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The efficacy and safety of ombitasvir/paritaprevir/ritonavir plus ribavirin in hepatitis C virus-infected patients with end-stage renal disease on regular hemodialysis

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Abstract

Background and aim

Infection with hepatitis C virus (HCV) is an important cause of mortality and morbidity in patients with end-stage renal disease. Direct-acting antiviral drugs allow for the treatment of this group of patients. The current research aims to assess the efficacy and safety of ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) combination therapy plus ribavirin in the treatment of HCV-infected Egyptian patients with chronic kidney disease stage V on regular hemodialysis.

Patients and methods

A total of 70 patients with chronic kidney disease stage V on regular hemodialysis with HCV infection were enrolled in this prospective cohort study, where 37 patients (group A) received OBV/PTV/RTV combination therapy plus ribavirin for 12 weeks. The remaining 33 patients (group B) refused treatment. The sustained virologic response and the adverse events were monitored.

Results

A total of 35 patients of group A [35/37 (94.6%)] completed 12 weeks of HCV therapy, and all of them [35/35 (100%)] achieved sustained virologic response 12. The patients suitably tolerated the therapy. Pruritis (65.7%), anemia (62.9%), gastrointestinal tract manifestations (60%), and fatigue (35%) were the most frequently reported adverse effects. There was a nonsignificant decrease in the hemoglobin and the hematocrit values in the treatment group.

Conclusion

OBV/PTV/RTV combination therapy plus ribavirin can be used safely and effectively in the treatment of chronic HCV-infected patients on regular hemodialysis. The drug combination is safe and tolerable.

Keywords: chronic hepatitis C virus, direct-acting antiviral therapy, efficacy, hemodialysis, ombitasvir/paritaprevir/ritonavir combination therapy, safety, sustained virological response, treatment

Introduction

Hemodialysis patients are commonly infected with the hepatitis C virus (HCV) to the extent that HCV infection prevalence may reach more than 70% in some countries [1]. Others reported a prevalence of 10–59% of HCV infection in patients on maintenance hemodialysis compared with 0.3–1.5% observed in the general population [2]. The prevalence of anti-HCV antibodies among dialysis patients was 40.3% in Turkey [3], 30% in India [4], and 43.9% in Saudi Arabia [5]. The condition is slightly different in developed countries, which reported a prevalence of HCV infection to be 10–20% in dialysis patients [6]. In the United States of America in 2000, 8.4% of

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hemodialysis patients were anti-HCV-positive [7]. In Egypt, the prevalence of HCV ranged from 10 to 100% [8]. Using contaminated machines, re-using filters, and nonobedience of the infection control measures by the medical and the paramedical staff are the main causes of HCV transmission in hemodialysis patients [9]. HCV infection increases the risk of mortality and morbidity of patients with end-stage renal disease (ESRD) [10]. So, HCV eradication is essential for such patients as well as kidney transplantation candidates [11]. The use of interferon-based therapy caused many problems in patients with ESRD owing to impaired clearance of the drugs, hence more adverse events [12]. Moreover, the efficacy of the interferon-based (%) regimen was suboptimal. Now, interferon-free regimens using safe and effective direct-acting antiviral drugs (DAAs) can be used for the treatment of HCV in this group of patients. However, DAAs can accumulate to toxic levels owing to renal impairment, emphasizing the importance of choosing suitable drugs [13]. The FDA had approved ombitasvir/paritaprevir/ritonavir (OBV/PTV/RTV) to treat HCV-infected patients with a severe renal disease without any dose adjustments [14]. However, further studies are especially needed for patients with ESRD infected with HCV genotype 4. This study aimed to assess the efficacy and safety of OBV/PTV/RTV combination therapy plus ribavirin in the treatment of HCV-infected Egyptian patients with chronic kidney disease (CKD) stage V on regular hemodialysis at Ahmad Maher Teaching Hospital.

Patients and Methods

This prospective cohort study was carried out in the Nephrology and Dialysis Department at Ahmad Maher Teaching Hospital. All the patients underwent chronic hemodialysis treatment for ESRD during the study period (June 2019–January 2020). Hemodialysis was carried out routinely three times weekly. Patients with chronic hepatitis C were enrolled in the Egyptian National Program to treat hepatitis C viral infection.

Inclusion criteria

The following were the inclusion criteria:

(1) Adult patients from both sexes.
(2) On maintenance hemodialysis.
(3) Age less than 65 years.
(4) Positive for HCV antibodies and HCV-RNA.
(5) Informed consent,
(6) Negative HIV antibody test and HBs antigen.
(7) Platelet count more than or equal to 150 000/mm^3.
(8) Hemoglobin (Hb) more than 10 g/dl.
(9) Serum total bilirubin less than 1.2 mg/dl.
(10) Serum albumin more than 3.5 g/dl.
(11) International normalization ratio less than 1.2.
(12) Child patients.
(13) Treatment-naïve patients.

Exclusion criteria

The following were the exclusion criteria:

(1) Age less than 18 or more than 65 years.
(2) Presence of coinfection with HBV or HIV.
(3) Previous treatment for HCV infection.
(4) Receiving immunosuppressive therapy.
(5) Active drug addiction.
(6) Severe and decompensated liver disease.

Before treatment, all the patients were subjected to assessment by complete history taking, clinical examination, BMI estimation, and laboratory investigations, which included complete blood picture, liver biochemical profile, viral hepatitis markers (anti-HCV antibodies and HBsAg), and HCV-RNA using PCR. Calculation of estimated glomerular filtration rate (eGFR) was also done. Patients were divided into two groups: group A included 37 patients who decided to receive DAAs, whereas group B included 33 patients who refused to receive therapy. The block diagram of the study's design is shown in Fig. 1.

Patients enrolled in the study received OBV 25 mg/PTV 150 mg/RTV 100 mg plus ribavirin 200 mg oral fixed daily dose for 12 weeks. On the dialysis day, ribavirin was received 4 h before the dialysis session, whereas OBV/PTV/RTV after the dialysis session. Effectiveness of the regimen is assessed by determining the rate of virological response by quantitative HCV viral load testing using PCR at the end of treatment (EOT) to detect virological response to the therapy and 12 weeks after completion of treatment to detect sustained virological response (SVR). Virological failure is defined as detectable HCV-RNA at any time during treatment or after treatment.

Adverse events such as pruritus, jaundice, anemia (Hb levels <10 g/dl or a drop of >2 g/dl from the baseline), and gastrointestinal tract (GIT) disturbances were reported. Serious adverse events, defined as any life-threatening event, were reported through monthly interviewing the patients. The current study complies with the declaration of Helsinki. Written informed consent was obtained from all study participants

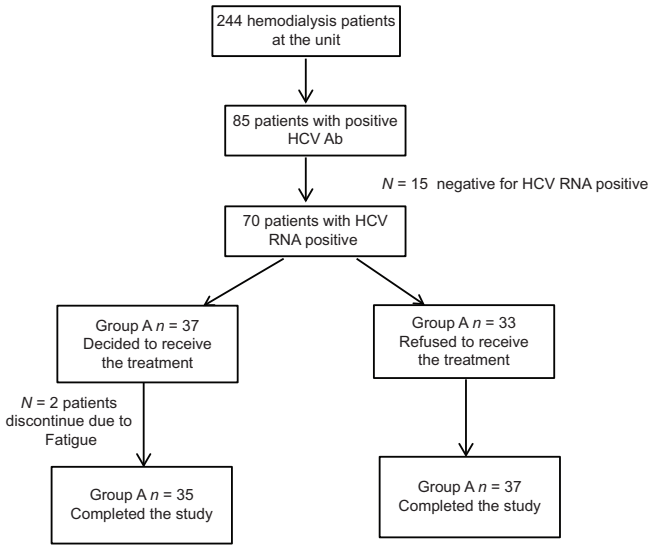

Figure 1: Block diagram of the study's design.

after explaining the study's purpose, methods, risks, and benefits. Data were managed in complete confidentiality. This retrospective study was under the institutional and national research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The institutional review board (IRB) approved this study.

Statistical analysis

Descriptive statistics and continuous parametric data were presented in frequency tables and expressed as means ± SD whenever appropriate. Analytical tests included paired *t* test for comparing values at baseline and during follow-up, and independent *t* test for comparison between two means. Analysis of variance (i.e. *F* test) was used for comparing means of more than two groups and χ^2 test for contingency table analysis. When the normal distribution is violated (when the data distribution does not follow a normal distribution), nonparametric tests were applied. *P* value was considered nonsignificant at the level more than 0.05, significant at the level less than 0.05, and highly significant at the level of less than 0.001.

Results

Of 244 hemodialysis patients, 85 (34.8%) were positive for HCV antibodies. Of the 85 patients, 70 (82.3%) were HCV-RNA positive. Patients who received treatment were well matched with those who refused to receive treatment in terms of age, sex, duration of dialysis, BMI, comorbidities, eGFR, and pretreatment HCV-RNA load (Table 1). A total of 35 (94.6%) patients completed the therapy and had a favorable virological response at EOT and SVR12 (100%).

Comparing biochemical parameters of group A before and after receiving the treatment, we found that there was a significant decrease in Hb and hematocrit (Hct) level after completing the treatment than the baseline (baseline Hb level was 10.15 ± 0.85 vs. 9.43 ± 1.2 after completing the treatment, with a significant decrease; $P = 0.018$). The baseline Hct level was 30.16 ± 4.93, and after completing the treatment, it was 27.83 ± 3.49, with a significant decrease ($P = 0.037$) (Table 2).

On comparing group A (patients who completed the treatment) with group B, who did not receive the treatment, we found that the mean Hb% of group A was 9.47 ± 1.23 and of group B was 9.79 ± 1.63, with the nonsignificant difference between the two groups; $P = 0.4$). The mean Hct of group A was 27.76 ± 4.03 versus 29.26 ± 4.88 in group B, with nonsignificant difference between the two groups ($P = 0.2$) (Table 3).

The patients tolerated therapy well. Adverse events were typical of those previously reported before therapy. Fatigue, pruritis, anemia, and GIT manifestations were the most frequent adverse effects and were reported in both groups, with nonsignificant differences. No patient experienced serious complications leading to hospitalization or death during the treatment period (Table 4). Two patients discontinued the treatment owing to their feeling of chronic fatigue and headache, which they described being not severe.

Table 1: Baseline demographic and clinical features of groups A and B

Variables	Group A (*n*=37)	Group B (*n*=33)	*P*
Age (years)	54.125±11.16	50.66±11.67	0.2
BMI (kg/m^2)	26.386±6.73	26.326±4.6	0.97
eGFR (ml/min)	9±2.696	8±3.3	0.2
Dialysis duration (years)	6.687±3.86	7.52±4.925	0.4
HCV-RNA load copy/ml	25.2±3.2	17.3±9.7	0.49
Sex [*n* (%)]			
Male	20 (54)	20 (60.6)	0.5
Female	17 (46)	13 (39.4)	0.5
Comorbidities [*n* (%)]			
Diabetes	5 (13.5)	4 (12.1)	0.8
Hypertension	22 (59.4)	19 (57.6)	0.8
Abdominal ultrasound [*n* (%)]			
Bright liver	15 (40.5)	11 (33.3)	0.5
Splenomegaly	5 (13.5)	3 (9)	0.5
Minimal ascites	3 (8)	2 (6)	0.5
Advanced nephropathy	37 (100)	33 (100)	0.7
Laboratory data			
Hb%	10.15±0.85	10.4±1.6	0.5
Hct	30.16±4.9	32.27±5	0.25
WBCs	8.3±8.6	7.5±2.59	0.75
PLT	209.7±52	275±54.8	0.14
AST	25.5±11.5	31±9.3	0.9
ALT	26.4±11.4	36±4.8	0.11

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hct, hematocrit; HCV, hepatitis C virus; PLT, platelet; WBC, white blood cell.

Table 2: Pretreatment viral load and virological response rates in both groups

Variables	Group A (*n*=35)	Group B (*n*=33)	*P*
HCV-RNA load copy/ml	25.2±3.2	17.3±9.7	0.49
EOT virological response (%)	100	0	<0.001
SVR12 (%)	100	0	<0.001

EOT, end of treatment; HCV, hepatitis C virus; SVR, sustained virologic response.

Table 3: Adverse events on both groups

Variables	Group A (*n*=35) [*n* (%)]	Group B (*n*=33) [*n* (%)]	*P*
Pruritus	23 (65.7)	18 (54.5)	0.34
Anemia	22 (62.9)	20 (60.6)	0.84
GIT disturbances	21 (60)	20 (60.6)	0.95
Blood transfusion	14 (40)	11 (33.3)	0.56
Erythropoietin therapy	27 (77.1)	22 (66.7)	0.33
Fatigue	13 (35)	15 (45.5)	0.48

GIT, gastrointestinal tract.

Table 4: Biochemical parameters of group A before and after completing the therapy

Variables	Group A ($n=35$)		*P*
	Before treatment	After completing the therapy	
AST	24.95±11.47	26.35±13.61	0.719
ALT	26.4±11.76	27.65±17.72	0.65
Total bilirubin	0.5±0.27	0.32±0.13	0.004
Hb%	10.15±0.85	9.43±1.2	0.018
Hct	30.16±4.93	27.83±3.49	0.037
WBCs	6.53±1.69	6.59±1.61	0.887
PLT	209.75±52	212.25±56	0.86

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; Hct, hematocrit; PLT, platelet; WBC, white blood cell.

Discussion

HCV is a significant public health problem [15]. Moreover, it is an important cause of mortality and morbidity among patients on maintenance hemodialysis [10]. The standard treatment for HCV was a combination of pegylated interferon and oral ribavirin until 2011. However, this regimen was poorly tolerated by patients with CKD, as it was associated with many adverse effects. Moreover, SVR was observed in ~35% of patients on regular hemodialysis [16]. Fabriz *et al*. [17] concluded that interferon-based regimens had provided limited efficacy and safety among patients with CKD. In contrast, the advent of the new DAAs for treating hepatitis C had allowed reaching SVR rates of 90% for many patient groups.

Despite being the first approved DAA with excellent safety and efficacy against HCV [18], the pan-genotypic, sofosbuvir (SOF) was not approved for the treatment of patients with severe kidney dysfunction (eGFR <30 ml/min/1.73 m^2) [19]. This is mostly because SOF metabolite GS-331007 undergoes renal excretion [20]. However, in real-life experience, several studies have demonstrated SOF's safety in patients with severe CKD [21,22]. However, others have reported deterioration of renal function on SOF-based therapy [23]. Fortunately, the NS3/4 A inhibitor PTV and RTV and the NS5A inhibitor OBV are not excreted by the kidneys, thus can be used in severe CKD and hemodialysis patients [24].

In Egypt, the National Committee for Control of Viral Hepatitis set a strategic plan aiming at the elimination of an ongoing nightmare of HCV by mass treatment of the infected patients, thus stopping the ongoing HCV transmission [25]. So, treatment targets all HCV-infected Egyptian patients, and according to the protocol designed by the Egyptian National Committee for Control of Viral Hepatitis, chronic HCV-infected patients on regular hemodialysis receive SOF-excluding regimens in the form of OBV 25 mg/PTV 150 mg/RTV 100 mg plus ribavirin 200 mg oral fixed daily dose for 12 weeks. In the current study, we found that this regimen was highly effective. The SVR at EOT and SVR12 were achieved in 100% of patients who completed the therapy.

All adverse events reported were comparable to those who refused to take the treatment. Pruritis (65.7%), anemia (62.9%), GIT manifestations (60%), and fatigue (35%) were the most frequent adverse effects and were reported in both groups, with a nonsignificant difference. Regarding the nature of the hemodialysis population, those adverse effects cannot be attributed to the drug. No patient had serious complications leading to hospitalization or death during the treatment period. We found a significant decrease in their Hb and the Hct level in patients who received and completed the treatment regimen. However, despite this significant decline, there was no significant difference in post-treatment Hb and Hct level on comparing group A patients who received treatment to group B who did not receive the regimen. Moreover, we found that the decline in Hb level was less than 2 g%.

Pockros *et al.* [14] studied the efficacy of PTV/RTV/OBV/dasabuvir combination therapy for patients with stage IV or V CKD infected with HCV genotype 1, of whom, 14 were on hemodialysis. They found that 90% of patients with CKD stage 4 and 5 and 93% of hemodialysis patients achieved SVR12. Regarding the adverse events, they were mild or moderate, including fatigue, diarrhea, nausea, headache, and dizziness. Overall, 62% of patients who received ribavirin developed anemia compared with a regimen not requiring ribavirin. Four of the patients who developed anemia required erythropoietin, and one developed a Hb less than 8 g/dl. A Japanese study included 10 chronic HCV genotype 1b infected patients on regular hemodialysis who received OBV/PTV/RTV combination therapy. A total of eight patients completed 12 weeks of therapy and achieved SVR12 (80%) [26].

Comparing patients who received and completed the treatment with those who did not receive treatment, we found that there was no significant difference between the two groups regarding dialysis duration, BMI, eGFR, Hb%, Hct, white blood cells, platelet, serum creatinine, blood urea, serum phosphorus, direct bilirubin, and total bilirubin (Table 5).

In the current study, two patients discontinued treatment owing to very mild nonspecific adverse events, mainly owing to their fear of continuing treatment. Other reported adverse effects included pruritis, anemia, gastrointestinal disturbances, and fatigue. The two groups reported these adverse events, with a nonsignificant difference. Similarly, Cox-North *et al.* [21] reported no serious adverse events and no treatment discontinuation. Atsukawa *et al.* [27] reported that the OBV/PTV/RTV combination is safe and effective for treating genotype 1b chronic hepatitis C-infected patients undergoing dialysis, with SVR rates of 96.8%. The incidence of adverse events was 35.5% (11/31), the most common of pruritus. One patient discontinued the treatment owing to erythema multiforme. On the contrary, Saxena *et al*. [23] reported treatment discontinuation in 4% of the treated patients owing to the development of serious

Table 5: Comparison of demographic and biochemical parameters of group A 12 weeks after completing treatment and group B

Variables	Group A (*n*=35)	Group B (*n*=33)	*P*
Age	54.125±11.16	47.66±11.67	0.048
Male (%)	54	60.6	
Duration of dialysis	6.687±3.86	7.52±4.925	0.4
BMI	26.386±6.73	26.326±4.6	0.97
eGFR	9±2.696	8±3.3	0.2
AST	22.88±13.13	16.28±6.435	0.04
ALT	22.5±17.56	12.8±9.3	0.02
Direct bilirubin	0.128±0.12	0.167±0.142	0.3
Total bilirubin	0.318±0.133	0.361±0.177	0.3
Hb%	9.47±1.23	9.79±1.63	0.4
Delta difference of Hb%	−0.78±1.4	0.11±1.3	0.122
Hct	27.767±4.038	29.265±4.88	0.2
WBCs	6.729±1.65	6.956±2.21	0.6
PLT	213.8±55.75	218.3±48.38	0.7
Serum creatinine	10.2±2.158	11.0±3.589	0.2
Urea	151.16±27.658	160.48±37.737	0.2
Serum albumin	4.15±0.598	4.25±0.389	0.4
Serum calcium	7.79±1.133	8.37±0.873	0.04
Serum phosphorus	5.05±1.85	4.83±1.65	0.6

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Hct, hematocrit; PLT, platelet; WBC, white blood cell.

adverse events. Moreover, Laura *et al.* [28] conducted an observational prospective study on 232 patients with CKD undergoing treatment with PTV/OBV/RTV dasabuvir chronic hepatitis C infection – genotype 1b. Renal and liver functions were assessed at the beginning of therapy, monthly during treatment, and 3 months after therapy completion. All patients achieved SVR. Common adverse effects were nausea, fatigue, and headache.

El-Gendya *et al.* [29] conducted a study on 40 hemodialysis patients with chronic HCV infection who received 12 weeks of OBV/PTV/RTV plus ribavirin. Of 40 patients, 35 (87.5%) completed the therapy and had a VR and SVR. Anemia was the main observed adverse effect, which led to discontinuation of the therapy in five (12.2%) patients, as those patients were not responding to anemia correction and modification of ribavirin dose. They concluded that OBV/PTV/RTV plus ribavirin could be used in the treatment of chronic HCV-infected patients on regular hemodialysis. Ko and Choe [16] reported clinical trial results on a cohort of 235 patients with CKD stages IV–V with HCV infection. Patients were treated with oral grazoprevir and elbasvir combination therapy, once daily for 12 weeks. The SVR12 rate was 99%. It is worth to note that 179 were hemodialysis dependent. Soon *et al.* [16] in 2018 concluded that elbasvir/grazoprevir or a combination of PTV/RTV/OBV with dasabuvir was the most recommended regimens in patients with stage IV or V CKD (with or without hemodialysis) infected with HCV genotype 1, as there is no need for dose modification.

Conclusion

OBV/PTV/RTV combination therapy plus ribavirin can be used safely and effectively in the treatment of chronic HCV-infected patients on regular hemodialysis. The drug combination is safe and tolerable. SVR12 could be achieved in 100% of cases.

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All authors contributed equally to this work regarding putting the study design. Dr Enass collected the data and followed up with the patients. All the authors participated in writing of the manuscript and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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