



Efficacy of Direct-acting Antivirals in Hemodialysis Patients with Chronic Hepatitis C: A Real-life Retrospective Study

Kronik Hepatit C'li Hemodiyaliz Hastalarında Doğrudan Etkili Antivirallerin Etkinliği: Gerçek Hayatta Retrospektif Bir Çalışma

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ABSTRACT

Objectives: Hepatitis C virus (HCV) infection is common among hemodialysis (HD) patients and is associated with increased morbidity and mortality. New generation direct-acting antiviral (DAA) agents are safe and effective in treatment HCV infection in HD patients. The aim of this a multi-center study was to assess the efficacy of DAAs in HD patients with HCV infection.

Materials and Methods: HD patients with HCV infection followed-up at five centers were included in this retrospective cohort study. Patients demographic and virological characteristics, liver fibrosis status, end of treatment and sustained virologic responses (SVR12) at 12 weeks after treatment were recorded. Treatment of the patients was arranged according to the genotype and drug interactions considering guidelines.

Results: Ninety percent of 20 patients were genotype 1b and were treated for 12 weeks with paritaprevir-ritonavir-ombitasvir-dasabuvir; one patient was genotype 4 and received PrOD + ribavirin (RBV) for 12 weeks; and one patient was genotype 3 and was treated with sofosbuvir + RBV for 24 weeks. HCV-RNA negativity was achieved in all patients at the end of treatment and SVR12 rate was 100%. Significant side effects were not observed in any patients, apart from sleeplessness in one patient and itching in another.

Conclusion: Our real-life data support that new generation DAAs achieve high SVR and are well tolerated in HD patients with HCV. In these patients, intolerance and side effects were not observed, which would otherwise require cessation of the DAA regimen.

Keywords: Hepatitis C, hemodialysis, direct-acting antiviral agent

ÖZ

Amaç: Hepatit C virüsü (HCV) enfeksiyonu hemodiyaliz (HD) hastalarında sık görülür ve artmış morbidite ve mortalite ile ilişkilidir. Yeni nesil direkt etkili antiviral (DAA) ajanları, HD hastalarında HCV enfeksiyonunun tedavisinde güvenli ve etkilidir. Bu çok merkezli çalışmada, HCV enfeksiyonu olan HD hastalarında DAA'nın etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmaya beş merkezde HCV enfeksiyonu ile takip edilen HD hastaları dahil edildi. Hastaların demografik ve virolojik özellikleri, karaciğer fibroz durumu, tedavinin sona ermesi ve tedaviden 12 hafta sonra kalıcı virolojik yanıtlar (SVR12) kaydedildi. Hastaların tedavisi kılavuz ilkeleri göz önünde bulundurularak genotip ve ilaç etkileşimlerine göre düzenlendi.

Bulgular: Yirmi hastanın %90'ı genotip 1b idi ve 12 hafta boyunca paritaprevir-ritonavir-ombitasvir-dasabuvir (PrOD) ile tedavi edildi, bir hasta genotip 4 idi ve 12 hafta boyunca PrOD + ribavirin (RBV) aldı, ve bir hasta genotip 3 idi ve 24 hafta boyunca sofosbuvir + RBV ile tedavi edildi. Tedavi sonunda tüm hastalarda HCV-RNA negatifliği sağlandı ve SVR12 oranı %100 idi. Bir hastada uykusuzluk, diğerinde kaşıntı dışında hiçbir hastada önemli yan etkiler gözlenmedi.

Sonuç: Gerçek yaşam verilerimiz, HCV'li HD hastalarında yeni nesil DAA'ların yüksek SVR sağladığını ve iyi tolere edildiğini desteklemektedir. Bu hastalarda, DAA rejiminin kesilmesini gerektiren intolerans ve yan etkiler gözlenmedi.

Anahtar Kelimeler: Hepatit C, hemodiyaliz, direkt etkili antiviral ajan

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Introduction

Hepatitis C virus (HCV) infection is the most common among hemodialysis (HD) patients and is an important cause of liver disease in this population. The risk of all-causes and liver-related mortality is higher in HD patients with HCV infection (1). The frequency of anti-HCV positivity in HD patients varied from 1.6% to 68% in the world (2).

In Turkey, the prevalence of HCV was ranged from 31.4-51% in HD patients at early 2000s (3). Currently, the prevalence of anti-HCV antibody in HD patients in Turkey is 5.2% (4). Studies have shown that prognosis in HD patients with HCV infection is significantly worse than in HD patients without HCV infection (5,6). Until recently, sustained virologic response (SVR) was achieved in approximately 50% of patients with chronic kidney disease (CKD) infected with HCV using the recommended gold standard therapy of pegylated interferon (peg-IFN) (7). However, severe side-effects and treatment compliance problems were observed in CKD patients using peg-IFN, and drug dosage adjustment and careful close follow-up were required (8). Major progress in the treatment of HCV has been made with the entry into use in recent years of direct-acting antivirals (DAAs), which target viral proteins, leading to increases in SVR and a marked decrease in side-effects (9). However, there is no standard treatment for HD patients with HCV infection. Insufficient data are available for the efficacy and reliability of DAAs in HD patients.

The aim of this study was to evaluate the efficacy of DAAs in HD patients with HCV infection.

Materials and Methods

Treatment-naïve or experienced [IFN/pegIFN ± ribavirin (RBV)] 20 HD patients treated with DAAs for HCV infection were included in the retrospective cohort study from five centers in Turkey between June 2016 and May 2018. These centers were the Karadeniz Technical University Faculty of Medicine, Giresun University Faculty of Medicine, Kanuni Training and Research Hospital, Ordu University Faculty of Medicine, and Recep Tayyip Erdoğan University Faculty of Medicine, Department of Infectious Diseases. Demographic characteristics, clinical findings and treatment outcomes of patients were recorded. HCV-RNA, HCV genotype, blood chemistry and blood count were performed before treatment initiation. Ninety percent of patients were non-cirrhotic and 10% were compensated cirrhotic. Two patients were diagnosed with cirrhosis according to the clinical findings, imaging and non-invasive fibrosis score of the treating clinician, and no liver biopsy was performed.

Eighteen patients (90%) were genotype 1b, one each patients were genotype 3 and 4. Genotype 1b patients were treated with a 12-week paritaprevir-ritonavir-ombitasvir-dasabuvir (PrOD) regimen. Genotype 3 and 4 patients were treated with sofosbuvir + RBV for 24 weeks, and PrOD + RBV for 12 weeks, respectively.

Virological, biochemical and serological responses were evaluated 4, 12 and 24 weeks after the start of treatment, and at 36 weeks in the patient receiving 24-week treatment for SVR. This study was approved by Karadeniz Technical University Ethics Committee (approval number: 2019/254, date:20.09.2019). Since our study was retrospective, informed consent was not used.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics (version 23.0) program for Windows. The Wilcoxon signed ranks test was applied to compare differences between pre-treatment and 12th week laboratory values. P values <0.05 were regarded as statistically significant.

Results

All of the 20 patients were completed treatment. The mean age of the patients was 57.8 (±10.5) years. Ninety percent were men and 10% were women. Eleven (55%) patients were treatment-experienced and nine (45%) were treatment-naïve. Five of the treatment-experienced patients (45.5%) were non-responders, and 6 patients (54.5%) were relapser. Ninety percent of patients were non-cirrhotic and 10% were compensated cirrhotic. The pre-treatment HCV-RNA median level (log₁₀ IU/mL) was 5.2.

Patients' characteristics and basal laboratory values are shown in Table 1.

HCV-RNA was negative in 17 (85%) patients by the 4th week, and with the exception of a patient received sofosbuvir + RBV regimen. In all patients HCV-RNA was negative at the end of treatment and SVR rate was 100% (Table 2). HCV-RNA levels decreased rapidly after patients were started on antiviral therapy (Figures 1,2). Viral responses were independent of previous treatments and liver fibrosis status.

Patients' biochemical markers were also assessed after treatment. Serum alanine aminotransferase (ALT), levels decreased after the start of treatment (Figure 3). Patients' pre-treatment HCV-RNA and ALT values decreased significantly by the 12th week after

Patients number	20
Mean age	57.8 (±10.5)
Male/Female	18/2 (90%/10%)
HCV Genotype (1B/3/4)	(18/1/1) (90%)/(5%)/(5%)
Basal hemoglobin level (g/dL)	12.8 (6.6-17.6)
Basal platelet level (x10 ³ /µl)	142 (46-271)
Basal ALT level (units)	23.5 (5-56)
Basal HCV-RNA level (log ₁₀ IU/ml)	5.2 (2.3-7.1)
Liver cirrhosis	2 (10%)
Pre-treatment status (naïve/experienced)	9/11 (45%)/(55%)

HCV: Hepatitis C virus, ALT: Alanine aminotransferase

Virologic response	n (%)
4 th week	17 (85)
12 th week	19 (95)
24 th week	20 (100)
End of treatment	20 (100)
SVR12*	20 (100)

HCV: Hepatitis C virus, *SVR12: Sustained virologic responses at 12 weeks

treatment ($p < 0.001$ and $p = 0.001$, respectively). No significant difference was determined in albumin or platelet levels.

Significant side effects were not observed in any patients, apart from sleeplessness in one patient and itching in another, and no complication developed. Both resolved spontaneously without additional treatment during follow-up. None of the patients developed side effects that required treatment interruption or discontinuation.

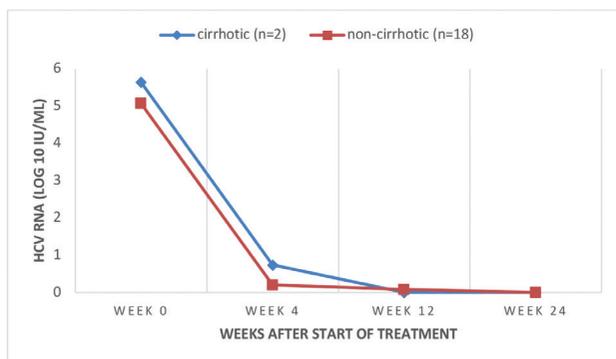


Figure 1. Mean HCV-RNA changes during treatment in cirrhotic and non-cirrhotic patients
HCV: Hepatitis C virus

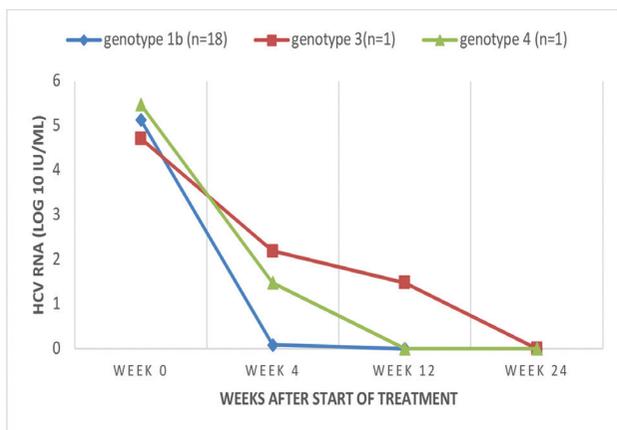


Figure 2. Mean HCV-RNA changes during treatment in genotype 1b, 3 and 4 patients
HCV: Hepatitis C virus

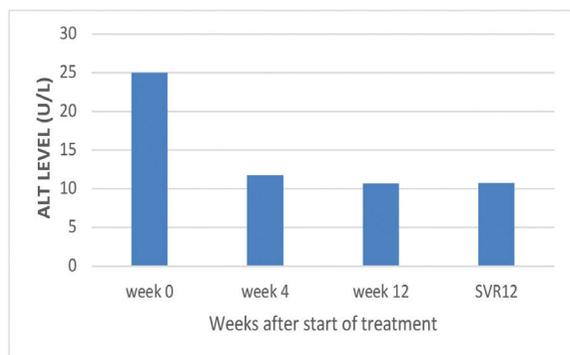


Figure 3. Changes in ALT after treatment
ALT: Alanine aminotransferase

Discussion

HCV infection is frequently seen in patients with CKD, including HD patients. Factors increasing the risk of HCV in HD patients include advanced age, number of blood transfusion, and the prevalence of HCV in the HD unit (10). HCV in CKD patients and pre- and post- kidney transplant patients increases the risk of all-causes and kidney-related mortality (1,10). The treatment of HCV in CKD patients is complex, but prognosis improves in case of treatment. Although HCV is frequently seen in HD units, experience of treatment is still limited (10). Peg-IFN, either alone or in combination with RBV, was until recently recommended as the standard treatment of CKD patients with HCV infection, and this treatment achieved a SVR rate of approximately 50% and has potential toxicity (7). Since RBV cannot be eliminated in patients with HD and CKD, accumulation results in significant side effects, particularly hemolytic anemia. This leads to RBV dose restriction (11). Recent studies have shown that DAAs are extremely well tolerated in CKD with HCV infection and have few side-effects (12,13).

Several clinical studies have confirmed the effectiveness and reliability of non-sofosbuvir containing regimens in patients with advanced kidney failure. In the RUBY-1 study, stage 4 and 5 CKD patients infected with non-cirrhotic genotype 1 were treated with PrOD for 12 weeks, and SVR12 was achieved at a rate of 90%. In the light of these data, it was concluded that the PrOD regimen can be safely used in stage 4 and 5 CKD patients without the need for dose adjustment (14). The EASL 2018 guideline also stated that no dose-adjustment is required for any approved DAA combinations in the treatment of mild and moderate kidney failure (1). The safety of sofosbuvir regimens has been questioned in patients with severe kidney failure. However, the data concerning the safety and efficacy of these regimens are inadequate (15). Sofosbuvir is eliminated by the renal pathway and its use is not recommended in CKD stage 4 or 5 or in patients requiring HD (1,8,15). However, Cox-North et al. (16) reported that treatment with sofosbuvir-based regimens is safe in patients with CKD stage 4 or 5 and infected with HCV if no alternative is available. The HCV-target study evaluated patients with decreased renal functions and determined a SVR rate of 83% for sofosbuvir-containing regimens, concluding that these have no adverse effect on renal functions (17).

In our study, 100% SVR12 was achieved in HD patients with genotype 1b HCV infection receiving PrOD therapy, including elderly patients and two with liver cirrhosis. Genotype 4 HCV infection was treated with PrOD + RBV and HCV-RNA was negative by the end of treatment and SVR12 was achieved. Treatment-experienced patients tolerated PrOD ± RBV better than regimens including peg-IFN. No significant side-effects were observed. One of the patients was non-cirrhotic and genotype 3 and was treated with sofosbuvir + RBV for 24 weeks. This patient's HCV-RNA was negative by the end of treatment, and SVR12 was achieved. No important side-effects other than sleeplessness were observed in our patients at the end of treatment. No suitable therapeutic dose of sofosbuvir for patients with advanced kidney failure has been determined in previous studies (1). Regimens not containing sofosbuvir must be employed for HCV infection in patients with advanced kidney failure or undergo dialysis. In case a sofosbuvir-based regimen has to be used, then close monitoring is required, and treatment must

be promptly modified if kidney functions are impaired or if any side-effect develops (1). Since no alternative was available in our patient infected with genotype 3, sofosbuvir + RBV therapy was initiated. The patient was placed under close observation, and no significant side-effect other than sleeplessness was observed.

Yaraş et al. (18) administered a PrOD regimen to 25 HD patients with HCV. In 92% of patients HCV-RNA was negative by the 4th week, and SVR12 was 100%.

HCV-related liver damage can accelerate immunosuppression. Antiviral therapy must therefore be considered in all HD patients scheduled for kidney transplantation (1). Studies have shown that renal transplanted patients, such as HD patients, have been successfully treated with non-interferon regimens (19,20,21).

Conclusion

Our study shows that DAAs are effective and reliable in HD patients. However, further studies with larger patient numbers examining the efficacy and reliability of these agents in HD patients are now needed. Establishing a course of treatment in HD patients is important for global eradication of HCV.

Ethics

Ethics Committee Approval: This study was approved by Karadeniz Technical University Ethics Committee (approval number: 2019/254, date: 20.09.2019).

Informed Consent: Since our study was retrospective, informed consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.N.A., Concept: N.N.A., FA., İ.K., Design: N.N.A., FA., Data Collection or Processing: N.N.A., FA., İ.Y., S.İ., A.A.Y., İ.E.Y., İ.K., Analysis or Interpretation: N.N.A., İ.Y., S.İ., A.A.Y., İ.E.Y., Literature Search: N.N.A., FA., İ.K., Writing: N.N.A.

Conflict of Interest: Authors declare no conflict of interest.

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