Gut and Gastroenterology

RESEARCH ARTICLE

Real life study of ombitasvir/paritaprevir/ritonavir in chronic kidney disease Egyptian patients infected with HCV genotype 4

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Abstract

Background: The availability of new direct acting antiviral drugs for HCV allow for treatment of HCV infection associated with renal impairment by interferon free regimens, but the choice of the suitable drug is important because some of these drugs can accumulate to a toxic level due to renal impairment.

Aims: The aim of this work was to confirm the efficacy and safety of ombitasvir/ paritaprevir/ ritonavir (OBV/PTV/r) and ribavirin in the treatment of HCV genotype 4 infected Egyptian patients with impaired renal functions.

Methods: The study enrolled 50 HCV infected patients with impaired renal functions. Pre-treatment assessment included complete liver functions with calculation of Child-Pugh score (patients with Child A only were included), renal function tests with calculation of estimated glomerular filtration rate (eGFR), HCV RNA, complete blood picture (CBC) and ultrasound abdomen.

The patients were given OBV/PTV/r two tablets daily, each tablet contains paritaprevir 75 mg/ ombitasvir 12.5 mg/ ritonavir 50 mg± ribavirin (the dose was decided according to the body weight, eGFR and heamoglobin level follow up during treatment) for 12 weeks. Patients were followed up during treatment by routine laboratory investigations, HCV RNA was done at end of treatment, 12 and 24 weeks post- treatment.

Results: According to eGFR; 15 (30%) patients had chronic kidney disease CKD stage 2 (eGFR 60-89 ml/min/1.73m2), 22 (44%) patients were CKD stage 3(eGFR 30-59 ml/min/1.73m2), two (4%) patients were CKD stage 4 (eGFR 15-29 ml/min/1.73m2) and 11 (22%) patients were on dialysis; CKD stage 5 (eGFR <15 ml/min/1.73m2). No serious side effects were detected during treatment except for pruritis and GIT disturbances which were detected in 12 (24%), jaundice (total serum bilirubin >2 mg/dl) was found in 7 patients (14%),anemia was observed in 8 patients (16%), which necessitated stoppage of ribavirin in five (10%) patients. SVR was achieved in 48(96%) patients.

Conclusions: The use of paritaprevir 150 mg/ombitasvir 25 mg/ ritonavir100 mg ± ribavirin for 12 weeks provided high rate of sustained virological response among chronic HCV genotype 4 infected patients with renal impairment without serious side effects.

Introduction

The association between hepatitis C virus infection (HCV) and renal impairment can develop as a result of many causes, for example, renal affection can be an extrahepatic manifestation of HCV [1]. Recently many researches showed that chronic HCV infection may be a risk factor for developing renal cell carcinoma [2]. Hemodialysis (HD) can be a source for infection by HCV with increased overall mortality risk when compared with those on dialysis who do not have HCV infection [3].

Treatment of hepatitis C in patients with renal impairment is important as it has been proved that HCV can accelerate the course of renal disease in some patients [4]. In patients with immune complex induced renal disease, it is urgent to treat HCV infection to prevent further renal damage [1]. In addition, the cure from HCV is recommended if renal transplantation is decided [5].

The use of interferon based therapy in patients with renal insufficiency is problematic because the kidney plays a role in the catabolism and filtration of interferon and ribavirin, so in renal impairment the clearance of these drugs is reduced leading to more exposure and lethal side effects [6].

The availability of new direct acting antiviral drugs (DAAs) for HCV allow for treatment of this group of patients by interferon free regimens, but the choice of the suitable drug is important because some of these drugs can accumulate to a toxic level due to renal impairment [7].

Sofosbuvir is excreted by the kidney and available data do not support its use when glomerular filtration rates are <30 mL/ min [8].

FDA has approved recently OBV/PTV/r for treatment of HCV infected patients with severe renal disease [9]. Some studies showed that no dose adjustments are needed in patients with renal impairment, as the metabolism of these compounds is mediated predominantly by the liver [10]. However, further researches are needed especially for HCV genotype 4 to prove

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the efficacy and safety of OBV/PTV/r in patients with renal insufficiency.

Patients and methods

This study is a retrospective, observational study, performed on 50 HCV GT4 infected Egyptian patients with varying degrees of renal impairment attending Tropical medicine department, Alexandria University clinic during the period from August 2017 to Feb 2018, all patients were treated with OBV/PTV/r (25/150/100 mg once daily) ± RBV. The dose of RBV was given according to body weight in patients with eGFR > 30ml/min (1000 mg if < 75 kg, 1200 mg if >75 kg), while in patients with eGFR < 30 ml/min; RBV dose was 200 mg daily.

If on dialysis, 200 mg of RBV was given 4 hours before dialysis 3 times weekly. Ribavirin use was restricted to patients who have a baseline hemoglobin greater than 10 g/dL and it was not used in patients who were intolerant or ineligible to receive it, such as those with haemoglobinopathies or with severe anaemia.

Planned treatment duration was 12 weeks, patients with decompensated cirrhosis with Child-Pugh score B or C and those previously treated with DAAs were excluded from this study. Phosphorus-binding drugs were administered at least 4 hours before or after antiviral therapy to avoid interference with drug absorption.

Evaluation and follow-up

Demographic, clinical biomarkers of liver function—AST, ALT, bilirubin—renal function—eGFR calculated with MDRD-4 and creatinine clearance—adverse events and virological data were collected before the start of therapy and at weeks 4, 8, and 12 during antiviral treatment.

Additional visits were scheduled by the clinician according to the state of every patient. Follow-up visit after the end of treatment was at 12 and 24 weeks. HCV RNA was measured at end of treatment (EOT), and week 12 (SVR12) and week 24 (SVR 24) post-treatment.

Effectiveness of the regimen was assessed by determining the rate of SVR12. Virological failure was defined as detectable HCV RNA at any time during treatment or post-treatment follow-up.

Serious adverse events were defined as any life-threatening event, an event leading to hospital admission, prolonging an existing hospital stay or resulting in death, or any event considered serious in the opinion of the treating physician. Anaemia was defined as haemoglobin levels <10 g/dL or a drop of >2 g/dL from the baseline.

Hepatic decompensation was defined as the presence of variceal haemorrhage, ascites, spontaneous bacterial peritonitis and/or hepatic encephalopathy.

The study was approved by the Research Ethical Committee of Alexandria University. Written informed consent was obtained from all patients.

Statistical analysis

The results obtained were statistically analysed using SPSS program. A normality test was done. Data were then presented in tables and figures and the different parameters were correlated with each other. Qualitative data were described using number and percent, while normally quantitative data was expressed in mean ± SD, abnormally distributed data was expressed in median (Min-Max) and was compared using Paired t-test

An internal comparison between each laboratory investigation before treatment, 4, 8 and 12 weeks on treatment was done using Wilcoxon Signed Ranked test to determine whether improvement or deterioration in laboratory investigations has occurred.

Results

Fifty patients with CKD stage 2,3, 4 and 5 infected with HCV GT4 were treated in this study, of which 28(56%) were men. Mean age was 58.2 ± 11.6 years, 43(86%) were treatment-naïve, and seven patients (14%) had received previous interferon-based antiviral therapy. 43(86%) patients were with a Child-Pugh score A5, only 7 (14%) patients were with a Child-Pugh score A6. Six (12%) patients had oesophageal varices. Baseline demographic and clinical characteristics are shown in (Table 1).

With regard to renal disease, 15(30%) patients had CKD2, 22(44%) CKD3, 2(4%) CKD4 and 11(22%) patients were on dialysis (CKD5), the baseline eGFR was ranging from 10-

	No. (%)
Age(years)	58.2 ± 11.6
Sex	
Male	28(56%)
Female	22(44%)
BMI	26 ± 6.4
Co-morbidities	
DM	31(62%)
HTN	25(50%)
Child score	
A5	43(86%)
A6	7(14%)
Treatment naïve	43(86%)
Ascites	0(0%)
Spleen	
Normal	18(36%)
Enlarged	32(64%)
Oesophegeal Varices	6(12%)
Hepatomegaly	3(6%)

(n = 50).

Table 1: Distribution of the studied cases according to baseline demographic data and clinical characteristics

67 with mean value of 55 and baseline serum creatinine was ranging from 0.5-5.8 with mean of 1.6 (Table 2) , concerning the aetiology of renal disease, diabetic nephropathy was found to be the leading cause accounting for 36% of cases, hypertensive nephropathy was responsible for 8% of the causes of renal impairment , combined diabetic and hypertensive nephropathy was found in 11% of the cases, however, the aetiology was unknown in 9% of the patients (Table 3)

The baseline laboratory investigations and liver function tests were illustrated in (Table 4)

	Baseline	After4 weeks	After8 weeks	After12 weeks
Creatinine	1.6(0.5-5.8)	1.5(0.5-5.9)	1.5(0.7-6)	1.3(0.6-5.8)
p	-	0.001*	<0.001*	<0.001*
eGFR	55(10-67)	-	-	51(12-102)
p	-	-	-	<0.001*
CKD stage	3(2-5)	-	-	3(1-5)
p		-	-	0.046*
1	0(0%)	-	-	1(2%)
2	15(30%)	-	-	17(34%)
3	22(44%)	-	-	19(38%)
4	2(4%)	-	-	2(4%)
5	11(22%)	-	-	11(22%)
Dialysis	11(22%)			

P: P values for Chi square test
*: Statistically significant at p ≤ 0.05

Table 2: Distribution of the studied cases according to baseline and follow up renal functions (n = 50).

Aetiology of renal disease	No. (%)
Unknown	9(18.0)
Hypertensive nephropathy	8(16.0)
Diabetic nephropathy	18(36.0)
Diabetic & hypertensive nephropathy	11(22.0)
Obstruction	4(8.0)

Table 3: Aetiology of renal disease in the studied group (n = 50).

Response to antiviral therapy

SVR12 was achieved in 48(96%) patients. at week 24 post-treatment; viral load remained undetectable (Table 5), significant difference was noted between the SVR in the RBV group in comparison to the group with RBV dose reduction & discontinuation (P= 0.044)

Tolerance and adverse events

Pruritis was the most frequently reported adverse event, jaundice was found in 7 patients (14%),anemia was observed in 8 patients (16%), GIT disturbances was noticed in 12 patients(24%), however, no serious adverse events were observed in any patient (Table 6,7)

Anemia events and its management

Six patients (12%) had baseline haemoglobin levels <10 g/dL. Overall, 28 patients (56.0%) received RBV. RBV dose reduction was done in 17 patients (34%), however RBV was discontinued in 5 patients (10%), fifteen patients (30%) used erythropoetin during this study and only two patients (4%) required blood transfusion. (Table 8)

Mean haemoglobin levels showed a tendency towards progressive reduction during treatment in patients using RBV, which was not observed in patients without RBV or with RBV dose reduction. Mean change from baseline to EOT in the RBV group was declined by 0.67 ± 1.76, whereas in patients without RBV or with RBV dose reduction, levels are elevated by 0.44 ± 0.95 (*P*=0.020). Haemoglobin levels normalized after treatment in both groups. RBV was

	Baseline	After 4 weeks	After 8 weeks	After 12weeks
AST	38(21-109)	31(22 - 60)	25(20-45)	25(22-74)
p		<0.001*	<0.001*	<0.001*
ALT	29(15-196)	24(20-73)	25(18- 48)	24(20-92)
p		<0.001*	<0.001*	<0.001*
Bilirubin	0.7(0.2-1.9)	1.4(0.7-3)	1.2(1-3)	1(1-1.6)
p		<0.001*	<0.001*	<0.001*
Albumin	3.9 ± 0.6	3.9±0.6	3.9±0.5	3.8±0.5
PT%	91.6 ± 11.6	90.8±11.4	90.5±11.7	90.7±11.3
AFP	8(1.2-12)	8.0(1.2 - 11)	8.0(1.2 - 11)	8.0(1.2 - 12)
HB levels	12.3 ± 2.2	11 ± 1.3	11.7 ± 1.3	12 ± 1
Grade I(>10)	44(88%)	34(68%)	42(84%)	44(88%)
Grade II(10 – 8)	6(12%)	16(32%)	6(12%)	6(12%)
Grade III(8 – 6)	0(0%)	0(0%)	2(4%)	0(0%)
p		<0.001*	0.003*	0.209
WBCs	7.5 ± 1.7	7.4 ± 1.1	7.6 ± 0.8	7.6 ± 0.6
p		0.603	0.580	0.624
PLT	240(88-353)	220(90-309)	224(87-308)	229(86-300)

P: P values for Chi square test
*: Statistically significant at p ≤ 0.05

Table 4: Baseline and follow up laboratory investigations of the studied group (n = 50).

	Baseline	After 12 weeks	After 24 weeks
PCR(x103)	4120(39-94600)	4460(20-8900)	4716.5(243-9190)
Negative	0(0%)	48(96%)	48(96%)
Positive	50(100%)	2(4%)	2(4%)
<800.000	17(34%)	-	-
≥800.000	33(66%)	-	-

Table 5: Response of the studied group to antiviral therapy (n = 50).

RBV dose reduction and Discontinuation	Response		P
	No Response	No Response	
	No. (%)	No. (%)	
No	0(0.0)	33(100.0)	0.044*
Yes	2(11.8)	15(88.2)	

P: P values for Chi square test
*: Statistically significant at p ≤ 0.05

Table 6: Virologic Response in cases with RBV dose reduction and Discontinuation (n = 50).

Adverse events	No. (%)
Jaundice > 2 mg/dl	7(14%)
Itching	12(24%)
Anemia	8(16%)
GIT disturbances	12(24%)
Serious adverse events	0(0.0%)

Table 7: Distribution of the studied cases according to adverse events (n = 50).

	No. (%)
Anemia (Basline)	
Grade II(10 – 8)	6(12%)
Grade III(8 – 6)	0(0%)
RBV dose reduction	17(34%)
RBV Discontinuation	5(10%)
Erythropoeitin	15(30%)
Blood transfer	2(4%)

Table 8: Anemia events and managements (n = 50).

suspended in 5(10%) due to anaemia grade 3 at four weeks of treatment [Figure 1].

Significant improvement in the estimated GFR was observed before and after treatment with DAAS therapy [Figure 2].

Discussion

Persons infected with hepatitis C virus (HCV) can develop kidney disease because of extrahepatic manifestations of HCV or as a disease process independent of the HCV infection. In addition, hemodialysis has been a risk factor for acquiring HCV infection, with 8.4% of hemodialysis patients in the United States having chronic HCV in the year 2000 [11]. Several studies have shown that patients on chronic hemodialysis have an increased overall mortality risk if they have chronic hepatitis C infection when compared with those on dialysis who do not have hepatitis C infection [11,5].

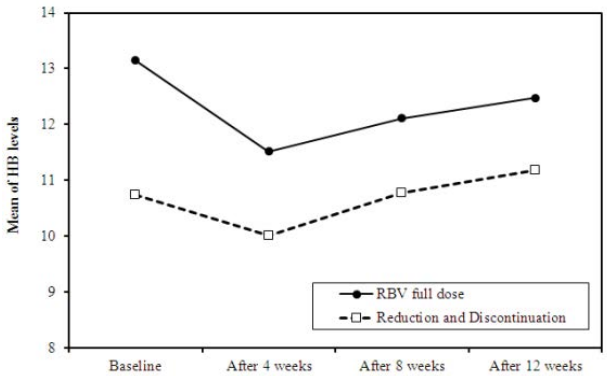

Figure 1: Haemoglobin levels (from baseline to EOT) and at week 12 post-treatment. Levels in patients treated with full dose RBV-containing regimens and those treated with RBV dose reduction and without RBV are shown separately.

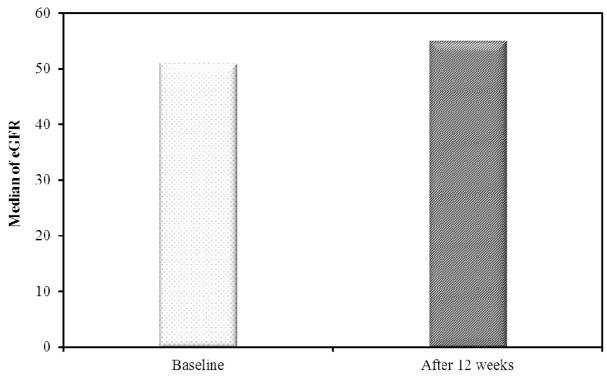

Figure 2: Comparison between median and interquartile range of renal function parameters during antiviral therapy (baseline through EOT) and in follow-up visit 12 weeks post-treatment in patients with CKD 2, 3 and 4.

There is a strong and likely causal association between chronic hepatitis HCV infection and glomerular disease, including mixed cryoglobulinemia, membrano-proliferative glomerulonephritis (MPGN), and possibly membranous nephropathy [12].

In addition, the prevalence of anti-HCV antibody is higher among patients on hemodialysis compared with healthy populations, suggesting that dialysis patients may be at higher risk of acquiring HCV infection. In fact, the prevalence of a positive HCV antibody test in the hemodialysis population in the United States is 5 to 10 percent [13,14].

Antiviral treatment in these patients can be complicated because many of the agents used for anti-HCV therapy can accumulate to toxic levels in the setting of renal impairment. Thus, patients with renal disease and chronic HCV infection represent an important population that warrants specific consideration [15].

The present study was conducted on 50 patients with chronic HCV genotype IV with variable degrees of renal impairment, 56% were males and 44% were females. 43% were treatment

naïve, 86% were child A5 and 14% were child A6. Also, 62% of the studied patients were diabetics and 50% were hypertensive.

In this study, treatment with daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) ± dose adjusted ribavirin daily for 12 weeks to all patients resulted in end of treatment response; SVR12 and SVR 24 rate of 96%

These results were comparable with RUBY-II trial which was a phase 3b, open-label, multi-center study that enrolled treatment-naïve patients with either GT 1 or GT4 infection without cirrhosis and end-stage renal disease (eGFR<30 ml/min), including those on HD. This trial achieved a SVR 12 of 92% [16].

In accordance to SURFER study which is the single randomizes controlled study (RCT) done so far with CKD patients, which evaluated elbasvir-grazoprevir in patients with Stage 4 or 5 kidney disease, the majority of whom (76%) were on HD, and showed SVR12 rates similar to those seen in patients without CKD (99%) **[17].**

In the HCV TARGET trial, investigators reported findings from a longitudinal cohort study of 1893 patients using one of four sofosbuvir-containing regimens: sofosbuvir plus peginterferon plus ribavirin, sofosbuvir plus ribavirin, sofosbuvir plus simeprevir, and sofosbuvir plus simeprevir plus ribavirin. Overall, the SVR12 rates were high (81 to 89%) across different levels of baseline renal insufficiency, with the one exception that cirrhotic patients with eGFR less than 30 ml/min/1.73m^2 had lower SVR12 rates [18].

Adjustments are needed for any of the medications used to treat HCV in renal impairment. The recommended ribavirin dose is 200 mg/day (typically starting at 200 mg three times weekly and titrating up to 200 mg/day as tolerated. Caution should be exerted when using ribavirin in patients with renal failure because of the risk of severe hemolysis. Ribavirin should be discontinued if the hemoglobin level decreases by more than 2 g/dL despite the use of erythropoietin according to American association for the study of liver diseases (AASLD) guidelines [11].

In the current work we have found that according to the hemoglobin level, significant reduction occurred at 4 weeks of treatment, but after ribavirin dose modification (in 34% of cases), addition of erythropoietin subcutaneous injections (in 30%), or even stoppage of ribavirin in 10% of patients, the hemoglobin levels were improved at week 8 and week 12 of treatment. SVR 12 was achieved in 88% of patients with ribavirin dose stoppage or modification.

This is in comparison to HCV TARGET trial phase 2 that showed that rates of treatment-related anemia were higher in patients with more advanced renal disease. But this trial used a 24-week course of sofosbuvir plus ribavirin for patients with hepatitis C genotype 1 or 3 and renal insufficiency (eGFR less than 30 ml/min and not on dialysis); in this trial sofosbuvir was given at a dose of either 200 mg or 400 mg once daily and ribavirin at a reduced dose of 200 mg once daily [18].

A higher incidence of anemia in CKD patients (~50%) compared with patients without CKD (~30%) was shown also, by Osinusi and Gane et al [19].

Furthermore, the current results showed a significant improvement in eGFR during treatment with improvement of their CKD stage that 4% turned CKD 2 instead of 3.

Tsuge and Ble et al, demonstrated also, improvements in CKD stage. Although DAAs have very substantially improved HCV 'cure' rates for patients without CKD, RCTs are needed to evaluate most of the available DAA regimens in CKD patients since these have not yet been carried out [20].

Overall, treatment of HCV in patients with CKD is highly effective, with SVR12 rates similar to those seen in patients without CKD. It is important to note that to date most studies of DAAs in this population have been small, so additional studies are needed to assess the efficacy and full adverse effect profile of DAAs and the impact of HCV cure on in patients with renal function impairment .

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