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Original article

Efficacy of Ombitasvir/Paritaprevir/Ritonavir plus Ribavirin in Treatment of Chronic Hepatitis C Patients with End Stage Renal Disease on Regular Hemodialysis

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ABSTRACT

Background: Hepatitis C virus [HCV] infection is associated with more significant morbidity and mortality among dialysis patients than in healthy populations. The fixed-dose tablet [ombitasvir/ paritaprevir/ritonavir] in combination with ribavirin was effective and generally well tolerated in treatment of chronic HCV infected patients with end stage renal disease [ESRD] on hemodialysis. However, limited published data are known about the usefulness of this regimen for treatment of HCV patients with ESRD on hemodialysis.

Aim of the work: The aim of this study was to evaluate the safety and efficacy of treatment regimen of ombitasvir [OBV] 25 mg /paritaprevir [PTV] 150 mg /ritonavir [RTV] 100 mg plus generic ribavirin [RBV] 200 mg in Egyptian HCV-infected naive patients with ESRD on regular hemodialysis.

Patients and methods: A prospective cohort study involved 40 chronic HCV on regular hemodialysis patients, who were eligible for treatment with combined oral antiviral therapy.

Results: The results showed that thirty-five patients [35/40[87.5%]] completed 12 weeks of HCV therapy; they had a virological response at end of therapy and sustained virological response. Anemia was the main observed side effect which lead to discontinuation of the treatment in five patients [12.2%]. As these patients were not responding to anemia correction measures [blood transfusion, erythropoietin-stimulating agents, and modification of RBV dose].

Conclusion: OBV/PTV/RTV plus Ribavirin can be used in treatment of chronic HCV patients with ESRD on regular hemodialysis.

Keywords: Direct-acting antiviral drugs; End-stage renal diseases; Hepatitis C; Viral infection; Hemodialysis.

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INTRODUCTION

Hepatitis C virus infection prevalence among hemodialysis [HD] patients ranges from 5% to approximately 60% in different countries[1, 2].

Increased risk of morbidity and mortality in these patients favor the treatment of HCV infection[3,4].

Eradication of HCV help to reduce its prevalence and risk of nosocomial transmission in HD units [5, 6].

Early experience of combined therapy with pegylated interferon and ribavirin in these patients showed 40% sustained virological response with very poor tolerance, leading to withdrawal of this regimen in more than 1/3 of patients[7].

Although these limitations, this combination demonstrated the durability of virological response even post renal transplantation[8].

Introducing of direct-acting antiviral drugs [DAAs] in treatment of HCV infection have led to a sustained virological response after 12 weeks of treatment [SVR12] in more than 90%-95% of the patients with improved tolerance. Fortunately, the NS5A inhibitor ombitasvir, the NS3/4A inhibitor paritaprevir and ritonavir are not excreted by the kidneys and do not need dose adjustment in severe CKD or in HD patients [9,10].

Observational studies from Europe and the United States reported the use of ombitasvir/ paritaprevir/ ritonavir ± dasabuvir ±ribavirin in treatment of HCV infection in end stage renal disease [ESRD][11,12].

An Egyptian study found that, ombitasvir/ paritaprevir/ritonavir in combination with ribavirin was generally well tolerated in treatment of HCV patients without cirrhosis or with compensated cirrhosis with 97 and 93 % SVR12 respectively[13].

AIM OF THE WORK

The aim of this study was to evaluate the safety and efficacy of a combination oral antiviral therapy [ombitasvir 25 mg /paritaprevir 150 mg/ ritonavir 100 mg] plus generic ribavirin [200 mg] in treatment of chronic HCV-infected patients with end stage renal disease [ESRD] on regular hemo-dialysis.

PATIENTS AND METHODS

This is a prospective cohort study involved 40 Egyptian naive patients with chronic HCV infection and ESRD, attended to the Dialysis Units at Al-Zahraa University Hospitals and Damietta University Hospitals, Faculty of Medicine, Al-Azhar University, Cairo and Damietta respectively, during the period from March 2017 to September 2017.

All patients were enrolled in the Egyptian National Program for treatment of hepatitis C viral infection and according to the protocol designed by the Egyptian National Committee for Control of Viral Hepatitis launched in December 2016.

Inclusion criteria:

- Adults patients from both sexes;
- with chronic hepatitis C viral infection proved by HCV antibodies and quantitative polymerase chain reaction of HCV RNA,
- had end stage renal disease proved by estimated glomerular filtration rate eGFR <15 mL/min/1.73 m^2 and imaging evidence, treatment naive,
- with fasting-blood-sugar [FBS] ≤ 140 mg/dL, with base line levels of platelets count ≥150 × 10^3/cc,
- Hemoglobin [Hb] ≥ 10 g/dL, base line levels for serum total bilirubin was ≤ 1.2 mg /dL, serum albumin was ≥3.5g/dL, and international normalization ratio [INR] was ≤1.2.

Exclusion criteria:

- Patients with low base line levels of platelets count <150×10^3 /mm^3, Hb <10 g/dL, serum total bilirubin more than 1.2 mg /dL, INR more than 1.2, serum albumin <3.5 g/dL and eGFR>15mL/min/1.73m^2.
- Patients with liver cirrhosis and or with Fib-4 score>1.45.
- Uncontrolled diabetic patients with glycated hemoglobin [HbA1c] > 9% and patients with associated uncontrolled co-morbidities [e.g. cardiac or neuropsychiatric disorders].

All patients were subjected to:

[A] - Careful history taking and thorough clinical examination.

[B]-Abdominal ultrasonography.

[C]- Laboratory investigations: Complete blood count [CBC], Liver function tests, Fasting blood sugar, HbA1c, Renal function test, Viral hepatitis markers; hepatitis C virus antibody [HCV-Ab] and hepatitis B surface antigen [HBs-Ag] were detected using enzyme linked immunosorbent assay [ELISA] and Quantitative HCV–RNA was detected by real-time polymerase chain reaction [PCR] .

The value of eGFR was calculated by MDRD study equation as follow:

eGFR [estimated glomerular filtration rate] =175 × [Standardized serum Creatinine] -1.154× [age]-0.203 × 0.742 [if female] according to S**tevens et al.** [14].

Fib-4 score was calculated for each patient as the following:

Fib-4 score= [Age × AST] / [Platelets × [sqrt [ALT]] .Where Fib4 score < 1.45 = F0-F1 and Fib4 score > 3.25 = F3-F4 as illustrated by **Martinez et al.** [15].

Patients were on regular hemodialysis, for more than 3 months, 3 sessions /week, 4h/session, bicarbonate-based dialysate. All of them received [Ombitasvir [OBV] 25 mg /paritaprevir [PTV] 150 mg /ritonavir [RTV] 100 mg] plus generic ribavirin [RBV] 200 mg oral fixed daily dose for 12 weeks.

On the day of dialysis, ribavirin was given four hours before dialysis session while OBV/PTV/ RTV after dialysis session. The patients had completed HCV treatment for 12 weeks. Every 4 weeks of treatment, CBC, creatinine level, and hepatic function panel were done. Using PCR assay, quantitative HCV viral load testing was evaluated at both end of treatment [EOT] to detect the virological response to therapy [ETR] and 12 weeks after end of treatment to detect sustained virological response [SVR12].

Statistical Methods: The data was coded and analyzed with the program of Statistical Package for Social Science [IBM-SPSS], under Window version 22. Continuous parametric data were expressed as mean ± standard deviation [SD], whereas non-parametric data were expressed as median.

Also, categorical data were expressed as frequencies [percentages]. Quantitative data with parametric distribution were done by using Analysis of variance [ANOVA].

Comparing groups were done by using Independent t-test and One-Way ANOVA test followed by post hoc test analysis using LSD.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered non-significant [NS] at the level of > 0.05, significant at the level of <0.05 and highly significant at the level of <0.001.

RESULTS

Forty chronic HCV patients [mean age was 53.85±11.6 years] with ESRD started HCV oral combination therapy by ombitasvir/paritaprevir/ ritonavir plus generic ribavirin. Demographic data of the studied patients showed that, there 30 patients [75%] were males and 10 patients [25%] were females. Fifteen patients [37.5%] were diabetics receiving insulin therapy and ten patients [25%] were hypertensive. All patients had Fib4 score < 1.45 = F0-F1 [Tables 1 and 2].

Thirty-five out of 40 patients [35/40[87.5%]] completed 12 weeks of therapy. All 35 patients who completed treatment achieved virological responses at end of treatment [EOT] and sustained virological response 12 weeks after EOT with undetectable HCVRNA. Five patients [12.5%] patients had stopped treatment due to occurrence of marked reduction in hemoglobin level, which failed to respond to correction measures [transfusion of 1000 cc packed RBCs, erythropoietin-stimulating agents 4000 IU SC weekly, and modification of RBV dose to be every other day] [Table [3].

Significant decreases were found in serum levels of ALT, AST and Hb during the course of treatment [week4, week8 and 12week] compared to their levels at the beginning [p < 0.05]. There was significant increase in platelets count at the end of treatment compared to its levels at the beginning [p < 0.05] [Table 4].

Table [1]: Basic characteristics of the studied patients

Number of patients [40]		
Variables	No	%
Gender:		
Males:	30	75
Females:	10	25
Comorbidity		
Diabetes:	15	37.5
Hypertension:	10	25
Abdominal ultrasonography:		
Liver:		
Bright echo pattern:	28	70%
Normal echo pattern:	12	30%
Patent portal vein	40	100%
Normal size spleen	40	100%
Absent Ascites:	40	100%
Kidneys:		
Grade IV nephropathy	40	100%
Fib-4 Score < 1.45	40	100%

Variables expressed as number and [%].

Table [2]: Basic laboratory data of the studied patients.

Number of patients [40]	
Variables	**Mean ±SD**
HCVRNA[IU/L]	1592896 ±574692
ALT[IU/L]	38±15.7
AST[IU/L]	32.6±14.9
Albumin[g/L]	4.3±0.3
Total bilirubin[mg/dl]	0.5±0.1
INR	1.1±0.1
Hb[g/L]	12.2±2.7
WBCs [×10^3] /cmm	6.4±2.7
Platelets [×10^3] /cmm	199±33
Serum Creatinine[mg/dl]	5.7±1.8
Creatinine Clearance	9.1±3.4

Variables expressed as Mean ±SD. WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio, HCV –RNA: hepatitis C virus –ribonucleic acid.

Table [3]: Characteristics of patients who discontinued the course of treatment.

Number of patients 5 [12.5%]	% of total		
Age [Mean ±SD]:	53.2±12.5		
Gender:			
Male	4 [10%]		
Female	1[2.5%]		
Diabetes	2[5%]		
Hypertension	3[7.5%]		
Fib-4 Score < 1.45	5[12.5%]		
Laboratory variable	Basic variables	4 WK	p-value
AST [IU/ L]	42.3 ±10.5	30.5± 7.4	0.12
ALT [IU/ L]	43.4±12.3	27.3±8.6	0.03
WBC [×10^3] /cmm	5.6±2.1	4.5±1.2	0.89
Hb [g/L]	11.3 ±2.4	7.8±1.5	0.01
Platelets [×10^3] /cmm	189±32.3	205±45.2	0.43

ALT: alanine aminotransferase, AST: aspartate aminotransferase; Hb: hemoglobin, WBCs: white blood cells. Means with different superscript letters are significantly different within the same row. Marked reduction in hemoglobin level despite significations improving in liver enzyme

Table [4]: Follow up results of some laboratory parameters throughout the treatment course.

Number of patients :35[87.5%]					
Variable	Base line	4th week	8thweek	12th week	p-value
AST [IU/L]	33 ±14.9 [a]	25.5±11.7[b]	24.3±11.9[b]	22.1±10.9[b]	0.008 [S]
ALT[IU/L]	34 ±15.7[a]	23.1±10.8[b]	21.4±9.7[b]	20.3±8.4[b]	0.001 [S]
WBC [×10^3] /cmm	6.5±2.4	6.4±2.7	7.2±2.6	7.1±1.4	0.19 [NS]
HB [g/L]	12.1±1.6[a]	10.2±2.3[b]	9.8±2.1[b]	10.1±1.5[b]	0.001 [S]
Platelets [×10^3] /cmm	196.1±33.8[a]	209±61.7[b]	219±67.4[c]	224±69.2[c]	0.03 [S]
Total bilirubin [mg/L]	0.5±0.1	0.5±0.3	0.5±0.2	0.5±0.1	1.00 [NS]

Variables expressed as Mean ±SD. S: significant, NS: non-significant. The bars with the different letters are significantly different at p <0.05. ALT: alanine aminotransferase, AST: aspartate aminotransferase; WBCs: white blood cells. HB: hemoglobin, INR: international normalization ration,

DISCUSSION

Elimination of Hepatitis C virus [HCV] infection in patients with end-stage renal disease [ESRD] or requiring hemodialysis decreases liver disease progression and liver-related morbidity/mortality **[16].** Also, reduces the risk of cardiovascular disease, diabetes and extra-hepatic cancers and improves their quality of life**[17].** The access to new DAAs that mainly metabolized in the liver with minimal renal elimination as the ombitasvir,, and ritonavir-boosted paritaprevir [OBV/PTV/RTV] is available in a fixed-dose combination pill**[18].** This combination is requiring no dose adjustment in patients with renal impairment. However, for maximum virological response ribavirin [RBV] is added to this combination in patients with genotype 1a**[19].**

Forty Egyptian naïve patients with ESRD were received combination of ombitasvir [25mg] / paritaprevir [150 mg]/ritonavir [100 mg], plus generic ribavirin [200 mg] for 12 weeks. There were 87.5 % of the patients completed 12 weeks of HCV therapy. Such patients showed 100% a sustained virological response. In Japan, 10 chronic HCV patients genotype 1b on regular hemodialysis received OBV/PTV/RTV combination therapy. Eight of them [80%] completed 12 weeks therapy and achieved SVR12, while, two [20%] patients discontinued the drugs because of its side effects **[20].** More adherent to the therapy and less withdrawal rate were reported by **Gómez et al. [11]** and **Pockros et al. [21]**

Anemia was the main side effect occurred during the course of treatment in the current study. Impaired renal clearance increases the potential risk of ribavirin-induced hemolytic anemia**[22].** Because of the distribution of RBV occurs mainly outside the plasma [primarily intracellular], since a very small amount of the drug in the body is available to be eliminated by dialysis **[23].** Safety and efficacy of the RBV-free regimen ombitasvir/ paritaprevir/ ritonavir ± dasabuvir in patients with ESRD [on hemodialysis] with HCV genotype 1a or 4 studied in RUBY-II clinical trial, which enrolled 18 treatment-naïve and non-cirrhotic adults patients. The overall SVR12 was 94% [17/18]; one patient discontinued the study to undergo an elective renal transplantation**[24].**This combination well tolerated with no serious side effect. The authors concluded that RBV may not be necessary in some genotype 1a- or 4-infected patients with ESRD [on hemodialysis] **[24].**

Conclusion: OBV/PTV/RTV plus Ribavirin was an effective therapy of Egyptian naïve chronic HCV patients with end stage renal disease on regular hemodialysis.

Recommendation: Use OBV/PTV/RTV without Ribavirin in treatment of chronic HCV patients with end stage renal disease on regular hemodialysis to avoid resistant anemia and improve patients' adherence to treatment.

Financial and Conflict of interest disclosure

Authors declare that there was no conflict of interest.

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