ORIGINAL ARTICLE

Response to direct-acting antiviral agents in chronic hepatitis C patients with end-stage renal disease: a clinical experience

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SUMMARY

OBJECTIVE: *The recent development of direct-acting antiviral agents (DAAs) has dramatically changed the treatment of chronic hepatitis C, and interferon-based regimes have become a poor treatment choice in clinical practice. Today DAAs offer shorter, well-tolerated, highly effective curative therapies. This study aimed to evaluate the effectiveness and safety of DAAs in patients with end-stage renal disease and HCV genotype 1 infection in real clinical practice.*

METHODS: *Thirty-six patients who attended our clinic, were diagnosed with chronic hepatitis C (CHC), undergoing hemodialysis, and fulfilled the criteria of age >18 years, genotype 1 infection, with a detectable HCV RNA level were considered for the study. Patients with GT1a infection received OBV/PTV/r plus DSV plus RBV for 12 weeks; GT1b infected patients received this regimen without RBV for 12 weeks.*

RESULTS: *The study was conducted on 33 patients. The mean age was 52.30 ±13.77 years, and 70 % of them were male. By the fourth week of treatment, HCV RNA levels decreased below 15 IU/ml in all patients. Sustained virologic response (SVR) 12 rate was 100%. Nine patients had side effects during treatment. Of the patients with side effects, 89.9% were in group 1a and 11.1% in group 1b.*

CONCLUSION: *In this study, treatment with OBV/PTV/r and DSV with or without RBV resulted in high rates of sustained virologic response in HCV GT1-infected patients with end-stage renal disease (ESRD). SVR was achieved in all patients with few side effects.*

KEY WORDS: *Hepatitis C, End-Stage Renal Disease, Sustained Virologic Response*

INTRODUCTION

Chronic hepatitis C (CHC) infection is a serious global health problem that affects more than 170 million people worldwide. According to reports, 500,000 people worldwide die because of hepatitis C virus (HCV) related liver disease every year.[1] The national prevalence of HCV should be known in order to allow the national healthcare authorities to prioritize preventive measures and manage the use of treatment to reduce resources. Hepatitis C seroprevalence is about 1% in our country. [2] The prevalence of HCV infection

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in patients undergoing hemodialysis is higher than in the general population. In our country, 8.2% of patients undergoing hemodialysis and 4.8 % of patients undergoing peritoneal dialysis are infected with HCV.[3]

The genotype 1 is the most common and includes 11 subgenotypes, of which 1a and 1b are responsible for the vast majority of infections, according to general worldwide statistics. Genotype 1 is also the most common in our country.[4]

Hemodialysis (HD) is one of the great risk factors for HCV, due to contaminated blood-blood product transfusions or exposure to contaminated HD equipment during treatment in uncontrolled places. Thus, HD patients are in risk group lists by the CDC (Center for disease control and prevention) and are recommended to test for HCV routinely. HCV related morbidity and mortality significantly increased in HD patients, especially in developing countries. It is well known that HCV is closely related to kidney function, approximately 10–16% of the patients with HCV infection develop renal disease.[5] In HCV infected patients with renal dysfunction, complications increase due to liver disease, while chronic HCV infection contributes to deteriorating renal function. The incidence of cirrhosis, hepatocellular carcinoma, liver-related mortality, and progression to end-stage renal disease (ESRD) is significantly higher in HCV-infected patients with chronic kidney disease (CKD).[6] In addition, the survival period is shorter in infected patients than that in noninfected ones.

Previously, interferon/pegylated interferon therapy was used in the hepatitis C treatment. Low renal clearance in CKD patients caused interferon-related side effects and increased toxicity.[7] Ribavirin was administered in this group at low doses because renal dose adjustment is required, and anemia is aggravated with ribavirin and interferon.[8] For these reasons, sustained virologic response (SVR) rates are also low (33-37%).[9]

The recent development of direct-acting antiviral agents (DAAs) has dramatically changed the treatment of CHC, and interferon-based regimes have become a poor treatment choice in clinical practice. Today the new direct-acting antiviral regimens (DAAs) offer shorter, well-tolerated, highly efficacious curative therapies. Rates of SVR approach 95%–100% for the treatment of HCV genotype 1 infection. Also, ombitasvir (OBV), paritaprevir (PTV), ritonavir (R) and dasabuvir (DSV) are mainly eliminated by the liver; so, with DAAs, not only the oral use has advantages compared to IFN based therapy, which is an invasive method and administered subcutaneously, but also dose adjustment is not necessary.[10]

This study aimed to evaluate the effectiveness and safety of OBV/PTV/R plus DSV with/without ribavirin (RBV) in patients with ESRD and HCV genotype 1infection in real clinical practice.

METHODS

Patient selection

Thirty-six patients, who attended our clinic between August 2016 and May 2017, were diagnosed with CHC (anti HCV positivity > 6 months), undergoing hemodialysis, and fulfilled the criteria of age >18 years, genotype 1 infection, with a detectable HCV RNA level were coinsidered for the study.

Patients with coinfection by hepatitis B virus or human immunodeficiency virus, non-genotype 1 infection, a history of solid organ transplantation, or on peritoneal hemodialysis were excluded.

At baseline, patients were tested for Anti HCV, HBsAg, Anti HBs, Anti HBcIGg, Anti HIV (ELISA, Liaison, Diasorin, Italy), HCV RNA (Roche COBAS TaqMan real-time reverse transcriptase-polymerase chain reaction assay, version 2.0, lower limit of quantification<15 ıu/ml), genotype (Versant HCV Genotype Inno LiPA Assay, version 2.0), hemogram (Beckman Coulter LH780), and biochemical test (AU 5800 Beckman Coulter kinetical UV method).

Informed consent was obtained from all participants included in the study.

Treatment Regimen

Patients with GT1a infection received OBV/PTV/R (25/150/100 mg once daily) plus DSV (250 mg twice daily) plus RBV (200 mg once daily) for 12 weeks; GT1b infected patients received this regimen without RBV for 12 weeks; the treatments they received for their additional diseases were re-adjusted.

During treatment, patients were monitored at 1, 2, 4, 8, and 12 weeks. At each visit, HCV, RNA, ALT, AST, and hemoglobin levels were measured.

STATISTICS

The analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, New York, ABD). The descriptive statistics were given as a unit number (n), percentage (%), mean ± standard deviation ($\bar{x}$ ± ss), median (IQR). Pearson

Chi-square and Ficher's exact test were used to evaluate the categorical variables. Normal distributions of the quantitative variables were evaluated by Shapiro Wilk, normality test, and Q-Q graphs. Mann-Whitney U analysis was used for the normal distribution of the two groups, and the Independent Sample T-test was used for the normal distribution. Mann-Whitney U analysis was used in variables with no normal distribution. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Thirty-six ESRD patients who were followed with the diagnosis of CHC were included in the study. Of these, three patients were excluded due to death, missed visits, and abandoning treatment. The study was conducted on 33 patients. The mean age was 52.30 ±13.77 years (22-74), and 70 % of them were male. All patients had been on hemodialysis for 7.6 ± 4.5years.

The mean body mass index (BMI) was 23.52 ±3.77. Demographics, disease characteristics, and laboratory values are presented in Table 1. Thirteen patients were infected with genotype 1b, and 15 with genotype 1a. In five patients, the subtype of genotype 1 could not be analyzed, so it was considered as genotype 1a.

Nineteen patients were treatment-naive, 11 patients had received pegylated IFN, three had received a telaprevir-based regimen. Of the 14 treatment-experienced patients, ten (seven received pegylated IFN, and three received a telaprevir-based regimen) had a partial response, and four had a virologic breakthrough.

Before the start of direct-acting antiviral therapies, median HCV RNA was 2048176±5037964 IU/mL (2170- 18400000). Virologic response rates of genotype 1a and 1b groups at baseline and weeks 1, 2, 4, and 12, and SVR 12 are presented in Table 2. By the fourth week of treatment, HCV RNA levels decreased below 15 IU/ ml in all patients. SVR 12 rate was 100%.

TABLE 1. DEMOGRAGHICS AND DISEASE CHARACTERISTICS (MEAN±STANDART DEVIASION)

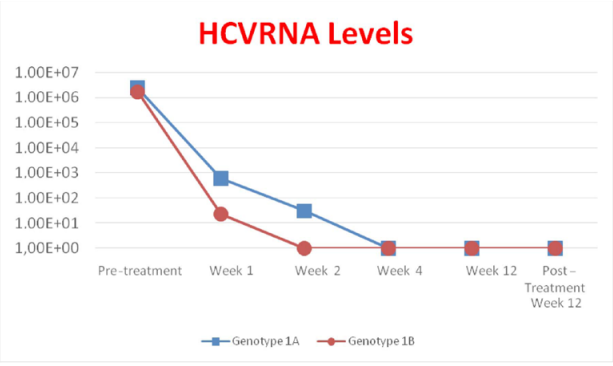
	1A	1B	P-value
Age (year)	51.4±12.1	55.6±13.9	.393
BMI (kg/m2)	24.3±3.2	22.6±3.9	.282
Serum urea (mg/dl)	76.8±36.9	71.5±48.2	.744
Serum creatin (mg/dL)	6.2±2.0	5.9±1.7	.745
Hb (gr/dL)	12.9±1.5	13.8±1.5	.137
WBC (x10^3/u)	7189±2026	7897±2297	.452
ALT (U/L)	33.0±24.1	23.9±13.5	.35
AST (U/L)	26.9±18.2	25.2±12.4	.92
Total Bilirubine (mg/dL)	0.7±0.3	0.6±0.2	.46
PLT (x10^3/uL)	178±65	193±65	.539
AFP (µg/L)	5.3±3.1	2.6±1.5	.019

(BMI; Body Mass Index, Hb; hemoglobin, WBC; White Blood Cell, ALT; Alanine aminotransferase, AST; aspartate aminotransferase, PLT; Platelet, AFP; alpha-fetoprotein)

Nine patients had side effects during treatment. Of these, 89.9% were in group 1A and 11.1% in group 1B. Most side effects were mild, and the most common were fatigue, headache, arthralgia, pruritus, loss of appetite, and stomach pain. Two patients had urticeria, and one had scleral icterus. During the treatment, total bilirubin levels were elevated in five patients for the first two weeks and decreased below normal limits in the first month. (Hyperbilirubinemia was defined as a total bilirubin level of >1.2 mg/dL). During the follow-up, there was no elevation in aminotransferase levels (> 35 U/L). Hemoglobin, leukocyte, and platelet counts at the 12th week after the end of treatment were not significantly different from the baseline values during treatment. There was no difference in the hemoglobin values between treatment regimens with or without RBV.

By the fourth week of treatment, HCV RNA levels decreased below 15 IU/ml in all patients. SVR 12 rate was 100% (Figure 1).

FIGURE 1. VIROLOGIC RESPONSE RATES OF GENOTYPE 1A AND 1B GROUPS.



DISCUSSION

Our study showed that ombitasvir/paritaprevir/ritonavir and dasabuvir are safe and effective in HCV infected CKD patients, and all patients achieved SVR 12.

According to old literature, IFN with or without RBV combination used to be the standard treatment for CHC. Interferon-based therapies in CKD patients have low efficacy, high toxicity, and poor

drug tolerance. Furthermore, side effects such as flu-like symptoms, gastrointestinal, hematological, psychological, and thyroid function test disorders are more common in comparison to patients with normal renal function. Ribavirin also exacerbates anemia. As a result, side effects lead to premature discontinuation of IFN-based therapy protocols.[7,9-11]

Currently, the new DAAs regimens are shorter, interferon-free, well-tolerated, and highly effective therapies. Studies have shown that rates of SVR approach 95%–100% for HCV genotype 1.[12-14]

In the RUBY-I clinical trial, 20 treatment-naive, non-cirrhotic patients with stage 4 or 5 CKD and infected with genotype 1 were evaluated.[15] Thirteen patients with GT1a were administered OBV/PTV/R and DSV, plus RBV (200 mg once daily), and seven patients with GT1b received this regimen without RBV for 12 weeks; the SVR rate reported was 90%. In a study from our country performed by Torun et al. the efficacy and safety of combined therapy of OBV/PTV/R and DSV, with or without ribavirin, were studied in patients who were awaiting a kidney transplant. Patients were divided into two groups according to the genotype; 3/10 were genotype 1a, 7/10 genotype 1b, and the reported SVR 12 rate was 100%.[16] The study published by Etik et al. evaluated 30 CHC patients(18 patients with ESRD and 12 kidney transplant recipients). They reported that SVR 12 was 94% of patients in the ESRD group and 92% in the kidney transplant group.[17]

Sperl et all. evaluated 23 CKD patients infected with HCV GT1 (21 GT1b, 2 GT1a). Six of them had compensated liver cirrhosis.[18] All patients treated with OBV/PTV/R and DSV ± RBV for 12 weeks achieved SVR 12. In our study, the rate of SVR 12 was 100%. Similarly, in the multicenter study carried out by Abad et al., 35 CKD patients infected with genotypes 1 or 4 HCV (seven were cirrhotic) were included, and the SVR rate found was 100%.[19] Although ribavirin was administered at a low dose in hemodialysis patients, there was no decrease in SVR rates.

Miyasaka et al. studied the effectiveness and safety of PTV/OBV/R in 58 (18 were compensated liver cirrhosis) genotype-1 HCV infected patients.[20] The SVR 24 rate reported was 96.6%. Adverse events occurred in 15 patients, but none were severe. They reported that PTV/OBV/R treatment was effective and safe for patients who had chronic hepatitis or compensated hepatic cirrhosis.

We observed that the rate of side effects in genotype 1a was more frequent than in genotype 1b. This also suggests that ribavirin is responsible for side effects. Most side effects were, and the most common were fatigue, headache, arthralgia, pruritus, loss of appetite, and stomach pain. Two patients had urticaria, and one had scleral icterus. Sperl et al. reported that the most common adverse events were nausea, hypotension, diarrhea, and hyperkalemia.[18]

No significant difference was observed in hemoglobin, leukocyte, platelet, and aminotransferase values from baseline and between genotype 1a and 1b. It is known that ribavirin causes dose-dependent anemia; however, anemia was not observed in our study. That may be due to low-dose and short-term use. Torun et

TABLE 2. VIROLOGIC RESPONSE RATES OF GENOTYPE 1A AND 1B GROUPS (MEDIAN - IQR)

	Genotype	Number	Mean	Median	St.Deviation	Minimum	Maximum	p
HCVRNA (IU/ml) Baseline	1A	20	2048176	248000	5037964	2170	18400000	0.828
	1B	13	1716952	149000	2861566	4180	9940000	
HCVRNA(IU/ml) 1st week	1A	10	525		.4 7.5 1479.1	0	4720	0.679
	1B	5	23		.4 0 44.4	0	102	
HCVRNA(IU/ml) 2nd week	1A	12	25	0	79.6	0	277	-
	1B	7	0	-	-	0	0	
HCVRNA (IU/ml) 4th week	1A	17	0	0	-	0	0	-
	1B	12	0	0	-	0	0	
HCVRNA (IU/ml) 12th week	1A	20	0	0	-	0	0	-
	1B	13	0	0	-	0	0	
HCVRNA (IU/ml) post-treatment 12th week	1A	20	0	0	-	0	0	-
	1B	13	0	0	-	0	0	

al. reported that hemoglobin level, white cell blood count, and thrombocyte count were similar to pre-treatment levels and SVR12.[16]

During treatment, total bilirubin levels were elevated in five patients during the first two weeks and decreased below normal limits in the first month.

In a study conducted by Miyasaka et al., 11 of 58 patients had hyperbilirubinemia during treatment. Their focus was that no patient had grade 3 elevated bilirubin levels.[20]

This study has several limitations; The first was its single-center design and the limited number of patients included. The second was that the fibrosis score was not evaluated, and treatment response of other genotypes was lacking; however, the most prevalent genotype in our country is genotype 1. Finally, the post-treatment follow-up period was short to evaluate virologic relapse.

CONCLUSION

In this study, treatment with OBV/PTV/R and DSV, with or without RBV, resulted in high rates of sustained virologic response in HCV GT1-infected patients with ESRD. SVR was achieved in all patients with few side effects.

All HD patients infected with HCV should necessarily be treated if there is no contraindication since they are candidates for renal transplantation, and it is important to prevent HCV complications, such as rejection, proteinuria, diabetes, infection, glomerulopathy associated with HCV, and liver complications in the post-transplant period.

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Authors Contributions

Bengu Tatar: writing, methodology
Şükran Köse: conceptualization, data curation
Nadide Colak Ergun: methodology
Melda Turken: methodology, formal analysis
Yusuf Onlen: supervision
Yusuf Yılmaz: supervision
Sıla Akhan: supervision

RESUMO

O recente desenvolvimento de agentes antivirais de ação direta (DAAs) mudou drasticamente o tratamento da hepatite C crônica, e os regimes livres de interferon tornaram-se pobres escolhas para tratamento na prática clínica. Hoje os DAAs oferecem terapias curativas mais curtas, bem toleradas e altamente eficazes. O objetivo deste estudo foi avaliar a eficácia e segurança dos DAAs em pacientes com doença renal em estágio terminal e infecção pelo genótipo 1 do HCV na prática clínica real.

MÉTODOS: *Trinta e seis pacientes, que se inscreveram em nossa clínica com diagnóstico de hepatite C crônica (CHC), inclusive no programa de hemodiálise, e preencheram os critérios de idade >18 anos, foram considerados para infecção pelo genótipo 1 com nível detectável de RNA do HCV. Os pacientes com infecção por GT1a receberam OBV/PTV/r mais DSV mais RBV por 12 semanas. Os pacientes infectados com GT1b receberam este regime sem RBV por 12 semanas.*

RESULTADOS: *O estudo foi realizado em 33 pacientes. A idade média foi de 52,30±13,77 anos e 70% deles eram do sexo masculino. Na semana 4 do tratamento, os níveis de ARN do VHC diminuíram para menos de 15 UI/ml em todos os pacientes. A taxa de resposta virológica sustentada (RVS) 12 foi de 100%. Nove pacientes apresentaram efeitos colaterais durante o tratamento. Dos pacientes com efeitos colaterais, 89,9% estavam no grupo 1a e 11,1% no grupo 1b.*

CONCLUSÃO: *Neste estudo, o tratamento com OBV/PTV/r e DSV com ou sem RBV resultou em altas taxas de resposta virológica sustentada em pacientes infectados pelo VGC GT1 com doença renal em estágio final (ESRD). A RVS foi alcançada em todos os pacientes com poucos efeitos colaterais.*

PALAVRAS-CHAVE: *Hepatitícos C. Doença renal em estágio terminal. Resposta virológica sustentada.*

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