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The Efficacy of Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir with or without Ribavirin in Patients with Hepatitis C Undergoing Chronic Haemodialysis: A Single Center Experience

Hepatit C Pozitif Kronik Hemodiyaliz Hastalarında Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir ± Ribavirin Tedavisinin Etkinliği: Tek Merkez Deneyimi

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ABSTRACT

Objectives: Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) seems to be highly effective and safe in chronic haemodialysis (CHD) patients. We presented our experiences of treatment with PrOD in CHD patients.

Materials and Methods: Between July 2016 and September 2018, a total of 25 CHD patients treated with PrOD were enrolled. The patients with hepatitis C virus (HCV) genotype 1a were treated with PrOD plus ribavirin (RBV) (12 or 24 weeks according to whether or not they had compensated cirrhosis), while the patients with genotype 1b were treated with PrOD alone. Liver functions, renal functions, and HCV-RNA levels were measured at baseline, 4, 12, and if applicable, 24 weeks after the initiation of treatment as well as 4 and 12 weeks after therapy.

Results: Nineteen patients received PrOD, while 6 received PrOD plus RBV treatment. Two patients failed to complete the treatment. Two patients with compensated cirrhosis were treated over 24 weeks, while others received 12 weeks. In 23 patients completed 12 weeks, all were HCV-RNA negative at the end of the treatment, and had sustained virologic response (SVR) after the 12 weeks of treatment. The most common side effects were pruritus and anaemia.

Conclusion: The PrOD treatment resulted in a high rate of SVR in HCV-infected CHD.

Keywords: Hepatitis C virus, Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir, haemodialysis

ÖZ

Amaç: Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) rejimi kronik hemodiyaliz (KHD) hastalarında etkili ve güvenlidir. Biz bu çalışmada KHD hastalarında PrOD tedavisi ile ilgili deneyimlerimizi sunmayı amaçladık.

Gereç ve Yöntemler: Temmuz 2016- Eylül 2018 tarihleri arasında, PrOD ile tedavi edilen 25 KHD hastası çalışmaya dahil edildi. Hepatit C virüsü (HCV) genotip 1a olan hastalar PrOD ± ribavirin (RBV) ile tedavi edilirken (tedavi süresi hastanın kompanze sirotik olup olmama durumuna göre 12 veya 24 hafta), genotip 1b olanlar PrOD tedavisi aldılar. Tedavinin başında, 4., 12., varsa 24. haftasında ve tedavi bitimi 4. ve 12. haftalarda hastaların böbrek ve karaciğer testleri ile HCV-RNA düzeyleri kaydedildi.

Bulgular: On dokuz hasta sadece PrOD tedavisi alırken, 6 hasta PrOD ± RBV ile tedavi edildiler. İki hasta tedaviyi tamamlayamadı. İki hasta 24 hafta boyunca tedavi alırken, diğerleri 12 hafta boyunca tedavi aldılar. On iki hafta tedaviyi tamamlayan 23 hasta hem tedavi bitimi hem de tedavi bitiminden 12 hafta sonra HCV-RNA negatiftiler. En sık gözlenen yan etkiler kaşıntı ve anemi idi.

Sonuç: PrOD tedavisi HCV ile enfekte KHD hastalarında kalıcı viral yanıta sahiptir.

Anahtar Kelimeler: Hepatit C virüs, Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir, hemodiyaliz

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Introduction

The estimated prevalence of hepatitis C Virus (HCV) in Turkey is 0.5-1.0% (1). According to the Turkish Society of Nephrology Registry in 2013, the positivity rate of HCV antibody (anti-HCV) was 6.94% in chronic haemodialysis (CHD) patients (2). In addition to liver-related mortality, HCV infection increases all kinds of mortality in CHD patients (3). In order to decrease the mortality, and to eliminate the source of infection, HCV must be treated in patients undergoing CHD. Interferon-based therapies were demanding and less effective in these patients; however, Direct Acting Antivirals (DAAs) seem to be highly effective and safe in patients with chronic renal failure. In this study, we presented our experiences with Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir (PrOD) regime in patients undergoing CHD.

Materials and Methods

This retrospective and medical record review study was performed in HCV-infected CHD patients, who were treated with PrOD regimen between July 2016 and September 2018. Both treatment-naive and those previously treated with pegylated interferon + ribavirin (RBV) patients with or without compensated liver diseases due to chronic HCV (genotype 1a and 1b) were included. Patients with decompensated cirrhosis, presence of hepatitis B virus, human immunodeficiency virus infections, and those who refused the treatment were excluded from the study.

Treatment Modality

The patients with HCV genotype 1a were treated with PrOD plus RBV as follows; the patients having genotype 1a HCV without cirrhosis were treated for 12 weeks, while cirrhotic patients were treated for 24 weeks. On the other hand, the patients infected with HCV genotype 1b were treated with PrOD alone for 12 weeks. Liver function tests, complete blood cell count, and HCV-RNA levels were recorded before treatment, at 4, 12, and if applicable, 24 weeks after the initiation of treatment as well as the 4 and 12 weeks after the end of treatment. Sustained Virologic Response (SVR) was defined as undetectable HCV-RNA at 12 weeks after end of treatment. Virologic failure was defined as virologic breakthrough or detectable HCV-RNA at the end of treatment or during follow-up. HCV-RNA levels were measured via real-time PCR (Abbott Molecular©, Des Moines, IL, USA; with a lower detection limit 12 IU/mL). The clinical trials ethics committee of Ege University Faculty of Medicine approved this study, with the approval number 99166796-050.06.04, in December 2018. Informed consent form was obtained from each patient.

Statistical Analysis

Results were determined via an intent-to-treat analysis with descriptive statistics. Continuous variables were expressed as means with standard deviations and ranges, and categorical variables were expressed as percentages. Categorical variables were analyzed with the chi-square test or Fischer's exact test. For quantitative variables, differences between groups were analyzed by Student's t-test. A p value less than 0.05 was considered as statistically significant.

Results

Thirteen females and 12 males, with a median age of 58 (minimum 37-maximum 74), were included. Two patients had compensated liver cirrhosis and 6 had a history of previous renal transplantation. The patients with prior renal transplantation were not using any immunsupresive drugs at enrollment. Baseline characteristics of the patients are summarized in Table 1. All genotype 1a patients were given RBV 200 mg/day at the beginning of the treatment. Five patients could tolerate 200 mg/day RBV; in one patient, RBV was given 200 mg every other day due to anaemia; but one patient could not tolerate RBV. Nineteen patients received PrOD, while 6 received PrOD + RBV treatment, but total of 23 patients could complete the treatment period. Two patients with liver cirrhosis received therapy over 24 weeks, while all of the other participants received 12 weeks. Treatment modalities and their efficacy are presented in the Table 2. The median HCV-RNA level was 292.759 (914-3.106.349) IU/mL at the initiation of treatment (Table 1).

Table 1. The baseline characteristics of all patients

Variables	n=25
Sex	
Female, n (%)	13 (52%)
Male, n (%)	12 (48%)
Age (years), mean ± SD	55±12
ALT (IU/L mean ± SD	24.6±12.6
HCV-RNA (IU/mL), median (range)	292.759 (914.0-3.106.349)
Genotype	
1a+1b	2 (8%)
1b	18 (72%)
1a	5 (20%)
History of treatment	
Naive	11 (44%)
Treatment-experienced	11 (44%)
No data	3 (12%)

SD: Standard deviation, ALT: Alanine aminotransferase, HCV: Hepatitis C virus

Table 2. The treatment modalities and their efficacy

Planned duration of treatment
Two patients with cirrhosis: 24 weeks
Twenty-three patients without cirrhosis: 12 weeks
Treatment regimen
Nineteen patients treated with PrOD
Six patients treated with PrOD and Ribavirin (200 mg/day starting dose)
Termination of treatments
One patient died at first week
One patient discontinued treatment due to pruritus
SVR12
Twenty-three patients reached to SVR12

PrOD: Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir, SVR: Sustained virologic response

Virologic Response

After 4 weeks of treatment, among 22 patients, HCV-RNA were reported to be negative in 19 (76%) patients and <100 IU/mL (but detectable) in 3 (12%) patients(13, 63, and 16 IU/mL). In 23 patients, who completed 12 weeks of the treatment, SVR at 12 weeks after the end of treatment (SVR12) was 100%. (Figure 1, 2).

Safety and Tolerability of the Treatment

The most common side effect was pruritus, which occurred in 3 (12%) patients. While one patient with genotype 1b discontinued PrOD treatment due to pruritis, she achieved SVR12 after Sofosbuvir + Ledipasvir treatment. The other patient, who could not finish the therapy, because she died at the 4th week due to heart failure (tricuspid valve insufficiency), one patient had grade 3 anaemia, and hence RBV dose was given every other day. Mean alanine aminotransferase (ALT) level was 24.6±12.6 IU/L at the beginning of treatment; 10.9±8.9 IU/L at the week 4, and 11±3.7 IU/L at the end of treatment [(Baseline ALT vs at 4th week, p=0.006), and (at 4th ALT vs at end of the treatment, p=0.772 respectively)]. Compared to reference values (normal values <34 IU/mL), serum mean ALT levels significantly decreased during the treatment.

Discussion

HCV infection in patients with end-stage renal disease (ESRD) may result in more rapid progression in liver disease, and it also increases the rate of liver-related mortality (3). Therefore, it is well known that, HCV infection in CHD patients reduces life expectancy.

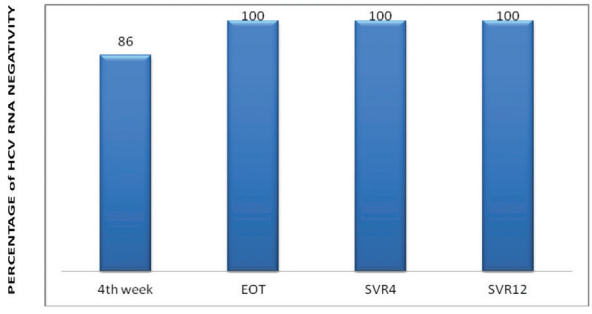

Figure 1. Per protocol analysis for virologic response
EOT: Time of end of the treatment, SVR: Sustained virologic response

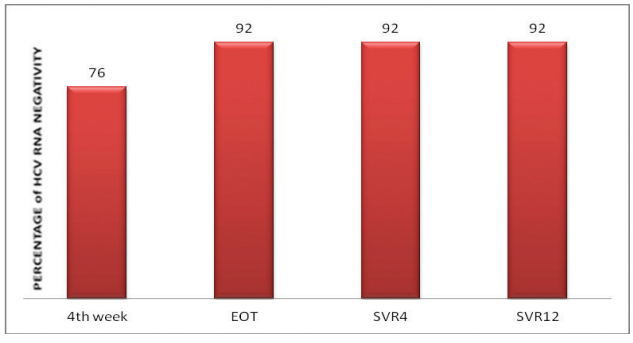

Figure 2. Intent to treat analyses for virologic response
EOT: Time of end of the treatment, SVR: Sustained virologic response, SVR: Sustained virologic response

According to a meta-analysis performed in 11.589 CHD patients, HCV positivity increased the risk of mortality with a HR: 1.34 [95% confidence interval: 1.13-1.59]. Death due to hepatocellular carcinoma and liver cirrhosis were more common in HCV-positive CHD patients than those with HCV-negative (4). Therefore, the treatment of HCV-positive CHD patients is more crucial. Before the use of DAAs for dialysis patients, HCV therapy was a therapeutic challenge during the treatment with interferons (IFNs) and RBV (5,6,7). The most common side effect of IFN/RBV combination was anaemia, especially due to RBV treatment (6,7). Although SVR was better with the combination of pegylated-IFN (PEG-IFN) and RBV than PEG-IFN alone (64% vs 33%, respectively), the Kidney Disease Improving Global Outcomes guidelines do not recommend combination therapy with pegylated-IFN and RBV for the patients having glomerular filtration rate <15 mL/min or undergoing CHD (3,4,5,6,7).

After RUBY-I trial was published, SVR rate >95% was observed and eradication of HCV in ESRD patients became much more possible (8). The real-life experiences published after RUBY-I showed that SVR rates were equal to or greater than those reported in RUBY-I trial (9,10,11,12,13).

The estimated prevalence of HCV infection in haemodialysis patients in Turkey was 6.94% according to Turkish Society of Nephrology registry, in 2013. After DAAs, the prevalence was reduced to 3.94% in the same population at the end of 2017 (14). Turkish Viral Hepatitis Diagnosis and Treatment Guidelines strongly recommend the treatment of ESRD patients with HCV (15). The rate of anti-HCV may be lower than HCV-RNA positivity in CHD patients, because HCV-RNA can be positive in ESRD patients, even if anti-HCV is negative. So it is reasonable to screen CHD patients not with only anti-HCV but also with HCV-RNA levels. Haemodialysis patients should be treated if they have HCV infection (16). PrOD treatment is available in Turkey since June 2016. Real-life data from Turkey has started to be published recently. A multi-center trial from Turkey collected 75 patients with renal failure, 53 of whom were on haemodialysis. Success of the PrOD therapy was 98.6% at the end of therapy and SVR12 rate was 96% (10). Another study published by Yaraş et al. (12) showed that SVR12 was 100% in all (n=25) patients. In our trial, SVR12 was 92% according to ITT analysis and 100% according to per protocol analysis, and also this result was similar to the literature.

In the literature, the most common side effects of PrOD were fatigue and pruritus (9,10,11,12). In our study the most common side effect was pruritus, which was observed in 3 patients. One patient could reach SVR12 by receiving Sofosbuvir/Ledipasvir combination even though could not finish the therapy due to pruritus with PrOD. Indeed, there is a growing evidence on use of Sofosbuvir-based regimens in patients with ESRD. A recent prospective open label observational study assessed the safety and efficacy of Ledipasvir/Sofosbuvir combination in CHD patients with HCV genotype 1 and showed excellent SVR12 rates without any major side effects (17). Other side effect that was observed in only one patient in our study was Grade 3 anaemia. Anaemia was the second (9). These side effects were similar to the real life data of HCV-positive haemodialysis patients treated with DAA and RBV (9,10,11,12).

Study Limitations

The limitations of our study were small number of patients and short follow-up duration compared to the big trials.

Conclusion

The PrOD with or without RBV treatment resulted in a high rate of SVR in HCV-infected patients on haemodialysis. With the success of this treatment, in patients with chronic renal failure on CHD who have a high risk of morbidity and mortality, HCV may no longer be an important comorbidity.

Ethics

Ethics Committee Approval: The clinical trials Ethics Committee of Ege University Faculty of Medicine approved this study, with the approval number 99166796-050.06.04, in December 2018.

Informed Consent: Informed consent form was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.D., H.P., G.E., T.Y., Design: N.D., U.S.A., H.P., Data Collection or Processing: N.D., H.P., T.Y., G.E., İ.T., Z.K., U.S.A., Analysis or Interpretation: N.D., U.S.A., Literature Search: N.D., U.S.A., N.Ü., F.G., Writing: N.D.

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References

1. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, Kaymakoglu S, Ergonul O. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: A fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020-1026.
2. National Nephrology, Dialysis and Transplantation Registry Report of Turkey 2013
3. Bunchorntavakul C, Tanwandee T. Treatment of chronic hepatitis C in special populations. Gastroenterol Clin North Am. 2015;44:883-900.
4. Fabrizi F, Lunghi G, Ganeshan SV, Martin P, Messa P. Hepatitis C virus infection and the dialysis patient. Semin Dial. 2007;20:416-422.
5. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002;347:975-982.
6. Espinosa M, Hernàndez J, Arenas MD, Carnicer F, Caramelo C, Fabrizi F. Pegylated interferon (alone or with ribavirin) for chronic hepatitis C in haemodialysis population. Kidney Blood Press Res. 2015;40:258-265.
7. Liu CH, Huang CF, Liu CJ, Dai CY, Liang CC, Huang JF, Hung PH, Tsai HB, Tsai MK, Chen SI, Lin JW, Yang SS, Su TH, Yang HC, Chen PJ, Chen DS, Chuang WL, Yu ML, Kao JH. Pegylated interferon-α2a with or without low-dose ribavirin for treatment-naive patients with hepatitis C virus genotype 1 receiving hemodialysis: A randomized trial. Ann Intern Med. 2013;159:729-738.
8. Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, Bernstein DE, Cohen DE, Shulman NS, Wang D, Khatri A, Abunimeh M, Podsadecki T, Lawitz E. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology. 2016;150:1590-1598.
9. Abad S, Vega A, Rincón D, Hernández E, Mérida E, Macías N, Muñoz R, Milla M, Luño J, López-Gómez JM. Effectiveness of direct-acting antivirals in Hepatitis C virus infection in haemodialysis patients. Nefrologia. 2017;37:158-163.
10. Örmeci N, Sezgin O, Karaali R, Aygen B, Turan D, Yaras S, Erdem I, Yildiz O, Karakaya F, Ateş K, Asiller ÖÖ. Effectiveness of fixed-dose combination of paritaprevir, ritonavir, ombitasvir, and dasabuvir in patients with chronic hepatitis C virus infection and chronic kidney diseases: Real-life experiences. Eur J Gastroenterol Hepatol. 2019;31:534-539.
11. Torun D, Soydas B, Tekkarismaz N, Ozelsancak R, Micozkadioglu H, Haberal M. Experience with antiviral agents for treatment of hepatitis C virus infection in hemodialysis patients on the kidney wait list: Hemodial Int. 2019;23:E78-E82.
12. Yaraş S, Üçbilek E, Özdoğan O, Ates F, Altintas E, Sezgin O. Real-life results of treatment with ombitasvir, paritaprevir, dasabuvir, and ritonavir combination in patients with chronic renal failure infected with HCV in Turkey. Turk J Gastroenterol. 2019;30:331-335.
13. Sperl J, Kreidlova M, Merta D, Chmelova K, Senkerikova R, Frankova S. Paritaprevir/Ritonavir/Ombitasvir plus dasabuvir regimen in the treatment of genotype 1 chronic hepatitis C infection in patients with severe renal impairment and end-stage renal disease: A real-life cohort. Kidney Blood Press Res. 2018;43:594-605.
14. Nephrology TSo: National Nephrology, Dialysis and Transplantation Registry Report of Turkey. 2017.
15. VHSD Ta: Türkiye Viral Hepatitis Diagnosis and Treatment Guidelines. 2017.
16. Recommendations for testing, managing and treating hepatitis C [http://hcvguidelines.org]
17. Surendra M, Raju SB, Sridhar N, Vijay Kiran B, Rajesh G, Anvesh G, Raju N. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection in end stage renal disease patients: A prospective observational study. Hemodial Int. 2018;22:217-221.