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/or ribavirin treatment previously used in the treatment of HCV cannot be used effectively in hemodialysis patients due to dose adjustment and drug-related side effects. The direct-acting antiviral combination (DAA) is reported to be effective in hemodialysis patients. We evaluated the effectiveness of DAA in hemodialysis patients with chronic hepatitis C .

Method Twenty hemodialysis patients with chronic hepatitis C kept under surveillance at the policlinic of the Department of Gastroenterology, … , … between 2016 and 2018 were evaluated retrospectively.

Results Of the 20 patients, 12 were male, and 8 were female. The average age of the patients was 50,7 ± 8,6. Six patients had no treatment experience. A total of 14 patients (70%) had previously been treated with interferon and/or ribavirin, but SVR could not be achieved. Genotype Ib was detected in 14 patients (70%), genotype Ia was found in 4 patients (20%), and genotype I was detected in 2 patients (10%). Two of the patients were cirrhotic (10%) and the Child-Pugh Score (CPS) was A. Treatment was discontinued in 2 patients due to thrombus formation in AV fistula in the first month of DAA treatment. SVR12 was evaluated in 14 out of 18 patients and found to be 100%. One of the ten patients whose SVR24 was evaluated had a relapse. This is similar to SVR24 in the average population.

Conclusions OBV/PTV/r + DSV is an easily appropriate and effective regimen for the treatment of hemodialysis patients with chronic hepatitis C.

Background

Hepatitis C virus (HCV) is a hepatotropic virus which has 9.6 kilobases, enveloped, and single-stranded RNA, and belongs to the Flaviviridae family. The risk of becoming chronic is high, and the incidence is lower compared to other viruses (except HDV). Although the frequency in our country varies by region, it is 0.5-1% (1). The mode of transmission is parenteral. Risk factors related to transmission include hemodialysis, illegal drug use, transfusion of blood and blood products, tattoos, organ transplantations, and acupuncture (2). In a study report by Turkish Society of Nephrology and Transplantation, while positive rate of anti-HCV in hemodialysis patients was found as 5.2%, it was detected as 1.92% in peritoneal dialysis patients by the end of 2016. The prevalence was reported to be 0.35% in patients who underwent renal transplantation in 2016 (3). As it is seen, hemodialysis carries a higher risk of hepatitis C transmission compared to peritoneal dialysis.

Considering that the number of peritoneal dialysis patients has been decreasing due to various factors compared to 2008, the importance of HCV screening in this patient group becomes even more evident. In studies, the presence of chronic hepatitis C infection in hemodialysis patients has been determined to be significant and an independent risk factor for mortality. While hemodialysis patients with chronic hepatitis C are waiting for renal transplantation, they have to cope with cirrhosis and complications caused by HCV as well. In renal transplant patients with chronic hepatitis C, HCV-associated liver disease

increases the risk of graft rejection, proteinuria, diabetes, and infection after the transplantation. Therefore, HCV eradication is vital in this group of patients.

Interferon and/or ribavirin treatment previously used in the treatment of HCV cannot be used effectively in this patient group due to dose adjustment and drug-related side effects. Direct-acting antiviral agents (DAA) seem to be more useful because of the ease of administration, shorter treatment duration and higher rates of sustained virological response (SVR) in the treatment of chronic hepatitis C. Although there are limited patient groups, DAA is reported to be effective in hemodialysis patients. Here, we evaluated the effectiveness of DAA in hemodialysis patients with chronic hepatitis C kept under surveillance by us.

Method

Hemodialysis patients with chronic hepatitis C kept under surveillance at the policlinic of the Department of Gastroenterology, …, … between 2016 and 2018 were evaluated retrospectively. This study was carried out after receiving approval from the Local Ethics Committee (2019-2/21). Patient files of a total of 20 hemodialysis patients with chronic hepatitis C were examined. Biochemistry, hemogram and abdominal ultrasonography results of the patients were analyzed. SPSS software (2015) version 23 was used for statistical analysis. In the research data, descriptive statistical parameters (mean, standard deviation, median, percentage, and min-max values) were studied on.

Results

Of the 20 patients, 12 were male (60%), and 8 were female (40%). The average age of the patients was 50,7 ± 8,6. Six patients had no treatment experience (30%). A total of 14 patients (70%) had previously been treated with interferon and/or ribavirin, but SVR could not be achieved. The HCV RNA level of patients was 504.868,6 IU/mL (min 100, max 3218282,00). The demographic characteristics of the patients are given in Table-1. Genotype Ib was detected in 14 patients (70%), genotype Ia was found in 4 patients (20%), and genotype I was detected in 2 patients (10%). Two of the patients were cirrhotic (10%) and the Child-Pugh (CP) Score was A. No liver biopsy was performed on the patients due to bleeding diathesis. The patients were evaluated for cirrhosis with abdominal ultrasonography. Treatment with ombitasvir/paritaprevir/ritonavir (25/150/100 mg once a day) and dasabuvir (250 mg twice a day) were planned. Ribavirin was added to the treatment regimen of 6 patients with genotype 1 and 1a (30%). Only one patient was given a 24-week treatment regimen because of genotype 1a and cirrhosis. The other 19 patients were planned to receive 12-week treatment. The treatment had to be discontinued in 2 patients who were planned to be put on a 12-week treatment due to thrombus formation in arteriovenous (AV) fistula during the first month of treatment. No other side effects were observed in the other 18 patients. The end of treatment response (ETR) after the treatment was detected to be 100%. Since 2 out of 18 patients could not be reached, 12th - and 24th -week SVR values could not be analyzed in these patients. The 12th -week SVR of the 14 of the 16 patients were analyzed. The 12th -week SVR rate of the 14 patients was 100%. In 8 of the 14 patients whose SVR12 was analyzed, SVR24 was evaluated. The 24th -

week SVR rate of the eight patients was 100%. SVR24 of the two patients whose SVR12 could not be evaluated was analyzed. HCV RNA was negative in one patient, while it was measured as 133 IU/mL in the other patient.

Discussion

Although chronic hepatitis C increases mortality and morbidity in hemodialysis patients, it also prolongs the waiting time for renal transplantation since SVR cannot be obtained. Patients with untreated chronic hepatitis C are also under risk for complications such as liver cirrhosis and hepatocellular carcinoma (4). Chronic hepatitis C patients who underwent hemodialysis before DAAs, pegylated interferon alpha 2a monotherapy was administered. The use of other pegylated interferon alpha 2b and ribavirin used in the treatment of chronic hepatitis C was not recommended since they are excreted from the body by renal pathway and they accumulate and lead to secondary toxic side effects in patients with chronic renal failure (CRF) when the dose is increased for higher efficacy. In patients with CRF, the use of ribavirin was found inconvenient, and it was recommended to combine it with interferon doses of 200–800 mg through close surveillance. Due to the difficult application of interferon and the side effects of these drugs, the treatment was sometimes discontinued. In particular, patients who are considered for renal transplantation should be given antiviral therapy to negate or reduce HCV RNA. This is because high levels of HCV RNA increase the risk of resection of the renal transplanted.

The relationship of cryoglobulinemia, membranoproliferative glomerulonephritis, membranous glomerulonephritis and focal segmental glomerulosclerosis with HCV infection is known. In these patient groups, HCV treatment may also reduce the existing kidney failure.

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 AV fistula in the first month of DAA treatment. There is no data in the literature that DAA increases the risk of thrombus. Seventeen out of 18 patients received OBV/PTV/r + DSV ± ribavirin treatment for 12 weeks. Because the remaining one patient had cirrhosis and genotype 1, 24-week treatment was given. ETR 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 evaluated had a relapse. This is similar to SVR24 in the average population. In a study conducted by Pockros et al. on 20 patients with chronic hepatitis C and stage 4 and 5 CRF, OBV/PTV/r + DSV ± ribavirin treatment was reported to be effective (5). Beinhardt et al. investigated the efficacy of DAA in a total of 25 patients with chronic hepatitis C, 10 of whom were on dialysis, eight of whom were renal 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 emphasized that DAA treatment was effective and usable in renal transplant patients (6).

In hemodialysis patients, the use of DAAs which's clearance occurs utilizing renal should be avoided to prevent the accumulation of drugs or metabolites. The clearance of sofosbuvir metabolite, an NS5B

polymerase inhibitor, is renal and is not recommended to be used in those with glomerular filtration rate < 30 mL/ min / 1,73 m^2 (7–8). Although the clearance of simeprevir and daclatasvir is from the liver, there are some studies reporting toxicity in some patients with severe renal failure (9–10).

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are metabolized through the liver. In phase I trials, it was found that there was no need for dose adjustment in mild, moderate and severe renal failure (11). Today, ombitasvir/paritaprevir/ritonavir (25/150/100 mg once a day) and dasabuvir (250 mg twice a day) treatment is found to be effective in hemodialysis patients with chronic hepatitis C.

Conclusions

Although treatment alternatives for chronic hepatitis C have increased since 2010, DAAs may also occur as an alternative to the OBV/PTV/r + DSV treatment in hemodialysis patients. However, as in our study, OBV/PTV/r + DSV is an easily appropriate and effective regimen for the treatment of hemodialysis patients with chronic hepatitis C. Longer-term studies are required to evaluate DAA efficacy in hemodialysis patients.

Abbreviations

AV: Arteriovenous (AV)

CPS: Child-Pugh Score

CRF: Chronic renal failure

DAA: Direct-acting antiviral combination

ETR: The end of treatment response

HCV: Hepatitis C virus

OBV/PTV/r+ DSV: Ombitasvir, paritaprevir, ritonavir , and dasabuvir

SVR: Sustained virological response

Declarations

Ethics approval and consent to participate: Ethics approval was obtained from T.C. Uludağ University Medicine Faculty Clinical Research Ethics Comitee (2019-2/21) .

Consent for publication: All authors consent for publication.

Availability of data and material: Hemodialysis patients with chronic hepatitis C kept under surveillance at the policlinic of the Department of Gastroenterology, Uludağ University Medicine Faculty Hospital

between 2016 and 2018 were evaluated retrospectively. No additional data are available.

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Author contributions: Erurker OT and Gurel S designed the study; Erurker OT, Gurel S, Oruc A and Ersoy A performed the data collection; Erurker OT performed the data analysis; and Erurker OT wrote the manuscript. All of the authors read and approved the manuscript.

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Tables

Table-1 Demographic characteristics of the patients

Age	50,7 ± 8,6
F/M	8 / 12
HVC GT1b	14 (%70)
HCV RNA	504.868,6 (min 100 max 3218282,00)
Treatment experience	14 (%70)
Number of patients with cirrhosis	2 (%10)
Creatinine (mg/dL)	6,79 ± 2,3
Albumin (g/dL)	3,99 ± 0,2
Total bilirubin (mg/dL)	0,6 ± 0,2
Hemoglobin (g/dL)	12,5 ± 1,1
Platelets	169.591 (± 72.576)
INR	1 ± 0,1

Table-2 Virological response during and after the treatment

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