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Efficacy and Safety of the Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir Regimen for Chronic Hepatitis C in Hemodialysis Patients

Hemodiyaliz Hastalarındaki Hepatit C Tedavisinde Paritaprevir/Ritonavir/Ombitasvir ve Dasabuvir Rejiminin Etkinlik ve Güvenliği

Güven Gürkan TOSUN[1], Fidan SULTANOVA[1], Nihan AK[2], Kenan HIZEL[1]

[1]Gazi University Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[2]Gazi University, Department of Public Health, Ankara, Turkey

Abstract

Introduction: A higher percentage of sustained virologic response (SVR) has been reported with the introduction of direct-acting antivirals (DAAs) to the treatment of hepatitis C in recent years. However, there are still relatively limited data on the effectiveness and safety of the use of DAAs in hemodialysis patients. The aim of this study was to evaluate the efficacy and safety of chronic hepatitis C treatment with paritaprevir/ritonavir/ombitasvir and dasabuvir (3D) in hemodialysis patients.

Materials and Methods: Hemodialysis patients who were treated with 3D regimen between July 2016 and October 2018 were evaluated retrospectively. Patients coinfected with hepatitis B or human immunodeficiency virus and those with cirrhosis were excluded. Serum hepatitis C virus (HCV) RNA and alanine aminotransferase levels of the patients were recorded after one and three months of therapy. SVR was defined as negative HCV RNA at three months after cessation of HCV treatment. Any drug-related alterations in clinical or laboratory findings during the treatment period were evaluated as side effects.

Results: Fifteen patients who were treated with the 3D regimen during the study period were included. Genotype 1b and 1a were detected in 12 and three patients, respectively. Ribavirin was added to treatment for genotype 1a-infected patients. Hemoglobin levels were reduced in two of the three patients who received ribavirin. One patient had macular rash and another patient complained of fatigue. No serious side effects were observed. At the end of treatment, a low level of HCV RNA (63 IU/ml) was detected in only one patient. At the end of treatment, HCV RNA negativity was achieved in 12 out of 13 patients whose HCV RNA quantitation data were available. End-of-treatment success rate was 92%. SVR was achieved in all of the patients at three-months after treatment cessation (100% SVR12).

Conclusion: This study shows that the 3D regimen is safe and effective in the treatment of hemodialysis patients infected with hepatitis C.

Keywords: Hepatitis C virus, chronic renal failure, thrombocytopenia, adverse effect, chronic kidney insufficiency

Öz

Giriş: Son yıllarda kronik hepatit C (KHC) tedavisinde kullanıma giren doğrudan etkili antiviral (DEA) ilaçlar ile birlikte, tedavide yüksek oranda kalıcı virolojik yanıt (KVY) elde edilebilmektedir. Ancak DEA ilaçların hemodiyaliz hastalarında kullanımının etkinlik ve güvenliği hakkında hala nispeten kısıtlı veri bulunmaktadır. Bu çalışmanın amacı hemodiyaliz hastalarında paritaprevir/ritonavir/ombitasvir ve dasabuvir (3D rejimi) ile KHC tedavisinin etkinlik ve güvenliğini değerlendirmektir.

Gereç ve Yöntem: Temmuz 2016 ile Ekim 2018 tarihleri arasında 3D rejimiyle tedavi edilen hemodiyaliz hastaları retrospektif olarak taranmıştır. Hepatit B veya insan immün yetmezlik virüsü (HIV) koenfeksiyonu olan ve siroz bulguları bulunan hastalar çalışmaya dahil edilmemiştir. Hastaların

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Address for Correspondence/Yazışma Adresi: Güven Gürkan Tosun MD, Gazi University Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
Phone: +90 539 264 71 94 **E-mail:** gvn.grkn@hotmail.com
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birinci ay ve üçüncü ay ölçülen serum hepatit C virüsü (HCV) RNA ve alanin aminotransferaz düzeyleri kaydedilmiştir. Kalıcı virolojik yanıt HCV tedavisinden üç ay sonra HCV RNA negatifliğinin sağlanması olarak tanımlanmıştır. Tedavi sürecinde ilaca bağlı ortaya çıkan klinik bulgular ya da laboratuvar değişiklikleri yan etki açısından değerlendirilmiştir.

Bulgular: Çalışma süresi içerisinde 3D rejimi ile tedavi başlanan 15 hemodiyaliz hastası çalışmaya dahil edilmiştir. On iki hastada genotip 1b, üç hastada genotip 1a tespit edilmiştir. Genotip 1a tespit edilen hastaların tedavisine ribavirin eklenmiştir. Ribavirin alan üç hastanın ikisinde hemoglobin düşüşü gözlenmiştir. Bir hastada maküler döküntü, bir hastada halsizlik şikayeti gözlenmiştir. Ciddi yan etki saptanmamıştır. Tedavi sonunda bir hastada düşük düzeyde (63 IU/ml) HCV RNA pozitifliği saptanmıştır. Tedavi sonu HCV RNA kantitasyonu verisine ulaşılabilen 13 hastanın 12'sinde HCV RNA negatifliği görülmüş, tedavi sonu başarı %92 olarak hesaplanmıştır. Hastaların tamamında tedavi bitiminden 12 hafta sonra HCV RNA negatifliği (KVY12) sağlanmış, KVY12 %100 olarak bulunmuştur.

Sonuç: Bu çalışma HCV ile enfekte hemodiyaliz hastalarının tedavisinde paritaprevir/ritonavir/ombitasvir ve dasabuvir rejiminin etkin ve güvenli olduğunu göstermiştir.

Anahtar Kelimeler: Hepatit C virüs, kronik böbrek yetmezliği, trombositopeni, yan etki, kronik böbrek yetersizliği

Introduction

Hepatitis C virus (HCV) infection is a global public health problem. It is believed that more than 170 million people worldwide are infected with HCV and its prevalence is approximately 3%[1]. This rate is higher in hemodialysis patients, at 8-16%[2-4]. In Turkey, HCV seroprevalence ranges between 0.4% and 1.15% in the general population and up to 4.2% in hemodialysis patients[5-7]. Chronic hepatitis C (CHC) infection is effects also adversely the survival in dialysis patients[8].

Today, treating CHC with direct-acting antiviral agents (DAAs) results in high rates of sustained virologic response (SVR). However, there is still relatively limited data on the efficacy and safety of DAAs in hemodialysis patients. Guidelines recommend a combination of glecaprevir/pibrentasvir, grazoprevir/elbasvir, and ritonavir-fortified paritaprevir, ombitasvir, and dasabuvir (3D regimen) for the treatment of CHC patients undergoing hemodialysis due to severe kidney disease (creatinine clearance ≤30 ml/min) or end-stage kidney disease[9]. Guidelines from Turkey also state that the 3D regimen can be used in this patient group without the need for dose adjustment[10,11]. The aim of this study was to evaluate the efficacy and safety of the 3D regimen for the treatment of CHC in hemodialysis patients.

Materials and Methods

This study was conducted with the approval of the Gazi University Clinical Research Ethics Committee (12 November 2018, number 24074710-604.01.01-44). Hemodialysis patients treated with the 3D regimen in the Infectious Diseases and Clinical Microbiology outpatient clinic of our hospital between July 2016 and October 2018 were screened retrospectively. Patients who had hepatitis B or human immunodeficiency virus coinfection or signs of cirrhosis and those who did not have viral load testing at 12 weeks or whose test results were not reported were excluded from the study. The patients' serum HCV RNA levels, transaminase levels, and complete blood count values measured before treatment, after one month of treatment, at the end of treatment, and three months after the end of treatment were recorded. SVR was defined as maintaining HCV RNA negativity three months after cessation of HCV treatment. Drug-related clinical findings or changes in laboratory parameters during the course of treatment were evaluated as side effects.

All patients used paritaprevir/ritonavir/ombitasvir 150/100/25 mg once daily and dasabuvir 250 mg twice daily ± ribavirin 200 mg once daily. The patients' treatment adherence and side effects were assessed from electronic records based on their histories and laboratory results. HCV RNA quantitation was performed using QIAsymphony DSP Virus/Pathogen Midi Kit (Qiagen, Germany) and QIAsymphony SP/AS and Rotor gene Q device (Qiagen, Germany) (lower limit 35 IU/ml).

Statistical Analysis

SPSS 15.0 statistical software package was used for statistical analyses of the study data. As descriptive statistics, categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean ± standard deviation for normally distributed data and as median (minimum-maximum values) for data with nonnormal distribution. The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical tests (Kolmogorov-Smirnov/Shapiro-Wilk tests). Parameters in dependent groups that did not conform to normal distribution were compared via Wilcoxon test. Statistical significance was accepted as $p<0.05$.

Results

During the study period, 18 hemodialysis patients began treatment with the 3D regimen. Two patients with HBV coinfection and one patient not tested for SVR at 12 weeks were excluded. Of the remaining 15 patients included in the study, six were female and the mean age was 54.7 (33-78) years. HCV genotype was 1b in 12 patients whereas 1a in three patients. Four patients were treatment-experienced (three patients with genotype 1b, one patient with genotype 1a). The patients' demographic information and pretreatment values are summarized in Table 1.

Table 1. Demographic information and pretreatment values of the patients

	Number	Percentage
<60 years	12	80
Female	6	40
Anemia (hemoglobin <12 g/dl)	8	53
Thrombocytopenia (<130.000/µl)	1	6
Genotypes		
1a	3	20
1b	12	80
HCV RNA >800.000 IU/ml	11	73
ALT >40 IU/ml	3	20
Treatment-experienced (peginterferon + ribavirin)	4	27

ALT: Alanine aminotransferase, HCV: Hepatitis C virus

Table 2. Patients' HCV RNA negativity during the treatment course

Time point	1 month		3 months		SVR12*	
	Number (n/N)	Percentage (%)	Number (n/N)	Percentage (%)	Number (n/N)	Percentage (%)
HCV RNA negativity	11/11	100	12/13	92	15/15	100

*Three months posttreatment

n: number of HCV RNA-negative patients

N: number of patients tested for HCV RNA

HCV: Hepatitis C virus

Ribavirin was added to therapy in three patients with genotype 1a, as per guideline recommendation[9]. In two of those patients, initial hemoglobin values were 15 g/dl and 11.6 g/dl and decreases of 2.2 g/dl and 2.6 g/dl were observed in end-of-treatment hemoglobin values, while no decrease was observed in the other patient. Ribavirin therapy was not interrupted for any of the patients and none received blood transfusions during follow-up.

Platelet count normalized after treatment in one patient with thrombocytopenia (<130,000/µl) at the start of treatment. No new thrombocytopenia was observed in any of the patients who were started on treatment.

Median pretreatment and end-of-treatment alanine aminotransferase (ALT) values of the patients were 19.5 (5-57) IU/ml and 13 (4-44) IU/ml. Comparison of pretreatment and end-of-treatment ALT values revealed a significant decrease with treatment ($p<0.05$).

The patients' virologic responses during treatment are summarized in Table 2. HCV RNA levels were analyzed in 11 of the 15 patients after one month of treatment and all of the patients tested negative. A patient who was HCV RNA-negative after one month of treatment (genotype 1a, treatment-experienced) showed slight HCV RNA positivity (63 IU/mL) at end-of-treatment (three-month) follow-up, but the patient tested negative for HCV RNA at post-treatment 12 (SVR12) and 24 (SVR24) weeks. HCV RNA was negative in 12 of the 13 patients with available end-of-treatment HCV RNA quantitation data, for a posttreatment success rate of 92%. All patients were HCV RNA-negative at post-treatment three months, indicating SVR12 of 100%. Nine patients' HCV RNA levels were analyzed at post-treatment 24 weeks or later and all results were negative, consistent with SVR12.

One patient had a macular rash and itching, while another complained of fatigue during the course of treatment. However, both resolved spontaneously without additional treatment during follow-up. None of the patients developed side effects that required treatment interruption or discontinuation. Treatment adherence was high.

Discussion

Genome sequence analysis studies have identified seven different HCV genotypes and a large number of subtypes[12]. Genotype 1 is the most common genotype worldwide. Genotype 1b is more common in Europe and Japan, while genotype 1a is more common in the United States[1]. Various studies conducted in Turkey have shown the prevalence of genotype 1b to be between 72% and 84%[13-15]. HCV genotype distribution among dialysis patients is similar[14,16]. In the present study, 80% of the patients had genotype 1b, consistent with the literature data.

The main goal of CHC treatment is to eradicate the virus in order to prevent hepatic and extrahepatic involvement of the disease, improve quality of life, and eliminate infectivity. The absence of HCV RNA in the serum at 12 or 24 weeks after treatment is defined as SVR. In current guidelines, the endpoint of HCV treatment is defined as SVR12 or SVR24 assessed with sensitive molecular methods (lower limit of detection ≤15 IU/ml)[9]. Since a quantitative test with high sensitivity was used for the detection of HCV RNA in our study, SVR12 was used to evaluate treatment success.

There are studies in the literature showing that HCV RNA positivity may be observed during the course of treatment. In a study reporting real-life data on the use of the 3D regimen for the treatment of CHC in 209 patients, SVR12 was achieved in two patients who had completed the 12-week treatment period but demonstrated virologic nonresponse at the end of treatment[17]. In the same study, three of seven patients who could not complete the treatment period due to side effects demonstrated virologic nonresponse at the end of treatment, but SVR12 was still achieved in two of these patients. In the present study, SVR12 was achieved in one patient with end-of-treatment virologic nonresponse.

The DAA regimens used today have facilitated high treatment adherence and success in this unique and difficult-to-treat patient group[18-20]. Muñoz-Gómez et al.[19] evaluated stage 4-5 chronic kidney disease patients infected with HCV genotype 1 (9 genotype 1a, 32 genotype 1b) and genotype 4 started on treatment with the 3D regimen and reported that SVR12 was achieved in all 44 patients who completed treatment. SVR24 was achieved in all 38 patients with available 24-week data. Sperl et al.[20] reported that SVR12 was achieved in all of their 23 patients (2 genotype 1a, 21 genotype 1b) in another study presenting real-life data regarding the 3D regimen used in stage 4-5 chronic kidney disease patients infected with HCV genotype 1. In accordance with the literature data, high end-of-treatment success (92%) and SVR12 (100%) were also achieved in our study.

Another indicator of response to HCV treatment is a decrease in ALT levels due to the regression of liver inflammation. In a phase 3 trial including treatment-experienced, non-cirrhotic, genotype 1b-infected patients, pretreatment elevated ALT levels normalized after treatment in 96.9% of patients in the ribavirin group, while this rate was 100% in the ribavirin-free group[21]. Similarly, significant posttreatment decreases in ALT were also achieved in our study.

Interferon-based regimens used before the introduction of potent DAA drugs for the treatment of CHC limited their use by reducing patient compliance due to the long treatment duration and serious side effects[22,23]. Adverse effects associated with interferon were more frequent and severe in dialysis patients due to the reduced renal clearance of interferon. These side effects were increased by the use of ribavirin, which is cleared by the kidneys and minimally removed by hemodialysis, in combination with interferon[24,25]. Early treatment termination due to severe drug-related side effects and virologic nonresponse was very frequent[26]. However, side effects that impact the treatment process are rarely reported with DAAs. The most common side effects experienced by patients on the 3D regimen are fatigue, headache, nausea, vomiting, diarrhea, myalgia, and rashes. However, no adverse events requiring treatment interruption or discontinuation have been reported[21,27-29]. In the present study, one patient had skin rash and itching, while another complained of fatigue, but these did not affect the treatment course or outcome.

Although side effects associated with the combination of ritonavir-fortified paritaprevir, ombitasvir, and dasabuvir are uncommon, the addition of ribavirin in necessary cases increases the risk of side effects. The most common side effect associated with the addition of ribavirin to the treatment regimen is anemia[29,30]. In a trial investigating the efficacy and safety of the 3D regimen in patients with chronic kidney disease (RUBY-I), nine of 13 patients could not use ribavirin three months due to anemia[29]. Of these nine patients, one patient with level F3 fibrosis whose ribavirin therapy was discontinued on day 58 did not achieve SVR12 despite HCV RNA negativity at the end of treatment. However, it was reported that this patient showed poorer treatment adherence compared to the other patients in the treatment group. Another patient died due to causes unrelated to CHC. SVR12 was achieved in all of the remaining seven patients despite the fact that ribavirin could not be used at the planned dose and duration. Based on data from this study, Sperl et al.[20] prescribed ribavirin at a dose of 200 mg twice a week, taking into account the low ribavirin tolerance of treatment-experienced patients with peginterferon and ribavirin nonresponse. They did not detect any decreases in the patients' hemoglobin, platelet, or white blood cell counts during treatment or at posttreatment 12-week follow-up, and reported that SVR12 was achieved in all patients. In our study, a decrease in hemoglobin was observed in two of three genotype 1a-infected patients who received ribavirin 200 mg/day for three months. However, these patients did not require erythropoietin therapy or blood transfusion, and treatment was successful. Currently, ribavirin-free combinations are recommended for hemodialysis patients in order to reduce the risk of adverse effects, and the 3D regimen is only among the treatment options for genotype 1b-infected patients who do not require ribavirin[9].

Due to the retrospective design of this study, we could not evaluate certain mild side effects and drug interactions with other medications used by the patients. However, no severe side

effects affecting the course of treatment were observed. There are reports in the literature of electrolyte imbalance associated with the 3D treatment regimen[20]. Although kidney function tests and blood electrolyte levels of the patients in our study were regularly analyzed by the dialysis centers they attended, these data were not accessible. However, no electrolyte disturbance severe enough to affect treatment was reported. There are few studies on the clinical use of DAAs in Turkey[31,32]. Despite the aforementioned limitations, there are limited real-life data from Turkey pertaining to the 3D regimen, which was the only treatment option for this patient group covered by the national reimbursement system until recently. To our knowledge this study is the first extensive investigation on this subject carried out in Turkey.

Conclusion

This study demonstrates that the paritaprevir/ritonavir/ombitasvir/dasabuvir regimen has high SVR rates, good tolerability, and low incidence of side effects in the treatment of HCV-infected hemodialysis patients, and is therefore a safe and effective treatment option for this patient group. Anemia is the most common side effect, especially when ribavirin is added to the regimen, and should be closely monitored. Although the 3D regimen has lost the distinction of being the first-line option for the treatment of CHC in patients with chronic kidney disease in current international guidelines, it can be used as an effective and safe alternative in cases where first-line drugs are not available.

Ethics

Ethics Committee Approval: For this study, approval of Gazi University Clinical Research Ethics Committee dated 12 November 2018 and numbered 24074710-604.01.01-44 was obtained.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: K.H., Design: K.H., G.G.T., Data Collection or Processing: G.G.T., F.S., Analysis or Interpretation: N.A., G.G.T., Literature Search: G.G.T., K.H., Writing: G.G.T., K.H.

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