

# Hepatitis C Prevalence in Hemodialysis Patients and the Results of New Antiviral Therapy

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## Abstract

**Objective:** Hepatitis C virus (HCV) is more common in patients undergoing dialysis compared to the normal population. The objective of this study was to investigate the incidence of hepatitis C in patients undergoing hemodialysis and to share the results of the antiviral drugs used in the treatment of our patients with HCV.

**Materials and Methods:** A total of 235 dialysis patients who had applied to the Outpatient Department of Infectious Diseases and Nephrology between January 2017 and December 2017 were retrospectively evaluated.

**Results:** The percentage of the anti-HCV positivity was 12.7%, and 73% of patients with anti-HCV positivity showed the HCV-RNA positivity. Genotyping revealed that 77.2% were 1b, 18.1% were 1a, and 4.5% were 3a. The treatment was planned according to the results of the genotype analysis. The HCV-RNA analysis was not performed in two anti-HCV positive patients because they refused to give blood, and 10 patients refused the treatment. For 12 non-cirrhotic genotype 1b patients who were not treated previously, a treatment protocol by adding dasabuvir to a combination of ombitasvir and paritaprevir/ritonavir was prepared. All patients who completed a 12-week treatment course became 100% HCV-RNA negative in the 1<sup>st</sup>, 3<sup>rd</sup>, and 6<sup>th</sup> month.

**Conclusion:** The treatment of patients undergoing hemodialysis infected with the HCV genotype 1b with an ombitasvir/paritaprevir/ritonavir/dasabuvir combination was very effective.

**Keywords:** Hepatitis C, hemodialysis, antiviral treatment, prevalence

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## INTRODUCTION

Hepatitis C virus (HCV) infection is an important global health problem due to a high risk of hepatocellular cancer, transmission risk to the health care workers, the absence of an effective hyperimmunoglobulin, and vaccine (1, 2). The subpopulations with the highest HCV incidence are intravenous drug addicts (48%-92%), patients with hemophilia (59%-97%), and long-term hemodialysis patients (8%-85%) (3, 4, 5). Patients undergoing hemodialysis have a higher risk of the virus transmission due to an impaired immune system and a high frequency of parenteral interventions (6, 7). Therefore, there are several studies focused on the HCV prevalence, mode of transmission, and treatment options.

As it is well known, the HCV treatment is continuously updated. For decades, peginterferon (PEG-IFN) monotherapy or its combination with ribavirin (RBV) has been the standard treatment in patients with Stage IV chronic renal failure (CRF) (estimated glomerular filtration rate [eGFR] 15-30 mL/min/1.73 m<sup>2</sup>) or stage five chronic renal failure (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m<sup>2</sup>) (8). However, virological response was low in the CRF patients receiving this standard treatment, which also had serious side effects and required a dose adjustment and close monitoring (9). Ribavirin, which increases the virological response, is excreted from the kidney and thus may accumulate in patients with CRF. Therefore, serious side effects, particularly he-



molytic anemia, may be seen in patients with CRF treated with RBV. In this patient group, the RBV dose can be decreased from 800-1200 mg/day to 200 mg three times a week (10). In the recent years, direct-acting antiviral agents (DAA) introduced a major progress in the HCV treatment. These new agents enabled a sustained viral response (SVR) rates of up to 90%, treatments with a smaller number of side effects, and shorter durations. However, in spite of these developments in the treatment options, the efficacy, and safety profile of these agents have not been well established yet in patients with CRF (11).

In this study, our objective was to investigate the incidence of hepatitis C in dialysis patients and to report on the results of the newly developed antiviral agents in the HCV treatment.

## MATERIALS AND METHODS

A total of 235 patients who applied to the outpatient Department of Infectious Diseases and Nephrology between January 2017 and December 2017 were included in the study. There were 95 females and 140 males. The mean age was 57.5±15.9 years.

The study was conducted in accordance with the Declaration of Helsinki 2013, Brasil version, and was approved by the Erzurum Regional Training and Research Hospital Ethics Research Committee. All subjects gave their written informed consent prior to participation in the study. The obtained data were evaluated using the number and percentage calculations.

The patients were retrospectively investigated, and the hepatitis C markers were recorded. Thirty patients were anti-HCV positive (12.7%). Twelve of these anti-HCV positive patients were females, and the remaining 18 patients were males. Their

mean age was 54.3±12.7 years. The clinical and laboratory follow-up period of the anti-HCV positive patients was minimum 6 months. The HCV-RNA serology was evaluated in all of the anti-HCV positive patients. Twenty-two of the anti-HCV positive patients were also HCV-RNA positive (73%). Two anti-HCV positive patients refused to give blood for the second time, and their HCV-RNA analysis could not be performed. Regarding the genotypes, 17 patients were 1b (77.2%); four patients were 1a (18.1%); and one patient was 3a (4.5%). The treatment was planned according to the results of the genotype analysis. Twelve patients accepted to be treated with the new antiviral agents, while 10 patients refused. All patients, who accepted the treatment, were non-cirrhotic genotype 1b patients and did not receive any HCV treatment previously.

The patients received a combination of ombitasvir (25 mg) and paritaprevir (150 mg)/ritonavir (100 mg) (in a single daily dose), dasabuvir (250 mg twice daily). All patients' HCV-RNA became negative in the 1<sup>st</sup> and 3<sup>rd</sup> months of treatment. We observed that all patients' HCV-RNA was negative in the 3<sup>rd</sup> and 6<sup>th</sup> month after treatment completion. We did not encounter any side effect in patients during and after the treatment, and all patients completed the treatment period.

Anti-HCV values were measured by architect I 2000 sr, and HCV-RNA values by RT PCR Rotorgene (Giasymphny). For HCV genotyping, an HCV GT CTLS assay for the Cobas 4800 system (Roche) was used. A complete blood count (CBC) analysis was performed in the hematology laboratory of our hospital with an Abbott Cell-Dyn Ruby (USA) autoanalyzer. An Abbott Architect c 16000 (USA) autoanalyzer was used for measuring the values of total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT). The laboratory findings of anti-HCV positive patients are presented in Table 1.

## DISCUSSION

Hepatitis C virus infection is an important health problem because of the high hemodialysis rate in end-stage renal failure patients. Even though this rate drops with time, the HCV transmission is still an important problem in the dialysis units (12-15).

The mean incidence of the HCV infection is 3% and 70% in the global population and in the patients undergoing hemodialysis, respectively (16, 17).

In studies conducted in our country, such as those by Sönmez et al. (18) and Kadanali et al. (19), high rates of anti-HCV positivity were reported (37.5% and 81.4%, respectively). These rates dropped to 14.9% (20) and 9.5% (21). According to the records by Turkish Nephrology Society obtained from 72 centers, the anti-HCV positivity was found in 365 (5.2%) of 7015 hemodialysis patients (22). The global studies focused on patients with hemodialysis showed that the anti-HCV positivity started to de-

**Table 1.** Some laboratory values of Anti-HCV positive patients

Age	54.3±12.7
Gender % n/male	60% (30/18)
Genotype % (n)	77.2% (17) 1b, 18.1% (4) 1a, 4.5% (1) 3a
HCV-RNA (IU/mL)	4843625.1±9318366.2
ALT (U/L)	15.6±8.9
AST (U/L)	15.1±7.5
GGT (U/L)	32.9±33.6
WBC (10 <sup>3</sup> /μL)	5893.3±1738.3
PLT (μL)	182883.3±73096.7
Albumin (g/dL)	3.8±0.4
Total protein (g/dL)	8.9±1.1
INR	1.0±0.05
Prothrombin time (sec)	12.9±0.8

PLT: Platelet; INR: International Normalized Ratio; HCV-RNA: Hepatitis C Virus Ribonucleic Acid; WBC: White Blood Cell

cline globally over the years, although it was increasing in some countries. According to the data published by the Centers for Disease Control and Prevention (CDC), the HCV seroprevalence was 80% in Egypt, 57% in Saudi Arabia, 16.3% in France, and 8.9% in Atlanta in the 2000s (23). The HCV seroprevalence rate was 12.7% in our study. Although the HCV infection prevalence and incidence among patients undergoing hemodialysis are dropping in several countries, it is still an important problem.

Currently, four HCV markers are used for the diagnosis and follow-up of the treatment. These markers are total anti-HCV, HCV core antigen, HCV-RNA level, and HCV genotyping. Regarding the response to the treatment and the determination of the treatment duration, the HCV-RNA levels and HCV genotypes are guiding parameters (24).

Anti-HCV is used to determine the non-neutralizing antibodies produced against recombinant HCV antigens. Not all anti-HCV positive patients are HCV-RNA positive. HCV-RNA can only be determined in 52%-93% of the anti-HCV positive patients undergoing hemodialysis (25). In a study, it was found that 36.5% of 189 anti-HCV positive patients were also HCV-RNA positive (26). HCV-RNA, which is used to diagnose the HCV infection, is a sensitive method and is considered a gold standard. HCV becomes positive 1-2 weeks after the transmission (27). In our study, 73% of anti-HCV positive patients were also HCV-RNA positive. Two patients were anti-HCV positive but could not be evaluated for HCV-RNA, as they refused to give blood for the analysis.

HCV genotyping is crucial in determining the pathway to be followed in the course and treatment of the disease because of geographical differences (28). The HCV genotyping is important in determining and progression of the disease. There are no firm data concerning the distribution of the HCV genotype among patients undergoing hemodialysis. In studies conducted in the Netherlands, France, Morocco, Mexico, and Turkey, there was a predominance of genotype 1b among patients undergoing hemodialysis (29, 30). In a study from the United States, the subtype 1a was the most frequent among dialysis patients, while in Italian patients, the subtypes 2a and 3a predominated. Some of the studies showed a different genotype distribution in dialysis patients than in the general population, some others did not. In general, the subtype 1a seems to be more frequent in patients undergoing hemodialysis than in the general population (29).

In Turkey, the incidence changes from region to region. The most common genotype is 1b with a rate of 66.7%-100%. It is followed by the genotype 1a (2%-33.3%). It was reported that the rates of 2a, 3a, 4, and 4c were gradually increasing (31). Like in other studies, the genotype 1b had the highest rate (77.2%, n=17) and followed by the genotype 1a (18.1%, n=4) and the genotype 3a (4.5%, n=1) in our study.

A liver biopsy is the gold standard when determining the liver damage severity. However, it is risky for the evaluation of fibro-

sis in patients with CRF due to the bleeding tendency depending on coagulopathy, platelet dysfunction, thrombocytopenia, and the use of anticoagulants during HD (32). In our patients, liver biopsy was not performed, and the treatment was arranged according to the results of the genotype analysis.

The aim of the antiviral treatment in chronic HCV infections is to destruct HCV-RNA, obtain a sustained virological response (SVR), and prevent the liver complications. Each CRF patient is a renal transplantation candidate. Due to the risk of rejection after the transplantation, a chronic HCV infection treatment is controversial. Therefore, SVR should be achieved with an HCV treatment before the transplantation. The treatment of HCV infection before the kidney transplantation decreases the risk of a new onset of diabetes mellitus and de novo glomerulonephritis related to HCV and chronic graft nephropathy (33).

At the beginning of the century, a combination of pegylated interferon and ribavirin became the standard HCV treatment. However, adverse effects of treatment with interferon and ribavirin in patients with chronic kidney disease (CKD) and the resulting poor outcomes have greatly restricted the widespread use of this combination. A recent development of DAAs that disrupt viral replication has completely changed the prognosis of an HCV infection, with cure rates higher than 90% in the general population. In HCV-infected patients on hemodialysis, an experience with DAAs is limited to a small patient series. However, results are very encouraging, as the SVR is achieved in a vast majority of patients (34).

In Phase 3 trials, a combination of ombitasvir, paritaprevir, and ritonavir plus dasabuvir (PrOD) with or without ribavirin has been shown as effective and well tolerated in treatment-naïve and experienced non-cirrhotic patients with the HCV genotype 1 infection (35-37). DAAs target specific nonstructural (NS) proteins encoded by the single-stranded HCV-RNA virus. These include the NS3/4A protease inhibitors, the NS5A inhibitors, and the NS5B polymerase inhibitors, which are further subdivided into nucleoside and non-nucleoside polymerase inhibitors (36).

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are all metabolized by the liver, and Phase 1 studies demonstrated that no dose adjustments are needed in patients with mild, moderate, or severe renal impairment (38).

Our study showed that a combination of ombitasvir/paritaprevir/ritonavir/dasabuvir is safe and effective in patients infected with HCV (genotypes 1b).

In our study, the mean value of HCV-RNA was 4843625.1±9318366.2 IU/mL before the treatment. Following the treatment, 100% of patients became HCV-RNA negative in the 1<sup>st</sup>, 3<sup>rd</sup>, and 6<sup>th</sup> month. According to Sporea et al. (39), an early virological response (EVR) was achieved in 87.5% of

10 patients undergoing hemodialysis with chronic HCV. A SVR rate was 50% in the 6<sup>th</sup> month after the completion of the treatment. In another study, in 17 patients undergoing hemodialysis, interferon treatment provided an EVR of 82.4% and SVR of 64.7% (40). Although the subject size was limited in our study, we observed a significantly higher response to the new antiviral treatment compared to the interferon treatment. Studies conducted with more patients and different genotype groups are needed. It is encouraging that the patients did not encounter any side effect, the patients did not discontinue the treatment, and HCV-RNA results were negative in the 3rd and 6th month of their treatment.

In support to our study, another study showed that SVR was achieved in 100% of patients. In addition, side effects were negligible in their study and no patient had to discontinue treatment (34).

Preliminary data from a Phase III study of the genotype 1 patients with CKD (Stage IV or V) without cirrhosis or coinfection were reported in the Ruby-I trial. Thirteen genotype 1a patients were given PrOD plus RBV for 12 weeks, while 7 genotype 1b patients were given PrOD without RBV for 12 weeks. The majority of patients were male (85%), black (70%), without fibrosis (F0-F1 50%), and on dialysis (65%). A virologic response was assessed at the end of treatment (100% for n=14), sustained virological response 4 weeks after completion of therapy (SVR4) (100% for n=10), and sustained virological response 12 weeks after completion of therapy (SVR12) (100% for n=2). The Ruby-I trial showed that the use of PrOD was safe and effective in patients with end-stage renal disease, including those on dialysis (41).

In a study with naive non-cirrhotic 1b patients, permanent viral responses were found to be 95.2% after 12 weeks (42).

In another study, non-cirrhotic patients with HCV genotype 1b experienced SVR12 rates of 96% to 100% when ombitasvir/paritaprevir/ritonavir and dasabuvir were administered for 12 weeks, regardless of inclusion of ribavirin (43).

Demonstration of the liver damage with biochemical methods during the diagnosis is crucial. Although high values of transaminases are consistent with inflammation and fibrosis, normal values do not exclude liver damage (44). An infection in patients undergoing is usually asymptomatic, and serum aminotransferase and GGT levels are typically within the normal range (45).

The AST, ALT, and GGT levels were normal in our anti-HCV positive patients. In a study, 394 patients undergoing hemodialysis were evaluated, and serological and virological findings of an HCV infection were detected in 22.3% of the patients, but the liver function tests were normal in all HCV positive patients (46).

The rate of the treatment discontinuation due to the side effects is relatively high because of the decrease of the drug clearance depending on the renal dysfunction in patients with CRF. An access to the HCV treatment and chance to receive a proper treatment is particularly low among patients with HCV infection undergoing hemodialysis. According to data from the Dialysis Outcomes and Practice Patterns Study, antiviral treatment was administered only to 48 (1%) of the 4735 patients undergoing hemodialysis with HCV infection (9.5%) and to 3.7% of 617 renal transplant patients (47). In our study, 12 of the 22 HCV-RNA positive patients (54.5%) accepted and completed the treatment. All patients completed the treatment without any side effects. The ease of use of the antiviral agents and the lack of side effects were the main reasons for the high acceptance and completion rate of the treatment among our patients.

## CONCLUSION

The importance of hepatitis C, which is a common and a critical health problem in the dialysis patients, was emphasized. In addition, the successful treatment of the genotype 1b patients with the ombitasvir/paritaprevir/ritonavir/dasabuvir combination was encouraging for new patients. The lack of side effects confirmed that these drugs are a safe and reliable treatment for patients undergoing hemodialysis.

**Ethics Committee Approval:** This study was approved by the Erzurum Regional Training and Research Hospital Ethics Committee, approval number: 2018/05-33.

**Informed Consent:** Informed consent form received from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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