Safety and Efficacy of Ombitasvir, Paritaprevir and Ritonavir Combination with Ribavirin for Treatment of Chronic Hepatitis C Virus in Advanced Kidney Diseases Patients in Upper Egypt

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Abstract

Background: Formerly, treating hepatitis C virus (HCV) infection in individuals suffering from chronic renal disease was challenging due to the toxicity of interferon (IFN). Ombitasvir, paritaprevir, and ritonavir are examples of safe and effective pan-genotypic direct-acting antiviral (DAA) regimens that make it easier for individuals with chronic kidney disease to treat their hepatitis C virus (HCV).

Objectives: To assess the effectiveness and safety of Omibtasvir, paritaprevir, and ritonavir when used in conjunction with Ribavirin for the treatment of hepatitis C patients who have end-stage kidney disease.

Patients and methods: 100 individuals with severe renal illnesses and chronic hepatitis C virus were included in this cross-sectional investigation. The estimated glomerular filtration rate (eGFR) was calculated after each patient underwent a thorough medical history, physical examination, and laboratory testing that included a complete blood count, ALT, AST, and kidney function tests. Fibroscan and pelvic abdominal ultrasonography were carried out. The patients received ribavirin together with paritaprevir/ritonavir and ombitasvir (75/50/12.5mg) twice day for 12 weeks.

Results: Sustained virologic response (SVR) was 83 % (83 patients) overall patients. Patients were divided into two groups according to sustained virologic response. Child Pugh-turcotte (CPT) score was higher in non responders when compared with responders (5.7 ± 0.4 vs 5.4 ± 0.4; P-value = 0.002). Regarding to Safety and tolerability of DAAs, no severe adverse events were reported during the present study with no discontinuing treatment due to adverse events. The most frequent adverse events were anemia, headache, pruritus, anorexia and malaise.

Conclusion: OBV/PTV/RTV plus Ribavirin can be used in treatment of chronic HCV patients with ESRD with high virologic response and highly safety profile.

Keywords: End-stage renal disease; hepatitis C virus; Renal impairment; Sustained virologic Response.

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Introduction

The hepatitis C virus (HCV) is a serious health issue in many countries. The prevalence of HCV infection was 1.0 percent worldwide in 2015, with the Eastern Mediterranean Region having the greatest prevalence (2.3 percent), followed by Europe (1.5 percent). The projected number of deaths per year from complications connected to HCV is 700,000 **(Omran et al., 2018).** The treatment of chronic HCV infection has undergone a revolutionary change since the development of direct-acting antiviral drugs (DAAs), thanks to their high rates of sustained virologic response (SVR) **(Xia et al., 2020).**

In 2013, direct-acting antivirals (DAA) fundamentally changed the landscape of conventional hepatitis C virus (HCV) treatment by greatly simplifying the management of HCV-infected patients. Due to their poor tolerability, high toxicity, and limited efficacy, previous interferon-based regimens frequently required hepatologist consultation and were only accessible to a small number of HCV patients in tertiary or private settings. Real-world efficacy studies have revealed that DAA treatment is well tolerated and effectively cures more than 90% of patients **(Zhang et al., 2020).**

Individuals with HCV seropositive status are known to have a much greater prevalence of chronic kidney disease (CKD), including end stage renal disease (ESRD), than patients with HCV seronegative status **(Goodkin et al., 2013).**

Because the kidney is involved in the catabolism and filtration of interferon and ribavirin, the use of interferon-based regimen in patients with renal insufficiency is problematic **(Marra et al., 2021).** This results in increased exposure to the drug and potentially fatal side effects.

New direct acting antiviral medications (DAAs) for HCV are now available, enabling the use of interferon-free treatment regimens for this population of patients **(Gutierrez and Lawitz, 2015).** In non-cirrhotic previously untreated and previously treated patients with HCV genotype 4 infection, an interferon-free regimen of Ombitasvir plus Paritaprevir plus Ritonavir with or without Ribavirin led to high sustained virologic response rates (SVR) at 12 weeks after the end of treatment and was generally well tolerated with low rates of anaemia and treatment discontinuation **(Di Biagio et al., 2018).**

Aims of the Study: To assess the effectiveness and safety of Omibtasvir, Paritaprevir, and Ritonavir when used in conjunction with Ribavirin for the treatment of hepatitis C patients who have end-stage kidney disease.

Patients and methods

100 Egyptians who were 18 years of age or older and had a chronic HCV infection participated in this study. All patients who tested positive for serum HCV RNA PCR underwent 12 weeks of DAAs therapy.

Each participant provided written consent. The Qena Faculty of Medicine at South Valley University's regional ethics committee gave its approval to the project in August 2019 (Code: SVU-19-08).

Setting: Tropical Medicine and Gastroenterology Department's outpatient clinic at Qena University Hospital.

I. Inclusion criteria: The Egyptian National HCV Control Program's inclusion requirements were all followed. The group's ages ranged from 18 to 75. All

patients had serum HCV RNA PCR results that were positive.

II. Exclusion criteria:-applied in accordance with the directives of the Egyptian National HCV Control Program. These standards comprised the following:

1- Patients who also have HIV infection
2- Patients who are either under 18 or over 75
3- A pregnant woman
4- Hepatocellular carcinoma or any other malignancy
5- A total serum bilirubin level more than 3 mg/dl
6- Less than 2.8 g/dl of serum albumin
7- INR above 1.7
8- Platelet count less than 50,000/mm

All patients were subjected to the following:

I. History and Clinical Examination

1- A thorough history is taken, including information about any co-occurring diseases such diabetes, high blood pressure, heart disease, and drug use.

2- Complete clinical examination: looking for signs of chronic renal and liver illness.

3- Anthropometric measurements, such as calculating body mass index (BMI), height and weight.

II. Laboratory Investigations

Five milliliters of venous blood were collected from all participants and divided into two samples; the first (3 ml) was collected in a plain vacationer tube, centrifuged, and the resulting sera were used for biochemical investigations, the other (2ml) was collected into a tube containing an anticoagulant; EDTA tube used for CBC.All the patients were subjected to the following laboratory tests:

1) Cell Dyne-1800 for complete blood count (Abbot Diagnostic, Santa Clara, California, USA)

2) Using Cobas c311 to measure serum levels of alanine and aspartate aminotransferase, albumin, total bilirubin, urea, and creatinine (Roche Diagnostic Mannheim- Germany). PT measured with the STA compact Max Coagulation system (Stago-USA)

3) Hepatitis B and C indicators were discovered using the enzyme immunoassay (EIA) Cobas e411 (Roche Diagnostic Mannheim-Germany)

4) Quantitative real-time polymerase chain reaction (QT-PCR) assay for measuring the HCV RNA viral load utilizing the Cobas Amplicor and TaqMan HCV assay version 2.0 (Roche Diagnostic Mannheim, Germany).

5) Calculating the glomerular filtration rate: The CKD-EPI equation was used to determine the eGFR (Levey et al., 2009). When the eGFR fell below 60 ml/min/1.73 m2, it was considered to have CKD.

III. Imaging: Abdominal ultrasonography was used to screen all participants and evaluate the liver's surface area, echogenicity, and size in the midline and mid-clavicular lines.

IV.Treatment regimen: According to recommendations from the European Association for Study of Liver, patients got DAAs therapy **(EASL, 2018).** At the department of hepatology, gastro-enterology, and tropical medicine at Qena university hospital, patients were observed in outpatient clinics. The patients received ribavirin together with paritaprevir/ritonavir and ombitasvir (75/50/12.5mg) twice day for 12 weeks. Ribavirin dosage was changed in

accordance with the severity of renal impairment.

V. Monitoring of efficacy and safety: HCV-RNA virological level was assessed three times: at baseline (before to therapy), at stoppage of treatment (week 12), and at 12 weeks after treatment. Treatment failure was defined as confirmed HCV RNA above LLOQ 12 weeks after therapy, whereas sustained virologic response was evaluated when HCV RNA was less than the lower limit of detection (LLOD) at week 12 post-treatment (SVR12). Adverse events (AEs), treatment discontinuations due to AEs, and treatment-related deaths were all considered safety objectives.

Statistical analysis

The Statistical Software for Social Sciences (SPSS) version 26.0 was used to analyse the data. While qualitative data were presented as frequency and percentage number (percent), quantitative data were presented as mean standard deviation (M SD), and they were compared using the Student's t-test. Non-parametric data comparison was done using the chi-square test. It was deemed significant at P 0.05.

Results

Baseline characteristics

As regard demographic and laboratory data, Mean age was 71.3± 14,42 patients were diabetics (42%), 43 patients were hypertensive (43%). The mean of Child Pugh turcotte score was 5.2. 25 % of patients were on dialysis. Regarding laboratory profile, results showed that the mean of HGB, HBA1C, eGFR, AFP, HCV RNA were 10.1 g/dl, 5.3%, 21, 4.3, and 324 (x 10 log3/ul), respectively (**Table .1**).

Efficacy

The results of the current investigation revealed that 83 out of 83 individuals had sustained virologic responses (SVR). According to SVR; patients were separated into two groups: Group II included responders(83 patients) and Group I had non-responders (17 patients total) . Regarding Child Pugh Turcotte score, we discovered a statistically significant difference between responders and non-responders (CPT score). When compared to responders, nonresponders had higher CPT scores (5.7 0.4 vs 5.4 0.4; P-value = 0.002) (**Table .2**). Comparison between studied groups as impact of dialysis on SVR was presented in (**Table.3**).

Safety

Regarding the safety and tolerability of DAAs in ESRD, no major adverse events or treatment discontinuation due to adverse events were observed during the current research. The most frequent side effects were lethargy, anorexia, headache, itching, and anaemia (**Table. 4**).

Table 1. Demographic data of studied patientsat baseline

Variables	Studied patients (100)
Age (mean± SD)	71.3± 14
DM (N%)	42 (42%)
HTN (N%)	43(43%)
Patients on dialysis	25 (25%)
HGB (mean± SD)	10.1± 2.3
CPT score (mean± SD)	5.2± 0.4
HBA1C (mean± SD)	5.3± 0.8

eGFR (mean± SD)	21 ±5.8
AFP	4.3 (0.7-11)
HCV RNA	324000 (33000-21180000)

Table 2.Comparison between responder and non-responder regarding to demographic and laboratory data

Variables	Non-responders (n=17)	Responders (n=83)	P value
Age (mean± SD)	69.3 ± 20.1	72.3± 12.3	0.45
Gender (N%) • Female • Male	 14(82.4%) 3(17.6%)	 52(62.7%) 31(37.3%)	0. 1
DM (N%)	9(52.9%)	33(39.8%)	0.2
HTN (N%)	9(52.9%)	34(41%)	0.3
CPT score (mean± SD)	5.7± 0.4	5.4± 0.5	**0.002***
HGB (mean± SD)	10.3± 1.6	10.4 ± 2	0.2
HBA1C (mean± SD)	6.3 ± 0.6	5.2 ± 0.9	0.33
eGFR (mean± SD)	20.5 ± 5	21 .3 6	0.6
AFP (mean Rank)	56.4	49.2	0.32
HCV RNA (mean Rank)	54.5	49.6	0.5

*Chi-square test was used to compare proportions between groups
*statistically significant at <.05

Table 3. Comparison between studied groups as impact of dialysis on SVR

Variables		With dialysis (25)		Without dialysis (75)		P-value
SVR	Responders	21/25	84 %	62/75	82.6 %	0.877
	Non-responders	4/25	16 %	13/75	17.3 %	

*Chi-square test was used to compare proportions between groups
*statistically significant at <.05

Table 4. Reported side effects in our patients

Variables	N (%)
No adverse effects	57% (57%)
Anemia	43 (43%)
Headache	25 (25%)

Pruritus	17 (17%)
Anorexia	29 (29%)
Malaise	37 (37%)
Serious adverse events	0 (0%)
Discontinuations due to AEs	0 (0%)
Deaths	0 (0%)

Discussion

One hundred patients with chronic HCV infection and end-stage renal illness were enrolled in the current trial; all of them had received ombitasvir, paritaprevir, ritonavir, and ribavirin plus treatment for 12 weeks. According to the current study's findings, 83% of all patients had sustained virologic responses (SVR). No major adverse events or treatment discontinuation owing to adverse events were observed during the current research. Anemia, headaches, itchiness, pruritus, anorexia, and malaise were the most frequent adverse reactions.

In line with the current trial, **Lawitz et al. (2015)** examined the effectiveness and safety of ombitasvir/paritaprevir/ritonavir in patients with severe kidney illness and genotype 4 hepatitis C infection. They chose 65 patients, of whom 15 (23%) had compensated cirrhosis and 50 (76%) were receiving dialysis. They said that the SVR12 rate was 95% (63/66); 3 patients stopped treatment as a result of negative side effects. RBV dosage had to be modified in 73% (27/37) of the individuals who received it due to side effects.

Another study by **Mekky et al., 2019,** which included 110 patients, looked at the effectiveness of ombitasvir/ paritaprevir/ ritonavir with ribavirin in the treatment of HCV genotype 4 and end-stage kidney disease. Regarding SVR12, it was 96% in HD patients against 91.4 % in non-HD patients. Six patients had unsuccessful treatments. There were no grave adverse events that were reported. In the HD group, 66.6 percent of people had anaemia, compared to 31.4% of those in the non-HD group.

The study by **El Kassas et al. (2019)** observed high rates for the usage of ombitasvir/paritaprevir/ritonavir-containing regimens study that comprised 325 patients (age, 47.63 12.63 years); according to modified intention to treat analysis, SVR12 was obtained by all patients who received OBV/rPTV/RBV. Four individuals discontinued treatment at week four due to the most frequently reported negative effects, which included anaemia, tiredness, and high indirect bilirubin.

In a new observational, open-label prospective trial, which involved 103 individuals with various degrees of renal impairment and chronic HCV infection. The patients received ribavirin together with paritaprevir/ritonavir and ombitasvir (75/50/12.5mg) twice day for 12 weeks. 101 participants experienced a sustained virologic response 12 weeks after the completion of their treatment (98.1 percent). In 48 cases, anaemia was present. No patient experienced any severe side effects **(Abd-Elsalam et al., 2020).**

Our investigation demonstrated a highly significant difference between responders and non-responders as regard CPT-score (P <0.001) and a statistically significant correlation between virologic failure and degree of fibrosis.

Nelson et al. (2015) who enrolled 100 treatment-experienced and 51 treatment-naive genotype 3-infected

patients for a 12-week course of DAAs therapy, supported the findings of our study. Patients without cirrhosis had greater SVR12 rates (96%) than patients with cirrhosis did (63 percent ;) When SVR12 was evaluated by fibrosis stage using FibroTest scores of F0-F3 (93 percent) and F4 (70 percent), a similar pattern was seen.

According to Conti et al., LC has an effect on the outcome of DAAs. They used interferon-free regimens to treat 556 patients with advanced liver disease who were HCV-infected. SVR12 was obtained in 93.9 percent of cirrhotic individuals compared to 100 percent in the 38 patients with advanced fibrosis, indicating that liver cirrhosis had an impact on virologic response **(Conti et al., 2016).**

In accordance with current study**Salama et al. (2016)** showed that the response rate correlated with the fibrosis score,this study includes 475 patients with chronic HCV infection. The treatment was given for 12 weeks with 12 weeks follow-up to assess SVR12. The response rate ranged from 95 - 100 % in F1, F2 and it decreased to 80 - 93% in F3, F4. Non-responders were 32 (6.7%) patients out of 475 patients. In relation to fibrosis score, 29 out of 32 nonresponders were in F3, F4 **(Salama et al., 2016)**.

Shiha et al. (2018) examined the impact of 12 weeks of daily DAAs with or without ribavirin (RBV) in another sizable research conducted in Egypt. They discovered that patients without cirrhosis had a considerably higher SVR12 rate (97.4) than patients with cirrhosis (91.7).

Conclusion

OBV/PTV/RTV plus ribavirin has a strong virologic response and a great safety profile, making it an excellent choice for treating chronic HCV patients with ESRD.

Conflict of Interest

The authors have no conflict of interest related to this publication.

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