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Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir Regimen in Haemodialysis Patients With Hepatitis C Virus Infection: A Case Series

Učinkovitost i sigurnost kombinacije ombitasvir/paritaprevir/ritonavir ± dasabuvir u bolesnika na hemodijalizi s infekcijom virusom hepatitisa C: prikaz serije bolesnika

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Abstract

Background: Hepatitis C virus (HCV) infection is common among patients on haemodialysis (HD) therapy and is an important cause of morbidity and mortality. In patients with chronic kidney disease (CKD), the risks for negative outcomes are significantly higher in HCV-infected patients than in those without HCV infection, including progression to cirrhosis, hepatocellular carcinoma and liver-related mortality. Ombitasvir (OBV), paritaprevir (PTV), ritonavir (r), and dasabuvir (DSV) are all hepatically metabolized and, therefore, require no dose adjustment in patients with any degree of renal impairment.

Aims: We studied the safety and efficacy of OBV/PTV/r + DSV in a small group of HCV infected patients on haemodialysis therapy.

Methods: Treatment course with ombitasvir/paritaprevir/ritonavir and dasabuvir; (3-DAA regimen of OBV/PTV/r+DSV±RBV) was analysed. Pre-treatment evaluation of HCV infection included HCV RNA, genotype, and liver fibrosis assed by transient fibroelastography (FibroScan). The stage 5 CKD was defined as an eGFR of <15 mL/min/1.73 m2, respectively; those on haemodialysis were considered to have stage 5 CKD or end-stage renal disease (ESRD). Demographic data and concomitant medication were retrieved from patients' records. The primary endpoint was sustained virologic response at post-treatment week 12 (SVR12). We collected data on on-treatment adverse events (AEs), serious AEs, and laboratory abnormalities.

Results: Among 7 treated patients, 6 were male and 1 female, all were infected with genotype 1 (5 GT1b, 2 GT1a). Patient had compensated liver cirrhosis and six patients did not have liver cirrhosis, none were liver transplant recipients. All of seven patients completed 12 weeks of treatment and achieved SVR12. Concomitant medication had to be modified with the treatment initiation in 5 out of 7 patients. One of the patients presented with a significant decrease in haemoglobin level, white blood cell and platelet count during the treatment period. The most frequent adverse events were nausea, diarrhoea. Adverse events were primarily mild, and no patient discontinued treatment due to an AE.

Conclusions: Treatment with OBV/PTV/r +DSV ± RBV was well-tolerated and resulted in high rates of SVR12 (100%) for patients with HCV GT1b/1a on haemodialysis.

Sažetak

Uvod: Infekcija virusom hepatitisa C (HCV) česta je među bolesnicima na hemodijalizi (HD) i važan je uzrok morbiditeta i mortaliteta. Kod bolesnika s kroničnom bolesti bubrega (CKD), rizici za negativne ishode značajno su veći u pacijenata zaraženih HCV-om nego u onih bez HCV infekcije, uključujući napredovanje u cirozu, hepatocelularni karcinom i smrtnost povezanu s jetrom. Ombitasvir (OBV), paritaprevir (PTV), ritonavir (r) i dasabuvir (DSV) metaboliziraju se u jetri i stoga ne zahtijevaju prilagodbu doze u bolesnika s bilo kojim stupnjem oštećenja bubrega.

Ciljevi: Proučavali smo sigurnost i djelotvornost OBV/PTV/r+DSV u maloj skupini pacijenata zaraženih HCV-om na terapiji hemodijalizom.

Metode: Analizirali smo liječenje ombitasvir / paritaprevir / ritonavir i dasabuvir; (3-DAA režim OBV / PTV / r + DSV ± RBV). Primarna završna točka bila je održivi virološki odgovor 12 tjedana nakon liječenja (SVR12). Prikupili smo podatke o nuspojavama (AEs), ozbiljnim neželjenim učincima i abnormalnostima laboratorija.

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Rezultati: Od 7 liječenih bolesnika, 6 su bili muški i 1 ženski, a svi su bili zaraženi genotipom 1 (5 GT1b, 2 GT1a). Jedan pacijent imao je kompenziranu cirozu jetre, a šest bolesnika nije imalo cirozu jetre te niti jedan nije bio primatelj transplantata jetre. Svih sedam bolesnika završilo je 12 tjedana liječenja i postiglo SVR12. Istodobni lijekovi morali su se mijenjati s početkom liječenja kod 5 od 7 bolesnika. Jedan od bolesnika imao je značajno smanjenje razine hemoglobina, broja bijelih krvnih stanica i trombocita tijekom razdoblja liječenja. Najčešće nuspojave bile su mučnina, proljev. Nuspojave su primarno bile blage, a nijedan pacijent nije prekinuo liječenje zbog AE.

Zaključak: Liječenje OBV / PTV / r + DSV ± RBV bilo je dobro podnošljivo i rezultiralo je visokim stopama SVR12 (100%) za bolesnike s HCV GT1b/1a na hemodijalizi.

Introduction

HCV infection is one of the most important causes of chronic liver diseases, liver cirrhosis and hepatocellular carcinoma, as well as liver-related deaths. Global prevalence is 1.0%, with 71.1 million infected people worldwide, 399,000 of which die due to this infection every year[1,2]. The prevalence of HCV infection among HD patients varies widely, ranging from 5% to approximately 40%, depending on the geographic region. Thus, these patients still represent a high risk group for the acquisition of HCV infection[3].

Development of direct-acting antivirals (DAA) has represented major progress in the treatment of chronic hepatitis C (HCV) infection over the last five years. DAA-based regimens showed an excellent efficacy and tolerability also in specific group of patients who could not be treated with an interferon-based regimen in the past. An accurate selection of the DAA-based regimen, with respect to the HCV genotype, patient´s comorbidities and concomitant medication, seems to be crucial for successful treatment[3,4]. Paritaprevir/Ritonavir/Ombitasvir (Viekirax™, Abbvie Ltd) with Dasabuvir (Exviera™, Abbvie Ltd.) is a triple DAAs combination approved in 2015 for the treatment of chronic HCV infection (3D regimen - Paritaprevir/Ritonavir/ Ombitasvir and Dasabuvir). This regimen consists of a NS3/4A serine protease inhibitor boosted by Ritonavir, an NS5A protein inhibitor, and an NS5B non-nucleoside polymerase inhibitor, with or without Ribavirin (RBV), showed high antiviral efficacy in patients infected with HCV genotype 1, including those with liver cirrhosis, HIV coinfection, and liver transplant[5,6]. The favourable efficacy profile of 3D is seen especially in patients infected with HCV subtype 1b, who achieved sustained virological response (SVR) in 100% without RBV including patients with cirrhosis[7-12].

Patients with severe renal impairment and patients subject to haemodialysis represent special group of HCV patients with a high risk of drug-drug interactions. In general, these patients are of older age with frequent comorbidities and abundant concomitant medication[8,9]. We evaluated the safety and efficacy of 3D regimen in a group of 7 patients on maintenance haemodialysis, all infected with HCV genotype 1.

Materials and Methods

We retrospectively evaluated 7 patients on maintenance haemodialysis. All patients were referred to antiviral treatment as kidney transplant candidates.

HCV RNA was assessed by the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test v2.0 at baseline, after the treatment, and 12 weeks after the end of therapy. HCV genotype was assessed before treatment initiation using the SIEMENS Versant® HCV Genotype Linear Array HCV Genotyping test. All patients were regularly monitored for treatment efficacy and side effects during treatment and 12 weeks after the end of therapy. This included a check of the monthly records provided by the haemodialysis units containing complete concomitant medication overview and the course of haemodialysis therapy. Fibrosis stage was determined according to transient elastography (FibroScan).

Results

Among participants 6 were males, and 1 was female. Mean age was 42.1 years, ranging from 32 to 52 years.

The mean duration of the haemodialysis period was 18.2 years (range 8–26 years). All patients were infected with HCV genotype 1 (5 patients genotype 1b, 2 patients genotype 1a). None of the patients had HBV or HIV co-infection. The median reported duration of HCV infection was 17.5 years (range 8–25), 7 patients contracted HCV infection on haemodialysis. Two patients were previously treated with interferon-based therapy: one with the null response, and one had relapse.

Liver fibrosis stage (F0–F4) was derived from the liver stiffness values in kPa obtained by shear-wave elastography based on the table provided by the device manufacturer[12]. Patient with genotype 1b had liver cirrhosis Child-Pugh A, with no signs of synthetic or excretory dysfunction (albumin, bilirubin, and prothrombin time values within normal ranges, ascites or encephalopathy).

Patients with GT1a infection received OBV/PTV/r (25/150/100 mg once daily) plus DSV (250 mg twice daily) plus RBV (200 mg once daily) for 12 weeks; GT1b-infected patients received this regimen without RBV for 12 weeks. Study drug could be administered at any time without regard for timing of haemodialysis.

The primary endpoints were virologic response and sustained virologic response (serum HCV RNA <25 IU/mL) 12 weeks after treatment cessation (SVR12). Efficacy was assessed by achievement of an SVR12, defined as an HCV RNA below the level of quantification (LLOQ) using the Roche COBAS TaqMan real-time reverse transcriptase polymerase chain reaction assay, version 2.0. For this assay, the lower limit of detection for HCV RNA is 15 IU/mL and the LLOQ is 25 IU/mL. Baseline Patient Demographics are shown in Table 1.

Table 1. Baseline patient's demographic characteristics
Tablica 1. Osnovna demografska obilježja bolesnika

Variable	Number of patients
Age, *y*, median (range)	42.1 (32–52)
Male, (n)	6
HCV GT1b, (n)	5
Fibrosis stage, (n)	
F0–F1	4
F2	1
F3	0
F4	2
HCV RNA, $log_{10}IU/mL$, median (range)	7.04 (3.7–32.8)
History of diabetes, n (%)	1 (55)
Haemoglobin, *g/dL*, median (range)	12.0 (8.7–13.5)
Total bilirubin, *μmol/l*, median (range)	13.8 (5.0–23.6)
Albumin, *g/dL*, median (range)	4.2 (3.0–4.6)
Platelet count, $\times 10^9/L$ median (range)	228 (84–249)

All patients achieved virologic response at the end of therapy (100%), as well as sustained virological response defined as negative HCV RNA 12 weeks post-treatment.

The concomitant medication was classified into three groups: contraindicated administration with 3D, administration possible with dose adjustment, and drugs without anticipated interactions. The initial adjustment of concomitant medication was performed on the day of treatment initiation.

The adverse events (AE) were recorded as follows: any AE or serious adverse event (SAE), including any event requiring hospitalisation, life-threatening event, or death. The relation with the administered medication was also assessed. The haematological side effects (haemoglobin level ≤ 100 g/L, abnormal white blood cells ≤ 4, $0x10^9$/L or platelet count ≤ 70 $x10^9$/L), and liver toxicity (any abnormal ALT, AST, and bilirubin levels during treatment) were of special interest.

Two patients with elevated baseline ALT activity achieved ALT normalisation on 3D treatment and remained within normal value ranges during the follow-up period. Four patients presented with at least one adverse event. The most frequent adverse events were nausea (1 patient), fatigue (3 patients).

One patient had to interrupt ribavirin due to anaemia worsening and received two doses of deleukocytes erythrocyte.

The values of haemoglobin, leukocytes, and platelets during the treatment period and at week 12 after the end of therapy did not significantly differ from baseline values. The treatment was generally well tolerated.

Table 2. Side effects and changes in lab tests during treatment
Tablica 2. Neželjene reakcije i promjene u laboratorijskim nalazima tijekom liječenja

Variable	GT1a OBV/PTV/r + DSV + RBV (n =2)	GT1b OBV/PTV/r + DSV (n = 5)
Any AE	1	3
Serious AE	1	0
AE leading to study drug discontinuation	0	0
Death	0	0
AEs occurring in ≥15% of patients		
Anaemia	1	0
Fatigue	1	2
Nausea	1	0
Haemoglobin		
Grade 3 (<8–6.5 g/dL)	1	0
Total bilirubin		
Grade 2 (>1.5–3 × ULN)	1	1
Grade 3 (>3–20 × ULN)	0	0
Alanine aminotransferase		
Grade 3 (>5–20 × ULN)	0	0
Aspartate aminotransferase		
Grade 3 (>5–20 × ULN)	0	0

The most frequent drugs which had to be adjusted at the treatment initiation were: ACE inhibitors (5 patients) and H2 Receptor Blockers vs. Proton Pump Inhibitors (4 patients).

Interactions were assessed by using Liverpool HEP Drug Interaction Checker[13].

Discussion

DAA treatment has provided significant progress in patients with CHC, in comparison with PEGIFN/RBV, especially in patients with ESRD. Low sustained virologic response (SVR) rates of 33%–37% and discontinuation rates of 17%–30% further limit IFN's applicability[16,17].

According to data obtained from the haemodialysis centres of Republika Srpska, a total of 933 patients with kidney failure with replacement therapy were tested at nine haemodialysis centres. The prevalence of anti-HCV was 5.3% (47 of 933 patients), and viremia was detectable in 40 of 933 (4.28%) patients. Seven of 933 patients (0.75%) were anti-HCV positive with undetectable HCV RNA.

The results refer to the first seven patients who were treated in our clinic. The 3D regimen (with or without RBV) had rephrasing an absolute efficacy in our group of haemodialysed patients infected with HCV genotype 1, all of whom achieved SVR12. None of the patients discontinued treatment prematurely. The SVR rate in our group of patients is consistent with the results reported by other authors[18-20]. In the RUBY-I study, the achieved overall SVR rate was 90% (intent-to-treat 95%) in CKD4 and CKD5, genotype 1 infected patients. This study did not include patients with liver cirrhosis, more than half of whom were infected with HCV genotype 1. The SVR rate in patients infected with HCV subtype 1a was lower than in patients infected with subtype 1b as had been demonstrated in previous clinical trials dealing with patients with normal kidney function[21].

Adding a reduced dose of RBV to 3D did not have a negative impact on the achieved SVR rate. As the optimal RBV dose in haemodialysed patients has not been established so far, we compared the dose of RBV given to our patients (200 mg twice a week) with the RBV dose used in RUBY-I study (200 mg once a day).

Anaemia was the most common AE in the RUBY-I study, and RBV was interrupted in 9 out of 13 HCV subtype 1a patients to whom RBV was administered[21]. The most common AE in our group was nausea; in general, it was mild and transient. Shortly after the ingestion of tablets, patients complained of nausea, which disappeared within a few hours.

The most frequent drugs which had to be adjusted included ACE inhibitors and H2 blockers. It is our first experience in treating this group of patients.

Conclusion

The paritaprevir/ritonavir/ombitasvir/dasabuvir antiviral regimen was effective and well tolerated in our small group of patients on haemodialysis therapy. The treatment resulted in high rates of SVR12 (100%) for patients with HCV GT1b/1a.

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