The Egyptian Journal of Internal Medicine

RESEARCH

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Micro-elimination of hepatitis C in patients with chronic kidney disease: an Egyptian single-center study

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Abstract

Background and aims: Micro-elimination of hepatitis C in renal patients is crucial. This study aims to assess the efficacy and safety of directly acting antivirals in chronic kidney disease patients and the effect of treatment on kidney functions.

Results: This prospective cohort study included 77 chronic HCV-infected patients with chronic kidney disease. Patients were consented and treated for 12 weeks with either sofosbuvir and daclatasvir ± ribavirin if glomerular filtration rate was > 30 mL/min per 1.73m^2 or ritonavir-boosted paritaprevir-ombitasvir-ribavirin if it was < 30 mL/min per 1.73m^2. Patients were divided into two categories (responders versus non-responders). Predictors of response to treatment were statistically analyzed through logistic regression analysis. Sixty-two patients received ritonavir-boosted paritaprevir-ombitasvir-ribavirin, 3 received sofosbuvir and daclatasvir, and 12 received sofosbuvir and daclatasvir plus ribavirin. Most patients were on hemodialysis ($n = 36$) while 31 were stage 3 kidney disease. All patients completed their treatment course; ribavirin doses were adjusted or stopped in patients who developed anemia (40%). Seventy-two patients (93.5%) achieved sustained virological response 12 weeks following end-of-treatment. Five patients (6.5%) were non-responders, 4 of whom were on hemodialysis ($p = 0.179$). All non-responders were on ritonavir-boosted paritaprevir-ombitasvir-ribavirin. The mean serum creatinine level at weeks 4 and 8 of treatment demonstrated significant improvement compared to pretreatment values ($p < 0.001$) in patients on conservative therapy.

Conclusion: Treatment of chronic kidney disease patients for chronic hepatitis C with directly acting antivirals is safe, efficacious with high response rates and likely to improve renal functions if started early in the course of kidney disease.

Keywords: Micro-elimination, Hepatitis C, HCV, CKD, DAA, Direct-acting antivirals

Introduction

Chronic hepatitis C (HCV) is a significant public health problem. The World Health Organization (WHO) estimated the global burden of HCV during 2019 [1] to be around 58 million people with 1.5 million new chronic HCV infections.

Infected people have high morbidity and mortality because of liver-related complications including

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progression to cirrhosis, HCC, decompensation, and liver cell failure. Moreover, extrahepatic manifestations as cardiovascular diseases, impaired glucose metabolism, cryoglobulinemic vasculitis, chronic kidney disease (CKD), and B cell non-Hodgkin lymphoma are associated with HCV infection [2, 3].

Chronic hepatitis C can be considered as an independent risk factor in the development of chronic kidney disease CKD, as it is associated with more than 50% increase in the risk of proteinuria and a 43% increase in the incidence of CKD [4]. Moreover, cryoglobulinemic vasculitis is associated with membranoproliferative glomerulonephritis. HCV seropositive patients have a lower graft survival after kidney transplantation [3]. Also, persons with chronic HCV infection and CKD have a higher risk of progression to end-stage renal disease (ESRD) and an increased mortality in those on dialysis [5]. On the other hand, patients on hemodialysis have a significantly higher prevalence of HCV infection. Such strong association and poor prognosis signified the importance of treatment of HCV in CKD patients [3].

Before the directly acting antivirals (DAAs) era, treating HCV infection in patients with CKD was challenging owing to toxicities associated with interferon (INF). Reduced renal clearance of INF increased the risk and severity of INF-related complications. Low sustained virological response (SVR) rates and discontinuation rates limited INF applicability. The toxicity of INF was aggravated by the concomitant use of ribavirin (RBV) which was also renally excreted. In addition, the combination of RBV and INF was associated with hematologic toxicity in patients already at risk for anemia [6].

Sofosbuvir approval as a pan-genotypic NS5B inhibitor facilitated the treatment of HCV infection in the general population by leading to high rates of SVR with very few side effects. Most DAAs are hepatically cleared except for sofosbuvir which primarily undergoes renal clearance [7].

Being a major endemic health problem in Egypt, the treatment of HCV in Egypt has been a national priority since 2006. The Egyptian Ministry of Health and Population (MOH) launched the National Committee for Control of Viral Hepatitis (NCCVH) in 2006 to control the HCV epidemic in Egypt. Accordingly, a mass treatment program started using pegylated IFN and RBV between 2007 and 2015 [8].

Following the advent of DAAs, the prices were negotiated in 2014 and Egypt was the first low middle-income country to embark on a state-funded mass treatment program. This was followed, in 2018, by a nationwide screening and treatment program including adolescents targeting elimination of HCV by 2020. Almost 60 million adults and children have been tested and HCV-infected patients were referred to treatment. Almost 3.5 million patients have been treated in Egypt in an HCV elimination program considered to be the largest globally [9].

This study aimed at monitoring the safety and efficacy of DAAs in CKD patients as well as assessing the effect of the HCV treatment on kidney functions of CKD patients on conservative treatment.

Patients and methods

Study population and design

This prospective clinical study included CKD patients with chronic HCV infection referred to the viral hepatitis treatment center at Ain Shams Research Institute (MASRI) between January 2016 and June 2018. Seventy-seven patients were enrolled in this study. Chronic kidney affection was defined as (GFR < 60 ml/min/1.73 m^2 for more than 3 months) [10].

According to the national program protocol [11], inclusion criteria were as follows

Patients who were HCV-RNA positive by real-time polymerase chain reaction testing (RT-PCR) for at least 6 months before inclusion in the study and able to sign an informed consent who are CKD patients and whose age ranged between 18 and 75 years. Cardiac assessment using ECG, echocardiography, and cardiology consultation was applied for patients older than 65 years.

Exclusion criteria

The exclusion criteria are as follows: hyperbilirubinia > 3 mg/dl, hypoalbuminia < 2.8gm/dl, increased INR ≥ 1.7, thrombocytopenia < 50,000/mm^3, HBsAg positive, and past or current malignancy (extra hepatic) except after 2 years of disease-free interval. Also, hepatocellular carcinoma (HCC) except after 6 months of intervention aiming at cure, provided that there was no evidence of activity by dynamic imaging (CT or MRI). Pregnant and lactating women or those who were unable to use effective contraception and inadequately controlled diabetic patients (HbA1c ≥ 9%).

Glomerular filtration rate (GFR) was calculated for all patients by Modification of Diet in Renal Disease formula (MDRD); then, all enrolled patients were classified into 5 stages as follows [11]:

Stage 1: Normal or high GFR (GFR > 90 mL/min) (1 patient)
Stage 2: Mild CKD (GFR = 60–89 mL/min) (4 patients)
Stage 3: Moderate CKD (GFR = 30–59 mL/min) (31 patients)
Stage 4: Severe CKD (GFR = 15–29 mL/min) (5 patients)

Stage 5: End stage CKD (GFR < 15 mL/min) (36 patients)

The Egyptian national treatment protocol for HCV-infected patients [12] and available DAAs at the time of the study guided DAA selection in recruited patients in addition to the liver and renal function tests, full blood count, and presence of comorbidities.

Accordingly, 62 patients (from 5 stages) received ritonavir-boosted paritaprevir-ombitasvir-ribavirin (rPAR/OMB/RBV) for 12 weeks, 3 patients received sofosbuvir (400 mg/day) and daclatasvir (60 mg/day) (SOF/DAC) (1 patient with stage 2 and 2 patients with stage 3), and 12 patients received SOF/DAC/RBV (1 patient with stage 2, 9 patients with stage 3, and 2 patients with stage 5).

The two ESRD patients on hemodialysis were given SOF/DAC/RBV (with sofosbuvir given every other day) because they had deteriorated liver functions with mild elevation of INR and/or bilirubin (difficult to treat patients according to the Egyptian national protocol).

Nephrology consultation was requested before enrollment to determine treatment eligibility and recommended ribavirin dosing and timing in relation to dialysis. In patients on hemodialysis (36 patients), the patients were made aware of the risk of re-infection and this was included in the signed informed consent.

Baseline data

A standardized patient report form included full history, clinical examination, laboratory investigations including complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, total and direct bilirubin, prothrombin time, INR, creatinine, hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV-Ab), HBA1c if diabetic, serum alpha-fetoprotein (AFP), quantitative HCV-RNA (RT-PCR), and abdominal ultrasound.

These data were monitored monthly during drug administration for monitoring of complications and adverse events except for AFP, ultrasonography (unless there was marked elevation of transaminases), HBsAg, and HCV-Ab. Quantitative HCV-RNA was tested at weeks 4 and week 12 after the end of treatment.

Twelve weeks after the end of DAA therapy

Patients were reassessed by history taking, clinical examination, and laboratory data including CBC, ALT, AST, serum albumin, total and direct bilirubin, prothrombin time, INR, serum creatinine, AFP, ultrasonography, and quantitative HCV-RNA (RT-PCR).

Ethics

Every patient signed an informed consent after full explanation and assurance that the patient will receive complete medical service even if he/she did not join the study population and/or decide to withdraw from the study at any time point.

The study had been performed in accordance with the ethical standards. The Faculty of Medicine, Ain Shams University Ethical Committee (FWA00017585) approval was taken before starting the study in December 2015, and the study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki [13].

Statistical methods

Statistical SPSS Package program version 25 for Windows (SPSS, Inc., Chicago, IL) was used to conduct the statistical analysis. Descriptive quantitative data is represented as a minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative normally distributed data, while it was represented for qualitative data as number and percentage. For non-normally distributed data, median and IQR were used. All statistical analysis was significant at 0.05 level of probability ($P \leq 0.05$). Tests of significance used were two independent *t* test or Fisher's exact test.

Results

This study included 77 CKD patients enrolled from MASRI for treatment of chronic HCV infection. Patients' ages ranged between 46.5 and 65 years, and 45 (58.4%) patients were males. Out of the thirty-five cirrhotic patients, 34 were Child A score except one who was classified as Child B. Forty-two patients had chronic hepatitis C with non-cirrhotic liver on ultrasound confirmed by laboratory findings. Only one patient was interferon experienced while all other included patients were treatment naïve. Forty-four (57.1%) patients were hypertensive, 26 (33.8%) were diabetic, and 7 (9.1%) patients had ischemic heart disease (Table 1).

Associated co-morbidities and complications included 65 (84.4%) patients with diabetic and/or hypertensive kidney disease, 9 (11.7%) patients with obstructive uropathy, one (1.3%) patient with polycystic kidney disease, and one (1.3%) with cryoglobulinemia. Forty-one (53.2%) patients had end stage renal disease, 36 of whom were on hemodialysis.

Efficacy of DAAs

SVR 12 (negative RT-PCR for HCV after 12 weeks) was achieved in 72 (93.5%) patients (32 were on hemodialysis). Five (6.5%) patients were non-responders with

Table 1 Demographic and disease characteristics of studied patients with chronic kidney disease

Patients **Variable**	**Study population** ***n*** **= 77** ***N*** **(%)**	**r PAR/OMB/RBV** ***n*** **= 62** ***N*** **(%)**	**SOF/DAC** ***n*** **= 3** ***N*** **(%)**	**SOF/DAC/RBV** ***n*** **= 12** ***N*** **(%)**
Age				
Mean ± SD	54.75 (11.67)	52.68 (11.18)	61.33(15.31)	63.83 (8.92)
Median (IQR)	55 (46.5–65)	52.5 (44.75–61.5)	67 (44–73)	64.5 (58.5–71)
Gender: *n* (%)				
Female	32 (41.6)	28 (45.2)	1 (33.3)	3 (25)
Male	45 (58.4)	34 (54.8)	2 (66.7)	9 (75)
Liver ultrasonographic picture: *n* (%)				
Normal	42 (54.5)	36 (58.1)	2 (66.7)	4 (33.3)
Coarse echopattern	23 (29.9)	20 (32.3)	1 (33.3)	2 (16.7)
Cirrhotic	12 (15.6)	6 (9.7)	-	6 (50)
Liver state: *n* (%)				
Child score A 5–6/chronic hepatitis	76 (98.7)	62 (100)	3 (100)	11 (91.7)
B 7–9	1 (1.3)	-		1 (8.3)
Hemodialysis; n(%)				
No	41 (53.2)	28 (45.2)	3 (100)	10 (83.3)
Yes	36 (46.8)	34 (54.8)		2 (16.7)
Anemia during treatment: *n* (%)				
No	47 (61)	37 (59.7)	3 (100)	7 (58.3)
Yes	30 (39)	25 (40.3)	-	5 (41.7)
eGFR: *n* (%)				
Stage 1	1 (1.3)	1 (1.6)	-	-
Stage 2	4 (5.2)	2 (3.2)	1 (33.3)	1 (8.3)
Stage 3	31 (40.3)	20 (32.3)	2 (66.7)	9 (75)
Stage 4	5 (6.5)	5 (8.1)	-	-
Stage 5	36 (46.8)	34 (54.8)	-	2 (16.7)

r PAR/OMB/RBV ritonavir-boosted paritaprivir, ombitasvir, and ribavirin, *SOF/DAC* Sofosbuvir and daclatasvir, *SOF/DAC/RBV* Sofosbuvir, daclatasvir, and ribavirin, *eGFR* Estimated glomerular filtration rate

detectable HCV-RNA at 12 weeks. Four patients out of five in the non-responder group were on hemodialysis ($P = 0.179$).

HCV-RNA results were similar at both 4 and 12 weeks after treatment with 100% SVR 12 in both SOF/DAC and SOF/DAC/RBV-treated patients. The 5 non-responders were treated with rPAR/OMB/RBV.

Pre- and post-treatment laboratory and ultrasound data

The median values of serum creatinine level (in patients not on hemodialysis, $n = 41$) at weeks 4 and 8 of treatment showed significant improvement compared to the pretreatment value (Fig. 1). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, bilirubin, and other laboratory parameters along with ultrasonography findings among patients on all drug regimens did not show significant differences (Table 2). Also, on comparing responders and non-responders, there were no significant differences in pre- or post-treatment laboratory tests or demographic data between both groups (Tables 3 and 4).

Safety of DAA regimens

Anemia was the commonest treatment-related complication, occurring in 30 (39%) patients who were on ribavirin containing regimens; 18 (23.4%) patients had fatigue, itching, and epigastric pain; and one (1.3%) patient had diarrhea. Mild elevation of serum creatinine occurred in 2 (2.6%) patients who were not on hemodialysis, one was on rPAR/OMB/RBV and the other was on SOF/DAC but treatment was continued with close follow-up under the strict supervision of the nephrologists, and both achieved SVR with no permanent renal morbidity. Serious adverse events were reported in two patients, and one patient had hepatocellular carcinoma (HCC) discovered on follow-up 12 weeks after treatment. He took SOF/DAC for 24 weeks, and he was the only enrolled patient with Child score B. Another patient with end-stage renal disease

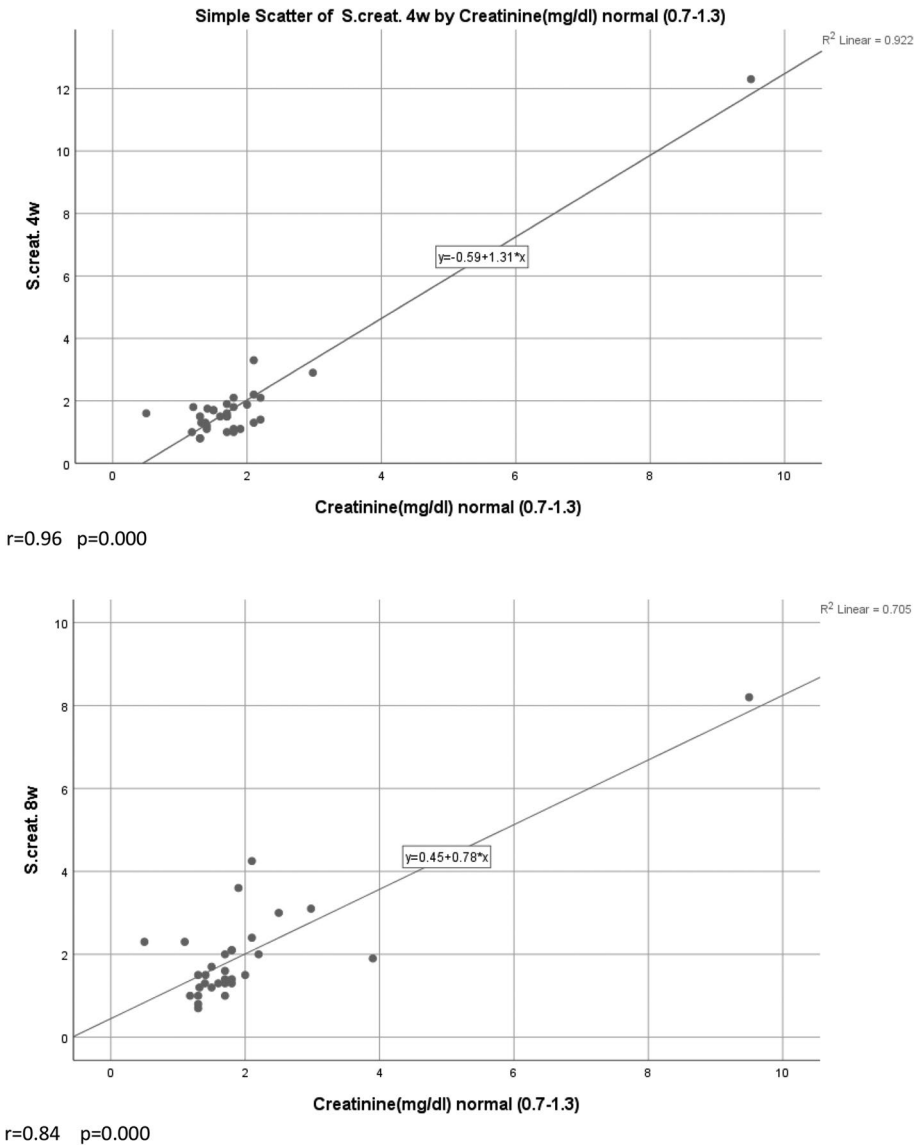

Fig. 1 Correlation between creatinine levels before and during treatment (weeks 4 and 8) in patients not on hemodialysis. Legend: 4 weeks ($r=0.96$, $P<0.001$) and 8 weeks ($r=0.84$, $P<0.001$) of follow-up serum creatinine (s.creat) levels in CKD patients not on hemodialysis ($n=41$)

(ESRD) on hemodialysis developed uncontrolled hypertension during treatment with rPAR/OMB/RBV which improved after cessation of DAAs.

All included patients completed their treatment course with no treatment discontinuations; however, ribavirin doses were adjusted or stopped in patients who developed anemia. The ribavirin was decreased when hemoglobin level dropped below 10 g/dL or declined by more than 3 g/dL. Ribavirin was stopped in patients whose hemoglobin less than 8.5 g/dL.

Discussion

Based on the detrimental outcomes of HCV infection in CKD patients, especially those on hemodialysis [14], and the high prevalence (4.7–41.9%) of hepatitis C in hemodialysis settings in developing countries [15], global efforts for elimination of HCV in renal patients have been implemented. The concept of "micro-elimination" has been introduced to approach the global burden of HCV infection in special populations in order to reach the aspired targets of combatting the viral predominance [16]. Screening, providing easy access to medications, and monitoring treatment and cure are the main methods to

Table 2 Comparisons between groups as regards follow-up laboratory tests

Variable	Group 1, *n* = 62 rPAR/OMB/RBV			Group 2, *n* = 3 SOF/DAC			Group 3, *n* = 12 SOF/DAC/RBV		
	Mean ± SD	SE	Median (IQR)	Mean ± SD	SE	Median (IQR)	Mean ± SD	SE	Median (IQR)
WBC wk 4	7.31 ± 2.83	0.41	6.55 (5.23–8.6)	6.5 ± 2.1	1.21	7.4	6.15 ± 1.86	0.62	6.1 (4.6–7.4)
WBC wk 8	6.85 ± 2.08	0.31	6.85 (5.53–8.33)	7.77 ± 1.2	0.69	7.7	6.6 ± 3.05	1.02	6.2 (4.5–8)
WBC wk 12	6.68 ± 2.28	0.36	6 (5.25–8.25)	5.85 ± 0.35	0.25	5.85	5.8 ± 2.61	0.87	5.5 (3.75–7.95)
HB wk 4	11.34 ± 2.41	0.32	11 (9.25–13)	12.43 ± 2.35	1.35	11.9	12.29 ± 2.61	0.75	12.8 (11.4–13.48)
HB wk 8	10.34 ± 2.19	0.29	10.05 (8.88–11.85)	12.17 ± 2.67	1.54	11.8	10.91 ± 3.04	0.88	12 (8.45–13.15)
HB wk 12	9.84 ± 2.2	0.32	10 (7.95–11.33)	12.05 ± 1.34	0.95	12.05	11.13 ± 2.33	0.78	11.6 (9.35–13.4)
Platelet wk 4	219.19 ± 91.01	11.95	201 (154.5–262.25)	180.33 ± 22.3	12.88	189	182.25 ± 54.44	15.72	183.5 (134.25–208.5)
Platelet wk 8	220.35 ± 80.32	10.64	210 (161–253.5)	189.67 ± 21.08	12.17	178	177.92 ± 60.17	17.37	178.5 (117–239.25)
Platelet wk 12	229.89 ± 96.17	14.34	225 (153.5–268)	169.5 ± 21.92	15.5	169.5	178.13 ± 59.54	21.05	177.5 (117.5–242.5)
ALT wk 4	22.23 ± 16.77	2.16	18 (11–28.75)	28.33 ± 21.73	12.55	20	26 ± 23.93	6.91	13.5 (10.25–47.75)
ALT wk 8	17.09 ± 9.34	1.27	15 (11–21)	18.67 ± 10.26	5.93	16	21.33 ± 17.83	5.15	16.5 (10.5–23)
ALT wk 12	16.24 ± 10.06	1.48	14 (11–18.25)	25.5 ± 23.33	16.5	25.5	14.9 ± 5.45	1.72	14.5 (10–20.5)
AST wk 4	23.99 ± 16.63	2.15	20 (14–28)	26 ± 16.52	9.54	25	31.33 ± 27.2	7.85	21 (13.25–43.25)
AST wk 8	20.82 ± 12.79	1.74	19 (13.88–25)	18 ± 6.08	3.51	21	27.42 ± 22.69	6.55	20.5 (14.5–31.25)
AST wk 12	19.33 ± 14.5	2.16	16 (12.5–21.5)	20 ± 14.14	10	20	19 ± 7.92	2.5	15.5 (13.75–27.25)
Total bilirubin wk 4	0.82 ± 0.41	0.06	0.7 (0.6–1)	0.87 ± 0.15	0.09	0.9	0.87 ± 0.39	0.12	0.8 (0.5–1.1)
Total bilirubin wk 8	0.74 ± 0.49	0.07	0.65 (0.5–0.9)	0.5 ± 0.000	0.000	0.5(0.5)	0.83 ± 0.47	0.14	0.7 (0.6–1.2)
Total bilirubin wk 12	0.69 ± 0.38	0.06	0.6 (0.4–0.9)	0.6 ± 0.09	0.07	0.6	0.76 ± 0.46	0.15	0.7 (0.48–0.98)
S.creatinine wk 4	5.19 ± 3.63	0.5	5.52 (1.73–7.85)	1.28 ± 0.67	0.48	1.28	2.46 ± 2.01	0.61	1.6 (1.5–2.1)
S.creatinine wk 8	5.09 ± 2.97	0.42	5.3 (2.1–7.25)	1.07 ± 0.4	0.23	1	2.81 ± 2.84	0.89	1.65 (1.28–3.1)
S.creatinine wk 12	4.48 ± 3.43	0.59	3.8 (1.53–6.57)	1.35 ± 0.83	0.59	1.35	3.26 ± 3.34	1.26	1.6 (1.3–5.5)
Albumin wk 4	4.01 ± 0.53	0.073	4 (3.78–4.3)	3.95 ± 0.071	0.050	3.95	3.57 ± 0.55	0.17	3.55 (3–4.13)
Albumin wk 8	3.94 ± 0.51	0.074	3.95 (3.53–4.28)	4 ± 0.1	0.058	4	3.58 ± 0.44	0.15	3.5 (3.2–3.95)
Albumin wk 12	3.88 ± 0.52	0.085	3.9 (3.55–4.15)	4.54 ± 0.198	0.14	4.54	3.57 ± 0.57	0.19	3.7 (3–4)

AST aspartate aminotransferase, *ALT* Alanine aminotransferase, *WBC* leucocytic count, *Hb* Hemoglobin

Table 3 Relation between response to treatment and the quantitative variables

	Responders *n* = 72 mean ± SD	Non-responders *n* = 5 mean ± SD	*t* test	*P* value
Age	54.88 ± 11.59	53 ± 14.02	0.375	0.731
platelets × 10^3/mm^3	198.22 ± 69.78	217.5 ± 70.48	–0.54	0.59
AST (IU/L)	36.74 ± 22.54	49.5 ± 21.64	–1.1	0.27
ALT (IU/L)	42.47 ± 27.54	44.25 ± 40.87	–0.123	0.9
INR	1.15 ± 0.15	1.07 ± 0.11	1.06	0.29
Albumin (g/dL)	3.87 ± 0.66	4 ± 0.00	–0.379	0.71
AFP (IU/L)	9.89 ± 37.42	9.5 ± 16.34	0.02	0.98
Total bilirubin (mg/dL)	0.63 ± 0.26	0.55 ± 0.264	0.62	0.54
WBCs × 10^3/mm^3	6.91 ± 2.65	8.15 ± 2.7	–0.91	0.37
Hb (g/L)	12.62 ± 2.47	12.33 ± 0.47	0.79	0.44
Creatinine (mg/dl)	3.51 ± 2.78	6.22 ± 3.83	–1.86	0.066

N.B. test of significance is two independent *t* test

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio,

AFP serum alpha-fetoprotein, *WBC* leucocytic count, *Hb* hemoglobin

Table 4 Relation between response to treatment and the qualitative variables

	Responders $n=72$	Non responders $n=5$	Fisher exact	*P* value	OR (95%CI)
Gender					
Female	28 (87.5)	4 (12.5)		0.154	0.159 (0.17–1.497)
Male	44 (97.8)	1 (2.2)			
ECG					
Normal	70 (93.3)	5 (6.7)		1	0.933 (0.879–0.992)
Abnormal	2 (100)	0			
Liver					
Normal	40 (95.2)	2 (4.8)	0.958	0.84	
Abnormal	21 (91.3)	2 (8.7)			
Cirrhotic	11 (91.7)	1 (8.3)			
Child score					
A5–6	71 (93.4)	5 (6.6)		1	0.934 (0.88–0.992)
B7–9	1 (100)	0			
Type of treatment					
PAR/OMB/RBV	57 (91.9)	5 (8.1)	0.793	0.661	
SOF/DAC	3 (100)	0			
SOF/DAC/RBV	12 (100)	0			
Hemodialysis					
No	40 (97.6)	1 (2.4)		0.179	5 (0.532–46.97)
Yes	32 (88.9)	4 (11.1)			
Anemia					
No	44(93.6)	3(6.4)		1	1.05 (0.17–6.67)
Yes	28(93.3)	2(6.7)			
eGFR					
Stage 1	1 (100)	0			
Stage 2	4 (100)	0	6.597	0.175	
Stage 3	31 (100)	0			
Stage 4	4 (80)	1 (20)			
Stage 5	32 (88.9)	4 (11.1)			

ECG electrocardiogram; *eGFR* estimated glomerular filtration rate; *r PAR/OMB/RBV* ritonavir-boosted paritaprivir, ombitasvir, and ribavirin; *SOF/DAC* sofosbuvir and daclatasvir; *SOF/DAC/RBV* sofosbuvir, daclatasvir, and ribavirin

achieve micro-elimination [17]. Since renal patients are prone to a higher risk of nosocomial viral transmission [18, 19], achieving treatment goals using DDAs should be thoroughly sought in this high-risk population specially in resource-limited settings where prevalence is highest [15].

The current study included 77 patients with CKD in stages 1–5 (Table 1) with 46.8% on regular hemodialysis during treatment (stage 5). Sofosbuvir and daclatasvir, the most commonly used combination in the Egyptian program, with or without ribavirin achieved 100% sustained virological response at 12 weeks albeit the number was very small. This combination is the most commonly used in resource-limited settings for its affordability and has been shown to induce sustained virological response, and therefore HCV cure, in 98% of the general population [20, 21]. Additionally, in an earlier study by Saxena et al. [22]. SVR was achieved in 83% of patients with impaired kidney functions (eGFR $\leq$ 45 ml/min/1.73 m2) treated with sofosbuvir-containing drug regimens.

Sustained virological response was achieved in 91.9% of the studied CKD cohort receiving rPAR/OMB/RBV. This agrees with Mahmoud et al. [23] who showed that (SVR) was 91% in the general population using the same drug regimen. Furthermore, Hézode et al. [24] reported a rate of SVR of 90.9% in 44 genotype-4 treatment-naïve patients with chronic HCV receiving rPAR/OMB/RBV. Another study reported an SVR of 94.7% in patients receiving SOF/DAC and 95.8% for those who received rPAR/OMB/RBV [25].

Only two of the studied patients on hemodialysis who had liver cirrhosis showed a decline in their coagulation profile and/or serum albumin and elevation of bilirubin level. After consultation with the attending nephrologist,

they were prescribed sofosbuvir 400 mg every other day plus daclatasvir 60 mg and ribavirin 200 mg daily. They both sustained viral clearance at week 12 after end of therapy with no major complications. These regimens were guided and in agreement with previous studies [26, 27]. At the time of conducting this study, the national protocol for treatment of HCV recommended treatment with sofosbuvir-based regimens only in patients with GFR more than 30 ml/min/1.73 m^2. Recent studies documented sofosbuvir safety in moderate and severe renal impairment and the use of sofosbuvir-based treatment in all stages of CKD [28–30] was recommended later in both national and international protocols [28, 31].

The adverse events reported in this study were majorly related to ribavirin use, where 39% of the patients experienced anemia during treatment. Ribavirin induces morphological change in the red cells favoring echinocytic form and increases phosphatidylserine exposure on red cell membrane which leads to premature RBC senescence and accelerated phagocytosis by the reticuloendothelial system. It was also suggested that ribavirin inhibits RBC release from the bone marrow through delay of erythroid differentiation [32]. Similarly, an Egyptian study including 171 CKD patients [33] indicated that ribavirin therapy was interrupted in 25% (43/171) of patients due to anemia necessitating blood transfusion in 16 patients.

Only 2 patients developed deterioration of kidney functions, concurring with previous randomized trials [30 34] showing that 1–2% of patients with advanced-CKD manifested decline of kidney functions after sofosbuvir-based treatment, but most patients recovered to their baseline kidney functions after cessation of treatment. Also, Suda et al. [35] showed that patients with no-CKD and early-CKD (eGFR≥60) had a lower risk of renal function worsening than advanced-CKD patients (eGFR<60) with DAAs. Furthermore, Roth et al. [36] stated that advanced-CKD patients manifested a higher risk of renal function deterioration, anemia, and early discontinuation of DAAs.

One of the study patients developed hepatocellular carcinoma, and this is contrary to most of recent studies including large cohorts of patients and confirming that sustained virologic clearance induced by DAAs lowers the risk of occurrence of de novo HCC after cure of HCV [37, 38].

Serum creatinine levels during treatment of HCV showed statistically significant improvement in CKD patients who were not on hemodialysis ($P<0.001$) (Fig. 1). This agrees with Sise et al. [30] who documented that estimated GFR increased by 9.3 ml/min per 1.73 m^2 in patients with CKD stage 3 at baseline during the 6-month period of follow-up after end of treatment. Another study of liver transplant recipients showed an improved or unchanged GFR in 65% of the studied patients treated with DAAs, while 35% of liver transplant recipients who achieved SVR12 showed worsened GFR, yet this was more prevalent in patients with impaired baseline renal function [39].

To achieve micro-elimination of HCV in CKD subpopulations, all available DAA-based therapies in developing countries should be investigated in order to increase the access to treatment in those settings and improve both hepatic and renal outcomes.

Conclusion

In conclusion elimination of HCV in patients with chronic kidney disease with rPAR/OMB/RBV or SOF/DAC ± ribavirin guided by creatinine is safe, efficacious with high SVR rates and likely to improve renal functions if started early in the course of CKD. Micro-elimination of HCV in this cohort is critical to prevent relentless progression of liver disease particularly in patients eligible for renal transplant while decreasing the risk of nosocomial transmission in hemodialysis centers especially in resource-limited settings.

Limitation of this study

The limitation of this study is the short duration of follow-up and relatively small sample size.

Abbreviations

HCV: Chronic hepatitis C; WHO: World Health Organization; CKD: Chronic kidney disease; ESRD: End-stage renal disease; DAAs: Directly acting antivirals; INF: Interferon; RBV: Ribavirin; SVR: Sustained virological response; MOH: Ministry of Health and Population; NCCVH: National Committee for Control of Viral Hepatitis; eGFR: Estimated glomerular filtration rate; RT-PCR: Real-time polymerase chain reaction testing; HCC: Hepatocellular carcinoma; rPAR/OMB/RBV: Ritonavir-boosted paritaprevir-ombitasvir-ribavirin; SOF/DAC: Sofosbuvir and daclatasvir; MDRD: Modification of Diet in Renal Disease formula; AST: Aspartate aminotransferase; AST: Alanine aminotransferase; CBC: Complete blood count; HBsAg: Hepatitis B surface antigen; HCV-Ab: Hepatitis C antibody; HBA1c: Glycated hemoglobin; AFP): Serum alpha-fetoprotein.

Acknowledgements

N/A

Authors' contributions

TGA contributed to the idea of the study, planning, data collection and follow-up of patients, and writing the manuscript. CAA contributed to the data collection and follow-up of patients and writing the manuscript. OAA, IS, YE, and MKS contributed to the data collection and follow-up of patients. ME, WH, SA, SYK, DMK, and GGN contributed to the writing and drafting the manuscript. EG contributed to the data analysis and interpretation. HD, AK, and WD contributed to the data revision and manuscript revision. MHE substantively revised and supervised the whole study from the data collection till the final drafting. The authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Faculty of Medicine, Ain Shams University Ethical Committee (FWA00017585) approval was taken before starting the study in December 2015. Every patient signed an informed consent after the full explanation and assurance that the patient will receive complete medical service even if he/she did not join the study population and/or decide to withdraw from the study at any time point.

Consent for publication

N/A

Competing interests

The authors declare that they have no competing interests.

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Received: 21 April 2022 Accepted: 11 June 2022
Published online: 08 July 2022

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