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Antonija Verhaz *

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Research Article

Elimination of hepatitis C virus infection in hemodialysis patients in the Republic of Srpska: Small Group

Antonija Verhaz [1,2]

[1] Clinic for Infectious Diseases, University Clinical Centre of the Republic of Srpska, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.

[2] Department of Infectious Diseases, Medical Faculty, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina.

***Correspondence Author:** Antonija Verhaz, Department of Infectious Diseases, Medical Faculty, University of Banja Luka, Save Mrkalja 14, Banja Luka 78000, Republic of Srpska, Bosnia and Herzegovina

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Abstract

Background and aims: 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. Micro-elimination of hepatitis C in renal patients is crucial. This study aims to assess the efficacy and safety of directly acting antivirals in chronic kidney disease patients and the effect of treatment on kidney functions.

Methods: The course of treatment with antiviral therapy in patients on chronic hemodialysis program was analyzed. 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: From 2008 until now, a total of 25 patients were treated for chronic HCV infection on a chronic hemodialysis program with three therapeutic antiviral modalities. Treatment with pegylated interferon (PEG-IFN) alfa 2a with or without ribavirin (RBV) was performed in 16 patients. This treatment showed the least effectiveness and great intolerability. Seven patients were treated with a 3D regimen - Paritaprevir/Ritonavir/ Ombitasvir and Dasabuvir with or without Ribavirin. Among the 7 treated patients, 6 were male and 1 female, all were infected with genotype 1 (5 GT1b, 2 GT1a). The patient had compensated liver cirrhosis, and six patients did not have liver cirrhosis, none were transplanted. All seven patients completed 12 weeks of treatment and achieved SVR12. One patient had significant decreases in hemoglobin, white blood cell, and platelet counts during the treatment period. The most common adverse events were nausea, diarrhea. Adverse events were generally mild and no patient discontinued due to an AE. Two patients were treated with the pangenotypic drug glecaprevir/pibrentasvir, the shortest therapeutic regimen of 8 weeks, with excellent efficacy and safety. This was the most comfortable therapy regimen. Due to implementation of HCV infection control procedures within dialysis units and elimination of HCV from the bloodstream, the frequency of HCV infection is gradually decreasing in many dialysis centers.

Conclusions: Treatment with OBV/PTV/r + DSV ± RBV and pangenotypic glecaprevir/ pibrentasvir was well tolerated and resulted in high SVR12 rates (100%) in hemodialysis patients. DAA treatment provided significant improvement in patients with HHC, compared to PEG-IFN/RBV in patients with ESRD.

Keywords: hepatitis C; treatment; haemodialysis

Introduction

Globally, it is estimated that about 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections per year. There are an estimated 3.2 million adolescents and children with chronic hepatitis C infection. The WHO estimated that approximately 290,000 people died from hepatitis C in 2019, mainly from cirrhosis and hepatocellular carcinoma (primary liver cancer) [1,2]. The prevalence of HCV infection among HD patients varies widely, ranging from 5% to approximately 40%, depending on the geographic region. Therefore, these patients still represent a high-risk group for acquiring HCV infection [3]. The beginnings of treatment of chronic infection with the hepatitis C virus are

related to the use of pegylated interferon (PEG-IFN) once a week. The treatment lasted from 24 to 48 weeks, depending on the genotype. Ribavirin (RBV) tablets may also be given to improve results. However, ribavirin can accumulate in the patient's kidneys and cause red blood cell destruction and anemia. Studies show that antiviral therapy for chronic hepatitis C with pegylated IFN alone or with ribavirin was neither effective nor safe. Patients on peg-IFN monotherapy showed SVR rates (about 40%) slightly higher than those of HCV-infected dialysis patients on conventional IFN monotherapy (about 30%). The addition of ribavirin did not lead to a demonstrable improvement in SVR rates compared with peg-IFN alone. The rate of discontinuation of therapy due to side effects was quite high, and the most important side effects were hematological. The addition of ribavirin resulted in withdrawal-related anemia, and the need for blood transfusion was greater in patients on combination antiviral therapy (peg-IFN plus ribavirin) than in those on peg-IFN monotherapy. The dose of erythropoietin was increased in all patients receiving erythropoietin at baseline. The relatively low virologic response rate and high dropout rate reported in the current study do not support IFN-based regimens for the treatment of HCV in the dialysis population [4].

The development of direct-acting antivirals (DAAs) represents a major advance in the treatment of chronic hepatitis C (HCV) infection over the past seven years. DAA-based regimens have shown excellent efficacy and tolerability in a specific group of patients who could not be treated with an interferon-based regimen in the past. The correct selection of a DAA-based regimen, taking into account the HCV genotype, the patient's comorbidities and concomitant medications, seems to be crucial for successful treatment [3,5]. Paritaprevir/ Ritonavir/Ombitasvir (ViekiraxTM, Abbvie Ltd) with Dasabuvir (ExvieraTM, Abbvie Ltd.) is a triple DAA combination approved in 2015 for the treatment of chronic HCV infection (3D regimen - Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir). This regimen, consisting of a ritonavir-boosted NS3/4A serine protease inhibitor, NS5A protein inhibitor, and NS5B non-nucleoside polymerase inhibitor, with or without ribavirin, has shown high antiviral efficacy in patients infected with HCV genotype 1, including those with liver cirrhosis, coinfection with HIV and transplanted liver [6,7]. The favorable efficacy profile of 3D is particularly evident in patients infected with HCV subtype 1b, who achieved sustained virological response (SVR) in 100% without RBV, including patients with cirrhosis [8-13]. Further progress in the treatment of HHC in patients on a hemodialysis program occurred with the introduction of the pangenotypic drug glecaprevir/pibrentasvir (Maviret Ltd.) [14]. Patients with severe impairment of kidney function and patients on hemodialysis are a special group of HCV patients with a high risk of drug interactions. In general, these are elderly patients with frequent comorbidities and abundant accompanying therapy [9,10]. We demonstrated the safety and efficacy of three different antiviral regimens for the treatment of chronic hepatitis C (HHC) in patients on a chronic hemodialysis program at our regional center.

In 2016, the World Health Organization (WHO) set the goal of eliminating chronic hepatitis C virus (HCV) as a major threat to public health by 2030. [15]. This is an ambitious goal, and for simplicity, it is suggested to first approach "microelimination" of HCV among high-risk subpopulations, including patients receiving HD, and thus accelerate the global elimination of HCV [16]. In response to this proposal, we propose some improvements to the existing guidelines for the screening and treatment of HD patients for HCV, as part of an overall strategy for the microelimination of HCV in this vulnerable population. Hemodialysis facilities will remain high-risk environments for HCV transmission as long as infected and susceptible patients receive concurrent treatment [17]. We also advocate the use of HCV-RNA assays for earlier detection of HCV viremia, resulting in increased treatment costs. Patients with chronic HCV infection are a priority for treatment using direct-acting antiviral drugs (DAAs) for the treatment of infected patients.Chronic hepatitis C in hemodialysis-dependent patients negatively affects overall survival and results in an increased risk of cirrhosis, hepatocellular carcinoma, and lower quality of life compared to their HCV-negative counterparts. Therefore, all patients with end-stage renal disease (ESRD) should be considered for antiviral therapy [6].There is currently no effective vaccine against HCV, and the first drug therapies that became available against HCV had limited efficacy and were poorly tolerated. For this reason, public health efforts are mainly focused on stopping transmission through improved hygiene in HD facilities. Nonspecific prevention measures reduced the prevalence of HCV infection among HD patients in the years before the introduction of DAAs.

Aims

This study aims to evaluate the efficacy and safety of pegylated interferon α-2a with or without ribavirin, and a direct-acting antiviral agent in patients with chronic kidney disease who have chronic HCV infection.

Materials and Methods

We retrospectively evaluated the efficacy and safety of three different antiviral regimens that were used in a total of 25 hemodialysis patients. All patients referred for antiviral treatment were potential candidates for kidney transplantation. HCV RNA was assessed using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Assay v2.0 at baseline, post-treatment and 12 weeks after completion of therapy. HCV genotype was assessed before starting treatment 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 and 24 weeks after the end of therapy. This included checking the monthly records of the hemodialysis department, which contained a complete overview of the drugs administered and the course of hemodialysis therapy. The stage of fibrosis was determined using transient elastography (FibroScan).

Results

The Clinic for Infectious Diseases of the University Clinical Center of the Republic of Srpska is a regional medical center that provides health care for about 1 million inhabitants. 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 [18]. From 2007 to 2013, at the Banja Luka Infectious Diseases Clinic, we treated a total of 16 patients on the chronic hemodialysis program, who received pegylated interferon (PEG-IFN) once a week. Treatment based on pegylated interferon alfa-2a (PEG-IFN) with and without ribavirin. Treatment is carried out from 24 to 48 weeks depending on the genotype. Ribavirin tablets may also be given to improve results. However, ribavirin can accumulate in the patient's kidneys and cause red blood cell destruction and anemia. Of the 16 patients, eight patients had genotype 4, five patients had genotype 1b, one patient had 1a, and two patients had genotype 3. We did not perform a liver biopsy on these patients and did not assess the degree of fibrosis. Five patients achieved a stable virological response (SVR24), unmeasurable PCR HCV RNA 24 weeks after the end of therapy. Eight patients discontinued treatment due to the occurrence of adverse events, and three patients did not achieve an early virological response and belong to the group of non-responders. The results of this study confirm the efficacy and safety of PEG-IFN therapy in hemodialysis patients with chronic hepatitis C. Treatment with PEG-IFN for 48 weeks resulted in a sustained virological response in 31.2% of patients. The development of direct-acting antivirals (DAAs) represents a major advance in the treatment of chronic hepatitis C (HHC) over the past seven years. DAA-based regimens have shown excellent efficacy and tolerability in a specific group of patients who could not be treated with an interferon-based regimen in the past. Paritaprevir/Ritonavir/ Ombitasvir (ViekiraxTM, Abbvie) with Dasabuvir (ExvieraTM, Abbvie) is a triple DAA combination approved in 2015 for the treatment of chronic HCV infection (3D regimen - Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir). This regimen consists of ritonavir, a potent NS3/4A serine protease inhibitor, NS5A protein inhibitor, and NS5B non-nucleoside polymerase inhibitor, with or without RBV, which has shown high antiviral efficacy in HCV genotype 1-infected patients, including those with liver cirrhosis, HIV co-infection and liver transplantation. A favorable 3D efficacy profile was observed in patients infected with HCV subtype 1b, who achieved

SVO in 100% without RBV, including patients with liver cirrhosis. There were 6 men and 1 woman among the participants. The average age was 42.1 years, ranging from 32 to 52 years.In this group of seven patients, the average duration of the hemodialysis period was 18.2 years (range 8-26 years). All patients were infected with HCV genotype 1 (5 patients with genotype 1b, 2 patients with genotype 1a). None of the patients had HBV or HIV co-infection. The median recorded duration of HCV infection was 17.5 years (range 8-25), 7 patients acquired HCV infection during hemodialysis. Baseline Patient Demographics are shown in table 1. Two patients were previously treated with interferon-based therapy: one with a null response and one with a relapse. Liver fibrosis stage (F0–F4) was derived from liver stiffness values in kPa obtained by shear wave elastography based on the table provided by the device manufacturer [13]. The patient with genotype 1b had Child-Pugh A cirrhosis of the liver, without signs of synthetic or excretory dysfunction (albumin, bilirubin and prothrombin time values within normal limits, 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.

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 F 4	0 2
HCV RNA, $log_{10}IU/mL$, median (range	7.04 (3.7–32.8)
History of diabetes, n (%)	1 (55)

Table 1. Basic patients demographics

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 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.

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 well tolerated. Adverse event are shown in table 2.

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

Variable	GT1a OBV/PTV/r + DSV + RBV (n =2)	GT1b OBV/PTV/r + DSV (n = 5)
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

Table 2. Side effects during treatment and side effects in the laboratory

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 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 (four patients). Interactions were assessed by using Liverpool HEP Drug Interaction Checker [19]. The rate of DDI in patients with CKD is significant. Comorbidity and polypharmacy are common in patients with chronic kidney disease. Most DDAs have DDIs with some cardiovascular drugs. Some statins are not recommended for concurrent use with glecaprevir/pibrentasvir treatment. There is a high rate of clinically significant DDIs between DAAs and antiepileptics. During treatment with DAAs, which are even metabolized in the liver, careful management of DDI is necessary in HCV-infected patients with CKD, using cardiovascular drugs, statins or antiepileptics [19].

The third antiviral regimen we applied in the Republic of Srpska, we started treatment with the pangenotypic drug glecaprevir/pibrentasvir in 2019, two patients were treated (table 3). One patient was naïve, and one was previously treated with PEG-IFN and belonged to the group that did not respond to treatment. The patient, who was naïve, had one previous failed kidney transplant in 1998.

Variable	1. patient	2. patient
Age, *year*	Female 54	Male 56
HCV GT	1	1a
Fibrosis stage	F0	F1
HCV RNA, $log_{10}IU/mL$	4,5x105 *IU/ml*	206 *IU/ml*
previous treatment	naive	PEG INF

Table 3. Patients receiving glecaprevir/pibrentasvir

Two patients were treated with glecaprevir/pibrentasvir for 8 weeks. During the treatment, the patients had no side effects, they tolerated the treatment well. There were no interactions between the drugs previously taken in their regular therapy. At the end of the treatment, a virological response was achieved, with undetectable HCV RNA. Both patients achieved a stable virological response 12 weeks after the end of treatment. After administration of the drug, a decrease in the mean level of ALT at the end of treatment was observed. Initial values and Hb levels after treatment could not be distinguished. There were no significant differences in the number of leukocytes, neutrophils and platelets and the levels of total proteins, serum albumin, serum creatinine, total bilirubin and α-fetoprotein between baseline and post-treatment. After that, both patients underwent a kidney transplant in Belarus.

Transplantation in ESRD patients infected with HCV is the preferred treatment, regardless of the donor's HCV status. Studies show improved survival of HCV-infected patients with transplantation versus dialysis [1,6].

Discussion

DAA treatment has provided significant progress in patients with CHC, in comparison with PEG-IFN/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 [17,18].

Interferon and ribavirin-based therapy was contraindicated and avoided after transplantation due to fear of inducing renal rejection and relapse after kidney transplantation. Nephrologists often did not choose to treat HCV, and some patients refused antiviral therapy because of concerns about treatment-related side effects. Liver enzymes remain normal in most HCV patients on dialysis, and physicians hesitate to perform liver biopsy in these

patients because of platelet dysfunction. 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 [19-25]. 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. DAAs are safe and effective before and after transplantation and have enabled the use of HCV-viremic kidneys in HCV-negative recipients [22]. 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 [22]. 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 common drugs that needed to be adjusted at the beginning of treatment were ACE inhibitors (5 patients) and H2 receptor blockers compared to proton pump inhibitors (4 patients). Interactions were assessed using the Liverpool HEP Drug Interaction Checker [16].Today, glecaprevir plus pibrentasvir is the preferred regimen for the treatment of hepatitis C in people with severe renal impairment.

Patients benefit from treatment, and doctors have a duty to avoid the harm of nosocomial infections. The cost of treating DAA and chronic HCV infection is high. Cost-effectiveness analyzes show that early diagnosis and treatment increase patients' quality of life and reduce costs in the long term [17].Currently, most of the approved DAAs such as elbasvir, grazoprevir, daclatasvir, asunaprevir, paritaprevir and ombitasvir, glecaprevir and pibrentasvir are not eliminated renally and there is no need for dose adjustment even in patients with severe chronic kidney disease or patients on hemodialysis. Among the currently approved DAAs, sofosbuvir is the only drug that is mainly excreted by the kidneys, with 72% renal elimination. Hepatitis C treatment guidelines published by the European Association for the Study of the Liver also suggest that sofosbuvir should be used with caution in patients with severe renal insufficiency and ESRD with eGFR < 30 ml/ (minute·1.73 m2), without a recommended dose. However, studies have shown sustained virologic responses reaching 88% to 96% for sofosbuvir-based DAA treatment in CKD patients with eGFR < 30 ml/(minute 1.73 m2). In addition, it was noted that sofosbuvir/vipatavir treatment (a pangenotypic DAA regimen) can be selected for patients with CKD stage 5D without dose adjustment according to the Hepatitis C Prevention and Treatment Guidelines [26]. In general, treatment as part of kidney transplantation, the time of HCV treatment can be before kidney transplantation, and if therapy is required after kidney transplantation, special attention should be paid to drug interactions with immunosuppressants. Treatment options for hepatitis C in the presence of chronic kidney disease also depend on the possibility of a kidney transplant in the near future, as well as the severity of the underlying liver disease [27].

The high costs and lack of availability of DAAs in some regions of the world limit the treatment strategies needed to achieve control in the HD population. Guidelines do not yet recommend preventive treatment strategies to control HCV transmission in the HD setting.

Conclusion

New therapeutic regimens without interferon and ribavirin were the most effective and safest. Treatment with OBV/PTV/r +DSV ± RBV and pangenotypic glecaprevir/ pibrentasvir was well tolerated and resulted in high SVR12 rates (100%) in hemodialysis patients. DAA treatment provided significant improvement in patients with HHC, compared to PEG-IFN/RBV in patients with ESRD.

The World Health Organization has set ambitious goals to eliminate viral hepatitis by 2030. However, most countries are currently not on track to achieve these goals. Microelimination is a more efficient and practical approach that breaks down national elimination targets into targets for smaller, more manageable key populations.

Microelimination of HCV from the HD population implies prevention of transmission and early diagnosis and treatment, and the goal is long-term profitability.

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