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Original Article

The Efficacy of The Direct-Acting Antiviral Combination in Hemodialysis Patients with Chronic Hepatitis C Virus Genotype 1 Infection

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ABSTRACT

Background Interferon and ribavirin treatments previously used in treating chronic hepatitis C virus (HCV) infection cannot be used effectively in hemodialysis patients due to dose adjustment and drug-related side effects. Direct-acting antivirals (DAAs) therapies have been reported to be effective in hemodialysis patients. This study aimed to evaluate the effectiveness of DAAs in hemodialysis patients with chronic hepatitis C.

Material and Methods Twenty hemodialysis patients with chronic hepatitis C followed in the gastroenterology outpatient clinic between 2016 and 2018 were evaluated retrospectively.

Results Twelve of the 20 patients were male, and eight were female. The mean age of the patients was 50.7±8.6 years. Six patients had no treatment experience. Fourteen patients had been previously treated with interferon and/or ribavirin but did not achieve sustained virological response (SVR). Genotype 1b was detected in 14 patients, genotype 1a in 4 patients, and genotype 1 in 2 patients. Patients were treated with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV) or ribavirin (RBV) for 12 or 24 weeks. Two patients were cirrhotic and had a Child-Pugh score of A. Treatment was discontinued in 2 patients due to thrombus formation in the arteriovenous fistula in the first month of DAAs treatment. SVR12 was evaluated in 14 of 18 patients and found to be 100%. One of the ten patients accepted as SVR24 had a relapse. This rate of SVR24 was similar to that in the general population.

Conclusions Our results supported that the OBV/PTV/r and DSV or RBV regimen was a safe and effective therapy for hemodialysis patients with chronic hepatitis C virus genotype 1.

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Introduction

Hepatitis C virus (HCV) is a hepatotropic virus with 9.6 kilobases, enveloped, and single-stranded RNA. The risk of becoming chronic is high, and the incidence is lower than other viruses (except hepatitis delta virus). Although the frequency of HCV varies according to regions in our country, it is 0.5-1%.[1] The transmission route is parenteral, and the main risk factors are hemodialysis, illegal drug use, blood and blood product transfusion, tattoos, organ transplants and acupuncture.[2] In the Transplantation Society registry data, the rate of HCV positivity (5.2%) in hemodialysis patients was reported to be higher than that of peritoneal dialysis patients (1.92%) and kidney transplant recipients (0.35%).[3] Hemodialysis carries a higher risk of hepatitis C transmission than peritoneal dialysis. In recent years, the number of peritoneal dialysis patients has decreased due to various factors, and HCV screening has become more prominent in this patient group. Chronic hepatitis C infection is a significant independent risk factor for mortality in hemodialysis patients. Chronic hepatitis C increases the risk of HCV-related liver disease, graft rejection, proteinuria, diabetes, and infection after kidney transplantation. Therefore, HCV eradication is of critical importance in this patient group. The first choice in treating HCV is interferon (INF) with or without ribavirin (RBV) therapy, but dose adjustment and nephrotoxicity risk limit its use in uremic patients. Direct-acting antivirals (DAAs) therapies have provided an advantage in treating chronic hepatitis C due to their ease of administration, shorter treatment duration, and higher sustained virological response (SVR) rates. This study aimed to evaluate the effectiveness of DAAs treatments in hemodialysis patients with chronic hepatitis C.

Material and Methods

Twenty hemodialysis patients with chronic hepatitis C followed in the gastroenterology outpatient clinic between 2016 and 2018 were included in this retrospective study. This study was conducted after the approval of the Local Ethics Committee (2019-2/21).

Six (30%) patients had not received any treatment before. Fourteen patients (70%) had been previously treated with INF and/or RBV but could not achieve SVR. A liver biopsy was not performed on the patients due to the risk of bleeding. All patients' medical information was obtained from hospital electronic system records. Hepatitis serologies, HCV-RNA, HCV genotype, complete blood count, biochemical test results and abdominal ultrasonography reports of the patients were recorded.

The patients were evaluated for cirrhosis by abdominal ultrasonography. Hepatitis C treatment was arranged according to the genotype type of the patients and the presence of liver cirrhosis. Nineteen patients were treated with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r: 25/150/100 mg once a day) and dasabuvir (DSV) (250 mg twice a day) for 12 weeks. Two of the 20 patients whose laboratory genotype 1 could not perform subtype (1a/1b) analysis were accepted as genotype 1a and treated. RBV 200 mg daily was added to the treatment regimen of 6 patients (30%) with genotypes 1 and 1a. A 24-week treatment regimen was given to a cirrhotic patient with genotype 1a. Virological, biochemical and serological responses were evaluated 4, 12 and 24 weeks after the start of treatment.

Statistical analysis was performed using SPSS software version 23.0. Data were studied on descriptive statistical parameters (mean, standard deviation, median, percentage and min-max values).

Results

Twelve (60%) of the patients were male, eight (40%) were female, and their mean age was 50.7±8.6 years. Twenty patients had a median HCV-RNA level of 504,868.6 IU/mL (min 100 - max 3,218,282).

The mean laboratory values of the patients were as follows; hemoglobin 12.5±1.1 g/dL, platelet 169.591±72.576/mm^3, INR 1±0.1, serum creatinine 6.79±2.3 mg/dL, albumin 3.99±0.2 g/dL, and total bilirubin 0.6±0.2 mg/dL. Genotype 1b was detected in 14 patients (70%), genotype 1a in 4 patients (20%), and genotype 1 in 2 patients (10%). Two patients (10%) were cirrhotic and had a Child-Pugh score of A.

Nineteen patients received OBV/PTV/r + DSV treatment for 12 weeks. RBV was given additionally in 6 patients with genotypes 1 and 1a (30%). Only one patient received a 24-week treatment regimen for genotype 1a and cirrhosis. In 2 patients who received 12 weeks of treatment, a thrombus formed in the arteriovenous (AV) fistula in the first month of therapy and treatment had to be discontinued. No other side effects were observed in the other 18 patients. Post-treatment response was 100%. Since 2 out of 18 patients could not be reached, SVR values at the 12th and 24th weeks could not be evaluated in these patients. The 12th-week SVR of 14 of 16 patients was analysed, and the SVR rate was 100%. SVR24 was assessed in 8 of 14 patients with SVR12. Eight patients had 100% SVR at week 24. SVR24 of both patients whose SVR12 could not be evaluated was analysed. While HCV-RNA was negative in one patient, it was measured as 133 IU/mL in the other. The virological responses of the patients are given in Table 1.

Table 1. Virological response during and after the treatment.

HCV-RNA <25 IU/mL	n (%)
During the treatment	
4th week	7 (87)
12th week	18 (100)
After the treatment	
12th week	14 (100)
24th week	9 (95)
Virology refraction during the treatment	0
Relapse	1 (5)

Discussion

Although chronic hepatitis C increases mortality and morbidity in hemodialysis patients, it also prolongs the waiting time for kidney transplantation since SVR cannot be obtained. The risk of liver disease increases in patients not treated for HCV. These risks are liver cirrhosis, hepatocellular carcinoma and decompensated cirrhosis-related complications such as variceal bleeding, ascites, and encephalopathy.[4] Patients may die from these complications while waiting for a transplant. For chronic hepatitis C patients who underwent hemodialysis before DAAs, pegylated INF alpha 2a monotherapy was administered. The use of other pegylated INF alpha 2b and RBV used in chronic hepatitis C was not recommended since they are excreted from the kidneys, and they accumulate and lead to secondary toxic side effects in patients with chronic renal failure when the dose is increased for higher efficacy. In these patients, using RBV was found inconvenient, and combining it with INF at 200-800 mg doses was recommended through close surveillance. Due to the complex application of INF and the side effects of these drugs, sometimes the treatment cannot be continued. The long treatment periods may delay the waiting time for transplantation. In particular, patients considered for kidney transplantation should be given antiviral therapy to negate or reduce HCV-RNA because high levels of HCV-RNA can increase the risk of graft rejection. The relationship between cryoglobulinemia, membranoproliferative glomerulonephritis, membranous glomerulonephritis and focal segmental glomerulosclerosis with HCV infection is known. HCV treatment may also reduce the existing kidney failure in these patient groups.

The use of new DAAs is promising in this challenging group of patients. In our study, 20 hemodialysis patients with chronic hepatitis C were evaluated. Treatment was discontinued in 2 patients due to thrombus formation in the AV fistula in the first month of DAAs treatment. There is no data in the literature that DAAs increase the thrombus risk. Seventeen out of 18 patients received OBV/PTV/r and DSV ± RBV treatment for 12 weeks. Because the remaining one patient had cirrhosis and genotype 1, 24-week treatment was given. Post-treatment response was found to be 100%. SVR12 was evaluated in 14 out of 18 patients and found to be 100%. One of the ten patients whose SVR24 was considered had a relapse. This is similar to SVR24 in the average population. In a study executed by Pockros et al.[5] on 20 patients with chronic hepatitis C and stage 4 and 5 chronic kidney disease, OBV/PTV/r and DSV ± ribavirin treatment was reported to be efficient. Beinhardt et al.[6] investigated the efficacy of DAAs in 25 patients with chron-

ic hepatitis C, 10 of whom were on dialysis, eight of whom were kidney transplant recipients, and seven of whom were kidney and orthotropic liver transplant recipients concurrently. Although the number of patients in the groups was small in the study, it was emphasised that DAAs treatment was effective and usable in kidney transplant patients.[6]

In hemodialysis patients, the use of DAAs, in which's clearance occurs utilising renal, should be avoided to prevent the accumulation of drugs or metabolites. In several studies, the clearance of sofosbuvir metabolite, an NS5B polymerase inhibitor, is renal and is not recommended to be used in that end-stage kidney disease.[7,8] In various studies, sofosbuvir (SOF)-included regimens are efficient in patients on hemodialysis.[9-13] According to drug introduction monitored from studies in hemodialysis patients, the recent drug certification indicates that, however, reliable data are not enough in hemodialysis patients. Hemodialysis patients can be treated with SOF and velpatasvir (SOF/VEL) with standard drug doses.[10] Even though the clearance of simeprevir and daclatasvir is from the liver, some studies report toxicity in some patients with severe renal failure.[14,15]

In recent days, hepatitis C treatment has been updated with new studies. Previously, while treatment was given according to HCV genotype, in the current approach, the type and duration of use of the drug are determined according to the treatment experience independent of HCV genotype. The liver biopsy requirement is removed. HCV treatment recommendations in EASL, AASLD and our country have some differences. In all three guidelines, HCV treatment varies according to previous treatment experience, the presence of cirrhosis, and whether it is decompensated. In EASL guidelines, patients without cirrhosis are recommended SOF/VEL for 12 weeks or glecaprevir/pibrentasvir (GLE/PIB) for eight weeks, regardless of treatment experience. On the other hand, if there is treatment experience in Child-Pugh A patients, GLE/PIB treatment was prolonged to 12 weeks. In decompensated cirrhosis, SOF-based regimens are recommended.[16] EASL do not suggest testing of genotype for treatment. The genotype does not change the treatment. In AASLD, on the other hand, Child-Pugh A patients recommend eight weeks of GLE/PIB regimen for all genotypes or 12 weeks of SOF/VEL treatment for all except resistant genotype 3. If there is resistance in genotype three patients, a 12-week SOF/VEL/voxilaprevir (VOX) regimen is recommended. If there is treatment experience, they recommend 12 weeks of SOF/VEL/VOX or 16 weeks of GLE/PIB or SOF/VEL/VOX and RBV 24 weeks or GLE/PIB and SOF and RBV 16 or 24 weeks. In decompensated cirrhosis, they recommend genotypes 1, 4, 5, and 6 SOF/LED/RBV 12 weeks or SOF/VEL 12 weeks. If the patient is intolerant to RBV or has failed treatment SOF or NS5A, the treatment can be prolonged to 24 weeks. In our country, SOF/VEL/VOX 8 weeks or GLE/PIB 8 weeks are recommended for patients without cirrhosis. Unlike Child-Pugh A and all treatments experienced, it is recommended to increase sofosbuvir-based therapy to 12 weeks. In decompensated cirrhosis, all patients except genotype three are offered SOF/LED/RBV 12 or 24 weeks treatment. Genotype 3 patients with decompensated cirrhosis do not have a chance for therapy in AASLD and our country. SOF/VEL/VOX is also used in hemodialysis patients.

Cornberg et al.[17] assessed the effectivity of GLE/PIB in 59 chronic hepatitis C patients on hemodialysis. The SVR12 rate was 99%.[17] In the studies of Gane et al.[18], 104 patients with end-stage kidney disease were treated with GLE/PIB for 12 weeks. The SVR12 rate was 98%. The two of them had a virological failure.[18] Pol et al.'s[19] studies in which GLE/PIB was used for 12 weeks in 2,238 patients found a total SVR rate of 98%; it was found efficient in both chronic kidney disease stage 1-3 (98%; 2,087/2,135) and stage 4-5 (98%; 101/103). No dose adjustment was needed in mild, moderate and severe renal failure for GLE/PIB or OBV/r/DSV.[20,21] OBV/PTV/r and DSV are metabolised through the liver. OBV/PTV/r and DSV treatment is efficient in hemodialysis patients with chronic hepatitis C.

Conclusions

Treatment alternatives for chronic hepatitis C have increased since 2010. Our study has shown that OBV/PTV/r and DSV are effective regimens to rapidly and appropriately treat hemodialysis patients with chronic hepatitis C. New studies showing the long-term efficacy of DAAs thera-

pies, especially in hemodialysis patients on kidney transplant waiting lists, will provide more intensive use of these regimens.

Conflict of interest

The authors have no conflicts of interest to declare.

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Authors' Contribution

Study Conception: SG, TEO, AO, AE; Study Design: SG, TEO, AO, AE; Supervision: SG, TEO, AO, AE; Literature Review: TEO; Critical Review: TEO, SG; Data Collection and/or Processing: SG, TEO, AO, AE; Statistical Analysis and/or Data Interpretation: TEO; Manuscript preparing: TEO.

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