Elshinnawy *et al. Egyptian Liver Journal* (2022) 12:36
https://doi.org/10.1186/s43066-022-00196-x

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Study the response of Qurevo (ombitasvir, paritaprevir, and ritonavir) in end-stage renal disease patients with hepatitis C virus

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Abstract

Background: Out of the 185 million people infected with hepatitis C virus (HCV) worldwide according to the World Health Organization (WHO), Egypt had the highest prevalence of HCV reaching 13% of its population with an estimated number of 12 million people. The prevalence of HCV infection among hemodialysis (HD) patients ranged from 6 to 60%. HD patients have an increased overall mortality risk if they have chronic HCV when compared to those without HCV infection. Treatment of HCV with the new direct-acting antiviral agent (DAA) therapy Qurevo "ombitasvir/paritaprevir/ritonavir" with ribavirin in ESRD was approved in many countries compared to traditional HCV treatment that faced restrictions in the setting of chronic kidney disease (CKD).

Aim of the study: To evaluate the efficacy and safety of Qurevo/ribavirin regimen in HCV-infected HD patients.

Patients and methods: A prospective cohort study evaluated the outcome of 12-week ombitasvir (NS5A inhibitor)/paritaprevir (NS3/4A protease inhibitor)/ritonavir with ribavirin combination therapy for 50 HCV-infected HD patients, over a period of 15 months from December 2016 to February 2018. The primary endpoint was sustained virologic response 12 weeks after therapy (SVR12) and after 24 weeks of therapy (SVR24).

Results: The SVR12 rate was 96% (48/50); 2 patients (4%) were non-responders to treatment at SVR12, and another 2 (4%) were relapsers after SVR12. As regards the adverse events, the most frequent were fatigue/asthenia in 44 patients (88%) and worsening anemia (Hb dropped to < 10 g/dl) in 42 patients (84%). GIT upset occurred in 10 patients (20%), sleep disorders in 8 patients (16%), decreased appetite in 8 patients (16%), respiratory distress in 6 patients (12%), headache and dizziness in 6 patients (12%), and muscle spasms in 4 patients (8%). Itching (pruritus) occurred in 3 patients (6%). Death occurred in 4 patients (8%) after SVR24 most probably not due to DAA but may be due to myocardial infarction, pulmonary edema, severe hypotension on hemodialysis sessions, and shock due to blood loss in retroperitoneal hematoma following peritoneal dialysis not related to DAA therapy. Hepatic decompensation, hypersensitivity (angioedema), teratogenicity, and drug interactions did not occur in any patient (0%). Other events occurred in 11 patients (22%). They were parenchymal liver changes in ultrasound at the end of therapy after being normal before therapy (in 3 patients), thrombocytopenia, increased alkaline phosphatase, hiccough, deterioration of hypertension, urinary tract infection, lower limb cellulitis, vaginal bleeding, and chest infection (in 1 patient each). SVR12 was achieved in 100% of patients who had to stop or modify the ribavirin dose; this means that ribavirin absence did not affect the SVR in these patients.

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Conclusion: Our results confirm the efficacy of Qurevo "ombitasvir/paritaprevir/ritonavir" with ribavirin combination therapy in ESRD patients (on regular hemodialysis) with HCV infection with anemia as the most frequent adverse event.

Keywords: Hepatitis C virus, End-stage renal disease, Ombitasvir/paritaprevir/ritonavir, Qurevo, Ribavirin

Introduction

People infected with HCV can develop kidney disease as a result of extrahepatic manifestation of HCV or as a disease process independent of the HCV infection. In addition, hemodialysis has been a risk factor for acquiring HCV infection. Several studies have shown that patients on chronic hemodialysis have an increased overall mortality risk if they have chronic HCV (when compared with those on dialysis who do not have HCV). There are some data showing that chronic hepatitis C may be a risk factor for developing renal cell carcinoma. Chronic HCV infection has also been associated with an accelerated course of renal disease in HIV-infected persons. Extrahepatic manifestations related to HCV, including immune complex-related renal disease, can require urgent HCV treatment to resolve or prevent further organ damage [1].

Chronic HCV infection was rarely treated in patients with end-stage renal disease during the interferon era because of its toxicities and low tolerability. Among the new direct-acting antivirals, sofosbuvir is cleared renally and therefore is not recommended in patients with estimated glomerular filtration rates below 30 ml/min per 1.73 m^2. Most other direct-acting antiviral agents are metabolized by the liver, but blood levels of simeprevir and daclatasvir can rise in the setting of severe renal impairment. In contrast, Qurevo (ombitasvir, paritaprevir, ritonavir) undergoes hepatic metabolism and did not require dose adjustment in phase I studies of patients with mild, moderate, or severe renal impairment [2].

The availability of new DAAs has sparked major enthusiasm for treating HCV-infected patients with renal impairment. Investigators treated HCV-infected patients with stage 4 or 5 renal disease, including patients on hemodialysis, with a 12-week regimen of Qurevo with or without ribavirin. In the preliminary analysis, 10 (100%) of 10 treated patients achieved a sustained virologic response 4 weeks after completion of therapy (SVR4), and no treatment-related serious adverse events occurred [3]. The most common adverse events were anemia (45% of patients), fatigue (35%), diarrhea (25%), and nausea (25%) [4]. Nearly half of the patients had to interrupt or discontinue ribavirin because of worsening anemia in some studies [5].

Egypt's Health Ministry approved the new oral interferon-free hepatitis C drug Qurevo (another trade name of Viekira Pak). It is produced specially for Egypt by the UK [6]. Based on that, our study was conducted aiming to evaluate the efficacy and safety of Qurevo/ribavirin regimen in ESRD Egyptian patients on regular hemodialysis who are infected with HCV.

Patients and methods

Patients

This cohort study was conducted on 50 patients with end-stage renal disease, on regular hemodialysis with hepatitis C virus who received Qurevo/ribavirin regimen at the hepatic virology clinic at Ain Shams University hospital from December 2016 to February 2018.

Inclusion criteria

Adults aged > 18 years old patients with end-stage renal disease (on regular hemodialysis), infected with hepatitis C virus with HCV RNA positivity, were included. They should have compensated liver (Child A cirrhosis or no cirrhosis), and Hb level is at least 10 g/dl with no associated uncontrolled co-morbidity (cardiac, neuro-psychiatric).

Exclusion criteria

The following are the exclusion criteria: Child B and C cirrhosis patients; platelet count < 50,000/mm^3; HCC, except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI); and extra-hepatic malignancy except after 2 years of disease-free interval. In cases of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission based on the treating oncologist's report. Pregnancy or inability to use effective contraception, also inadequately controlled diabetes mellitus (HbA1c > 9%).

Data processing

All patients were subjected to full history taking (including renal condition and hepatitis C infection), full clinical examination and baseline laboratory investigations: CBC, serum creatinine, HCV Ab, HBsAg, PCR for HCV, liver functions "total and direct bilirubin/serum albumin/INR," liver enzymes "AST/ALT," alpha feto protein, and pelvi-abdominal ultrasound.

Treatment with daily fixed-dose combination of 2 tabs Qurevo "paritaprevir (75 mg, NS3/4A protease

inhibitor)/ritonavir (50 mg)/ombitasvir (12.5 mg, NS5A inhibitor)" with meal + 200 mg ribavirin daily for 12 weeks was given, tracing the incidence of adverse events according to checklist and follow-up CBC, liver enzymes, and liver functions at weeks 4, 8, and 12 of treatment were done. PCR for HCV was repeated at 12 and 24 weeks after cessation of treatment to determine the SVR12.

The following are the definition of treatment responses:

- Patients were regarded as having a rapid virologic response (RVR) when serum HCV RNA was undetectable at 4 weeks of treatment.
- Patients who were negative for HCV RNA at 12 weeks after the completion of treatment were considered to have achieved sustained virologic response (SVR 12) [7].
- Non-responders are patients who failed to clear HCV RNA from serum after 12 weeks of therapy, but as the protocol followed in our hospital did not include a PCR test at end of treatment, non-responders were considered those who did not achieve a negative PCR 12 weeks after therapy, that is to say, a SVR.
- Relapsers are patients with the reappearance of HCV RNA in serum after achieving SVR12.

Statistical analysis

Statistical analysis was done on a personal computer using the Statistical Package for Social Sciences (IBM SPSS version 17. 0).

1. Descriptive statistics: mean, standard deviation [SD], range for numerical data, frequency, and percentage of non-numerical data.
2. Analytical Statistics:
   (a) Paired *t*-test: unpaired Student *T*-test was used to compare between related sample
   (b) Chi-square: the hypothesis that the row and column variables are independent, without indicating the strength or direction of the relationship. Pearson chi-square and likelihood ratio are used to compare the qualitative variables.

So, *P*-value is used as the level of significance: *P*-value > 0.05 is non-significant, *P*-value ≤ 0.05 is significant, and *P*-value < 0.01 is highly Significant.

Results

The sample included 50 patients with end-stage renal disease on regular hemodialysis with hepatitis C virus who received Qurevo/ribavirin regimen at the hepatic virology clinic at Ain Shams University hospital from December 2016 to February 2018.

Table 1 shows the demographic data and clinical characteristics of the study group (50 patients). As regards the co-morbidities, hypertension was the most common (56%), diabetes in (26%), then ischemic heart disease (8%). Other comorbidities included cerebral palsy and rheumatoid arthritis in 2 subjects (4%). As regards Child score calculation, it was mainly A5 in 42 patients (84%) while A6 was in 8 patients (16%). But liver ultrasound was normal in 22 patients (44%) and showed abnormal

Table 1 Demographic data and clinical characteristics of the study group

Demographic data and clinical characteristics	
Age (years)	
Mean ± SD	51.400 ± 12.838
Range	(23–77)
Gender (*N* (%))	
Male	25 (50%)
Female	25 (50%)
Co-morbidities (*N* (%))	
DM	13 (26%)
HTN	28 (56%)
ISHD	4 (8%)
Others	2 (4%)
Child score calculation (*N* (%))	
A5	42 (84%)
A6	8 (16%)
Liver by PAUS (*N* (%))	
Normal hepatic echopattern	22 (44%)
Chronic parenchymatous liver disease	17 (34%)
Coarse echopattern	11 (22%)
Spleen by PAUS	
Enlarged	7 (14%)
Normal	43 (86%)
Ascites by PAUS	
Yes	2 (4%)
No	48 (96%)
Baseline laboratory investigations (week 0), mean ± SD (range)	
Alpha feto protein (IU/l)	3.459 ± 3.948 (0.54–26)
Serum Creatinine (mg/dl)	7.345 ± 1.981 (3.6–12.75)
PCR for HCV (IU/ml) week 0	2,629,176.880 ± 4,598,628.996 (10,601–23,102,362)

DM diabetes mellitus, *HTN* hypertension, *ISHD* ischemic heart disease, *PCR* polymerase chain reaction, *HCV* hepatitis C virus, *PAUS* pelvi-abdominal ultrasound

hepatic echopattern in 17 patients (34%) and coarse hepatic echopattern in 11 patients (22%). The Child–Pugh score has been widely used to assess the severity of liver dysfunction in clinical work [8].

Table 2 shows that there was a highly significant progressive decline in the mean Hgb levels starting from week 4 (12.05 g/dl) to week 12 (8.959 g/dl) ($P<0.001$), progressive rise of platelet counts although non-significant from a mean of 208.82×10^3/ml at baseline to 229.38×10^3/ml at week 12 with a delta change of 20.560 ± 86.368 ($P=0.099$). There was a significant rise in total bilirubin throughout the study ($P=0.001$, 0.023, 0.012 at weeks 4, 8, 12, respectively) with a progressive decline in direct bilirubin, together with an improvement of the INR being significant at week 12 ($P=0.048$, $P=0.03$, respectively). As regards liver enzymes, there was a significant decline in ALT throughout the study and a significant decline in AST at week 8 ($P=0.046$).

Table 3 shows the response of the studied group to antiviral therapy. SVR 12 occurred in 48 out of 50 patients (96%). The PCR of another 2 patients turned positive after SVR12 (considered relapsers).

Table 4 shows that all 4 patients who had ribavirin reduced or stopped had negative PCR at week 24 (SVR12 rate 100%). So, there was no statistical correlation between them. This means that ribavirin dose reduction or discontinuation due to anemia did not affect the SVR12 rate.

Table 5 shows that the most common side effects were fatigue and asthenia in 44 patients (88%), anemia (Hb dropped to < 10 g/dl) in 42 patients (84%), GIT upset in 10 patients (20%), sleep disorders and decreased appetite in 8 patients (16%) each, and respiratory distress and headache with dizziness in 6 patients (12%) each, followed by muscle spasms in 4 patients (8%) and pruritis in 3 patients (6%).

Death occurred, after week 36 and within the 60 weeks of follow-up of the study, in 4 patients (8%) due to myocardial infarction, pulmonary edema, severe hypotension on hemodialysis sessions, and shock due to blood loss in retroperitoneal hematoma following peritoneal dialysis, most probably and was not related to DAA therapy. It occurred after a negative SVR 12 and SVR24.

Hepatic decompensation, hypersensitivity (angioedema), teratogenicity, and drug interactions did not occur in any patient (0%).

Other events occurred in 11 patients (22%). They were parenchymal liver changes in ultrasound at the end of therapy after being normal before therapy (in 3 patients), thrombocytopenia, increased alkaline phosphatase, hiccough, deterioration of hypertension, urinary tract infection, lower limb cellulitis, vaginal bleeding, and chest infection (in 1 patient each).

Table 6 shows the managements of patients with hemoglobin drop to < 10 g/dl.

Table 7 shows no significant correlation between reduced or stopped ribavirin and relapse or non-response to treatment.

Table 8 shows no statistically significant correlation between HCV viral load and failure of treatment.

Discussion

The worldwide burden of HCV is estimated at 185 million out of which 12 million Egyptians suffer from HCV. Known to us is the morbidity of HCV as a leading cause of cirrhosis, hepatocellular carcinoma, and also known to us are the hepatorenal effects of HCV eventually leading to a higher rate of mortality among hemodialysis patients in specific. Hemodialysis has been identified as a separate risk factor for contracting HCV and taking into account the limited access of antiviral drugs due to the known toxicity of traditional HCV treatment on dialysis patients, new DAAs appeared as a better choice with ribavirin in those patients namely Qurevo ombitasvir/paritaprevir/ritonavir [9–13].

Our results revealed, regarding the efficacy, our SVR12 rate was 96% (48/50); 2 patients had virologic failure. This goes in line with the RUBY-I and RUBY-II trials presented at the meeting of the American Association for the Study of Liver Diseases (AASLD) held in Boston in November 2016, in which the SVR12 rate was 96% (46/48) in RUBY-I [14] and 94% (17/18) in RUBY-II by Gane et al. [15]. Also, like the study in Japan by Atsukawa et al. [16], SVR12 rate was 96.8% (30/31), and like study in Egypt by Hanno et al. [17], SVR12 was also 96% (48/50). It was similar to a study in the USA by Lawitz et al. [18], the SVR12 rate was 95% (63/66), and in another study in Japan by Arai year 2018, SVR12 was 98.7%.

As regards the safety and adverse events, the most frequent were fatigue/asthenia in 44 patients (88%) and worsening anemia (Hb dropped to < 10 g/dl) in 42 patients (84%). GIT upset occurred in 10 patients (20%), sleep disorders in 8 patients (16%), decreased appetite in 8 patients (16%), respiratory distress in 6 patients (12%), and headache and dizziness in 6 patients (12%). Muscle spasms in 4 patients (8%). Itching (pruritis) occurred in 3 patients (6%). Two patients (4%) were non-responders to treatment, and another 2 (4%) were relapsers. Death was reported in 4 patients (8%), post-treatment probably unrelated to treatment, due to myocardial infarction, pulmonary edema, severe hypotension on hemodialysis sessions, and shock due to blood loss in retroperitoneal hematoma following peritoneal dialysis. Hepatic decompensation, hypersensitivity (angioedema), teratogenicity, and drug interactions did not occur in any patient (0%). Other

Table 2 Comparison between baseline (week 0) and Δ change in laboratory investigations from baseline at weeks 4, 8, and 12 as regards blood counts and liver function tests

Laboratory investigations	Baseline (week 0)	Week 4	Week 8	Week 12
WBC (10^3/ml)				
Mean ± SD	6.648 ± 2.947	6.759 ± 2.741	6.695 ± 3.641	6.530 ± 2.371
Range	(2.7– 20.7)	(3.5–16.2)	(3.2–27.43)	(3.5–14.2)
Δ change				
Mean ± SD		0.111 ± 2.917	0.047 ± 4.189	− 0.118 ± 2.958
P-value		0.789	0.938	0.780
HGB (g/dl)				
Mean ± SD	12.050 ± 1.835	10.282 ± 1.962	9.278 ± 1.747	8.959 ± 1.728
Range	(10–16.2)	(7–13.9)	(6.4–13)	(4.2–12.4)
Δ change				
Mean ± SD		− 1.768 ± 2.168	− 2.772 ± 2.309	− 3.091 ± 2.248
P-value		**< 0.001***	**< 0.001***	**< 0.001***
PLT (10^3/ml)				
Mean ± SD	208.820 ± 62.666	216.860 ± 84.864	224.300 ± 65.347	229.380 ± 84.586
Range	(108–372)	(92–589)	(105–437)	(114–570)
Δ change				
Mean ± SD		8.040 ± 88.070	15.480 ± 63.499	20.560 ± 86.368
P-value		0.522	0.091	0.099
Total bilirubin (mg/dl)				
Mean ± SD	0.543 ± 0.171	0.770 ± 0.404	0.635 ± 0.257	0.664 ± 0.315
Range	(0.19–1)	(0.3–2.5)	(0.1–1.5)	(0.11.9)
Δ change				
Mean ± SD		0.227 ± 0.443	0.092 ± 0.278	0.121 ± 0.328
P-value		**0.001***	**0.023***	**0.012***
Direct bilirubin (mg/dl)				
Mean ± SD	0.351 ± 0.353	0.270 ± 0.206	0.245 ± 0.190	0.238 ± 0.169
Range	(0–1.3)	(0–0.98)	(0–0.98)	(0.03–0.8)
Δ change				
Mean ± SD		− 0.081 ± 0.404	− 0.106 ± 0.379	− 0.113 ± 0.392
P-value		0.164	0.054	**0.048***
Serum albumin (g/dl)				
Mean ± SD	3.866 ± 0.560	4.018 ± 0.555	3.860 ± 0.589	3.864 ± 0.448
Range	(2–5.1)	(2.7–5.3)	(2–5.4)	(2.8–4.8)
Δ change				
Mean ± SD		0.152 ± 0.770	− 0.006 ± 0.669	− 0.002 ± 0.563
P-value		0.169	0.950	0.980
INR				
Mean ± SD	1.112 ± 0.114	1.083 ± 0.146	1.092 ± 0.113	1.069 ± 0.102
Range	(0.88–1.4)	(0.9–1.87)	(0.77–1.31)	(0.88–1.36)
Δ change				
Mean ± SD		− 0.029 ± 0.172	− 0.020 ± 0.145	− 0.043 ± 0.136
P-value		0.240	0.338	**0.030***
AST (IU/l)				
Mean ± SD	35.634 ± 33.177	27.440 ± 17.126	26.280 ± 12.876	29.350 ± 16.783
Range	(2–222)	(6–84)	(8–52)	(6–94)
Δ change				
Mean ± SD		− 8.194 ± 31.806	− 9.354 ± 32.381	− 6.284 ± 31.124
P-value		0.075	**0.046***	0.160

Table 2 (continued)

Laboratory investigations	Baseline (week 0)	Week 4	Week 8	Week 12
ALT (IU/l)				
Mean ± SD	34.736 ± 20.096	19.060 ± 13.549	14.390 ± 5.830	17.422 ± 10.136
Range	(9–94)	(4–64)	(4–30)	(5–64)
Δ change				
Mean ± SD		− 15.676 ± 19.446	− 20.346 ± 19.962	− 17.314 ± 19.893
P-value		**< 0.001***	**< 0.001***	**< 0.001***

WBC white blood cell count, *HGB* hemoglobin level, *PLT* platelet count, *INR* international normalized ratio, *AST* aspartate transaminase, *ALT* alanine transaminase

* highly significant

Table 3 HCV PCR of the studied group at weeks 24 and 36 of DAA therapy

PCR	Week 0		Week 24 (SVR 12)		Week 36 (SVR24)	
	N	%	*N*	%	*N*	%
Positive	50	100.00	2	4.00	4	8.00
Negative	0	0.00	48	96.00	46	92
Total	50	100.00	50	100.00	50	100.00

Table 4 Correlation between ribavirin dose reduction or discontinuation and PCR for HCV week 24 (SVR rate)

PCR for HCV, week 24	Ribavirin dose reduction or discontinuation						Chi-square	
	Yes		No		Total			
	N	%	*N*	%	*N*	%	X^2	*P*-value
Positive	0	0.00	2	4.35	2	4.00	0.181	0.670
Negative	4	100.00	44	95.65	48	96.00		
Total	4	100.00	46	100.00	50	100.00		

Table 5 Prevalence of different known side effects of DAA therapy among the studied group

Side effects	Number	Percent
Fatigue/asthenia	44	88.00
Anemia (Hb < 10 g/dl)	42	84.00
GIT upset	10	20.00
Psychiatric (sleep disorder)	8	16.00
Metabolic (decreased appetite)	8	16.00
Respiratory distress	6	12.00
Nervous system (headache/dizziness)	6	12.00
Musculoskeletal (muscle spasms)	4	8.00
Dermatologic (skin reactions/itching)	3	6.00
Hypersensitivity (angioedema)	0	0.00
Teratogenicity/embryo death	0	0.00
Drug interactions	0	0.00
Hepatic decompensation	0	0.00
Others	11	22.00

Table 6 Anemia (Hb < 10 g/dl) managements

Anemia		
Management done	*N*	%
ESA (added or increased dose)	26	52.00
Blood transfusion	7	14.00
Ribavirin stopped	3	6.00
Ribavirin reduced	1	2.00

ESA erythropoiesis-stimulating agents

events occurred in 11 patients (22%)% during therapy, not yet proved to be related or not to the drug. They were parenchymal liver changes in ultrasound at the end of therapy, after being normal before therapy (in 3 patients), thrombocytopenia, increased alkaline phosphatase, hiccough, deterioration of hypertension, urinary tract infection, lower limb cellulitis, vaginal bleeding, and chest infection (in 1 patient each). These results go in line with the RUBY-I trial [14] and Lawitz et al. [18] study in the USA, in which anemia was the

Table 7 Correlation between ribavirin dose reduction or discontinuation and relapse/non-response to treatment

Relapses and non-response to treatment	Ribavirin reduction or discontinuation						Chi-square	
	Yes		No		Total			
	N	%	*N*	%	*N*	%	X^2	*P*-value
No relapse, no non-response	4	100.00	42	91.30	46	92.00	0.378	0.828
Relapse	0	0.00	2	4.35	2	4.00		
Non-response to ttt	0	0.00	2	4.35	2	4.00		
Total	4	100.00	46	100.00	50	100.00		

Table 8 Relation between HCV viral load and failure of treatment (virologic failure or relapse)

PCR for HCV (IU/ml), week 0	Failure of treatment (virologic failure or relapse)		*T*-test	
	Yes	No	*t*	*P*-value
Range	421.581 – 4.000.000	10.601 – 23.102.362	– 0.158	0.875
Mean ± SD	2277895.250 ± 1991532.363	2659723.109 ± 4769782.021		

most common adverse event. But, unlike the study of Atsukawa et al. [16] in Japan, which used a ribavirin-free regimen, and Hanno et al. [17] in Egypt, which enrolled different CKD stages (2–5) in which pruritis was the most common adverse event.

As regards follow-up CBC, liver enzymes, and liver functions in weeks 4, 8, and 12, we found that HGB levels decrease, total and indirect bilirubin increase due to ribavirin (RBV)-associated hemolysis [19], and AST, ALT, and INR levels decrease. This is in agreement with Hanno et al. [17] study in Egypt.

As regards anemia being the most common adverse event, several studies including ours confirm 2 observations. First, anemia during HCV treatment occurs higher with more advanced renal failure (more in CKD 5 dialysis patients than CKD 2–5 than non-CKD) shown by Osinusi et al. [20]. Second, it occurs in the majority of the studies with ribavirin including regimens. This was obvious in our study which included both advanced renal failure, ESRD patients on regular hemodialysis, and ribavirin including regimen.

To overcome anemia in ESRD receiving HCV therapy, ribavirin dose is 200 mg/day (typically starting at 200 mg three times weekly and titrating up to 200 mg/day as tolerated). Ribavirin should be discontinued if the hemoglobin level decreases by more than 2 g/dl despite the use of erythropoietin according to (AASLD) guidelines [11]. SVR12 rate in our study was achieved in 100% of patients who had to stop or modify RBV dose; this means that RBV absence did not affect the SVR12 in these patients. This leads us to think of RBV-free regimens in ESRD patients as a safer option of treatment to avoid severe hemolytic anemia with ribavirin that occurs with these patients despite various anemia managements during therapy.

The current guidelines recommend two ribavirin-free regimens for patients with HCV infection and stage 4 or 5 CKD, elbasvir/grazoprevir, which is approved for the treatment of patients with GT1 or 4 infection, and glecaprevir/pibrentasvir, which has pan-genotypic activity. Both show high efficacy (SVR12) with no anemia as adverse event in ESRD. For this reason, the regimen used in our study ombitasvir/paritaprevir/ritonavir and ribavirin would be considered to be alternatives to the 2 recommended regimens [18]. However, these 2 regimens are not yet available in Egypt.

There were several limitations in our study. First, we could not study the effect of our drug on CKD staging because our patients were all ESRD, CKD 5 on regular hemodialysis. Second, ribavirin caused hemolytic anemia, which was an inconvenient adverse event. Third, only 4 patients had to stop or modify RBV which was a small number. So, we could not draw a firm conclusion about RBV-free ombitasvir/paritaprevir/ritonavir regimen as being effective alone in the treatment of HCV. Fourth, our study had 2 virologic failures and 2 relapses. We correlated between them and RBV dose modification and also HCV viral load but there was no statistically significant relation. It was difficult to know the exact causes of failure of treatment and relapse due to a small number of them. However, other studies attribute the cause to resistance-associated substitutions in the NS3/4A region before treatment. For instance, Q80K shows a threefold resistance to paritaprevir (NS3/4A protease inhibitor). The detection rate of pre-existing D168 substitution is also found [21]. Fifth, we did not do genotyping on the

patients assuming that genotype 4 is the most common variant of HCV throughout Egypt and represents more than 90% of HCV isolates from Egyptian patients [22]. So, we could not study the effect of our drug in different HCV genotypes (1–6) However, it is obvious that our drug shows high efficacy in genotype 4 assuming that most HCV Egyptians have genotype 4.

Conclusion

Our results confirm the efficacy of Qurevo "ombitasvir/paritaprevir/ritonavir" with ribavirin combination therapy in ESRD patients on regular hemodialysis with HCV infection, with anemia as the most frequent adverse event.

The following are the recommendations:

1. We recommend Qurevo (ombitasvir/paritaprevir/ritonavir) with ribavirin regimen.
2. For ESRD patients with HCV infection.
3. We also recommend monitoring of hemoglobin and total bilirubin levels at weeks 4, 8, and 12 for early detection of anemia or hepatic decompensation which may lead to drug discontinuation and as a result we highly recommend RBV-free new regimens in ESRD patients like elbasvir/grazoprevir or glecaprevir/pibrentasvir as a safer option of treatment to avoid severe hemolytic anemia with RBV that occurs with ESRD patients.
4. A specialized hepatologist and nephrologist should be found in hepatic virology clinics to help ESRD patients plan the most suitable HCV antiviral drug regimen for each patient.
5. Studies should be done on qualitative HCV genotyping to detect exact causes of virologic failure/relapse with the drug (resistance-associated substitutions in the NS3/4A region before treatment, e.g., presence of Q80K and pre-existing D168 substitution).

Abbreviations

WHO: World Health Organization; HCV: Hepatitis C virus; ESRD: End-stage renal disease; CKD: Chronic kidney disease; DAA: Direct-acting antiviral agents; Hb: Hemoglobin; GIT: Gastrointestinal tract; HIV: Human immunodeficiency virus; PCR: Polymerase chain reaction; AASLD: American Association for the Study of Liver Diseases; AST: Aspartate aminotransferase; ALT: Alanine transaminase; INR: International normalization ratio; RBV: Ribavirin; GT: Treatment-naïve genotype; SVR12: Sustained virologic response after 12 weeks; SVR24: Sustained virologic response after 24 weeks.

Acknowledgements

Not applicable.

Authors' contributions

Dr. IS followed up the patients from her dialysis unit ward during the research. Dr. OA provided the treatment protocol for the patients. Dr. HE revised the paper. Dr. CK provided the idea and manuscript editing and reviewing. Dr. MM collected the data. All authors read and approved the final manuscript.

Funding

This was self-funded by the authors.

Availability of data and materials

Please contact the authors for data requests.

Declarations

Ethics approval and consent to participate

This study has conformed with the ethics committee of the hospital and according to the Declaration of Helsinki for ethical principles WMA.

Consent for publication

Not applicable (no personal data of patients included).

Competing interests

The authors declare that they have no competing interests.

Received: 15 January 2022 Accepted: 3 June 2022
Published online: 14 June 2022

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