mirtazapine, escitalopram	2
Ursodoxycholic acid, pantoprazole, iron, folic acid, vitamin B12, vitamin B6, zinc	7
Bisoprolol, levothyroxine	2
Total	13

The data on the concomitant medication were available in 19 patients. No such medication was needed in 14 patients. In 5 of them, the concomitant medication included: antihypertensives, bronchodilators, thyreosuppressant and anti-anemic drugs, antiulcers drugs, levothyroxine and anti-depressants (Table 2).

Discussion

The DAA combination OBV/PTV/r + DSV + RBV used in this study assured complete 4-week RVR in 11 out of 17 patients (64.71%). Twelve-week ETR was achieved in 18 out of 21 (85.71%) patients, while the SVR was registered in 20 out of 21 (95.24%) patients. The results obtained are in agreement with the results of other similar clinical trials [11, 13–15]. The onset of antiviral action was fast and it was similar to the one reported in a Polish clinical trial, where RVR was achieved in 69.23% [11]. In a systematic review of 19 clinical trials using the same therapeutic combination in the patients with a chronic HCV hepatitis, the average SVR of 97% was found [14]. SVR, as a confirmation of the absence of HCV was considered as an endpoint of successful treatment and as a positive predictor of the patients' lower hepatic failure and mortality rates [16].

The SVRs obtained in the present study and in the other ones with the OBV/PTV/r + DSV + RBV antiviral combination were significantly higher than in the patients treated with pegylated interferon + RBV, 95–100% versus 70.5% [9]. The 2011 registration trials for the first generation protease inhibitors BOC and TVR, each combined with PEG-IFN+RBV, assured significantly lower SVRs of 59%–66% [17] and 64%–75% [18], respectively, while the subsequent real-life SVRs were even lower, 42%–55% [10, 19]. Besides, the onset of the antiviral effect of the OBV/PTV/r + DSV + RBV was faster, with the vast majority of the patients requiring only 12 weeks of treatment, while the duration of BOC or TVR regimens was 32–48 weeks [10, 19].

All the treated patients in this study had infection with HCV genotype 1, which is in accordance with the epidemiological data obtained from Europe and the USA, where this genotype is dominant, in contrast with the data from the Middle East, where genotype 4 prevails [12, 14, 20–22]. The local epidemiological and clinical studies also confirm the predominance of genotype 1 [6, 7, 9, 10].

Adverse events were mild and rare, occurring in 3 out of 21 (14.29%) patients, all of them in those ones receiving RBV and not necessitating the decrease of the dose of RBV. Anemia is known to be associated with the RBV therapy [23]. In some other studies, considerably higher incidence of adverse events (72.20%) was noted [14]. This difference could be explained by the fact that the population of patients in the present study was younger (average age of 41.70 ± 11.59), without significant comorbidities, leaner [body mass index (BMI) 25.43 ± 3.82 kg/m^2] and with better preserved hepatic function than in the other trials [24]. The safety of the OBV/PTV/r + DSV + RBV antiviral combination in the present report was better than the one of the BOC or the TVR-based triple regimens, where the incidence of adverse effects was very high, with anemia being the most important one (in 25% of patients), followed by neutropenia and thrombocytopenia [10]. It seems that overall quality of life of patients treated with OBV/PTV/r + DSV + RBV is better than the one with BOC or TVR.

Conclusion

In this real-life multicenter clinical study, DAA combination, OBV/PTV/r + DSV + RBV, assured excellent efficacy and tolerability in the patients with genotype 1 chronic HCV infection.

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