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Impact of direct acting antiviral agents on kidney function in hepatitis C virus infected patients with chronic kidney disease

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is strongly associated with chronic kidney disease (CKD). It is an independent risk factor for developing CKD and significantly increases morbidity and mortality in CKD patients. Treatment with newer direct-acting antiviral (DAA) regimens in patients with CKD is showing conflicting results as regards safety and efficacy.

Objectives: To evaluate the safety and efficacy of DAAs and their impact on kidney function in CKD patients.

Patients and Methods: We conducted a prospective observational study on 100 CKD patients stages 3-4, receiving treatment for HCV at MASRI (Faculty of Medicine Ain Shams University Research Institute), with two different DAAs regimens (sofosbuvir/daclatasvir with or without ribavirin and ombitasvir/paritaprevir/ritonavir [OMV/PTV/RTV] with ribavirin), completed over six months follow up. Serum creatinine, estimated glomerular filtration rate (eGFR), and proteinuria were followed during and after treatment.

Results: Sustained virological response (SVR) was achieved in all patients. Improvement of eGFR (8-15 mL/min/1.73 m2) and proteinuria was found in both study groups. Acute kidney injury (AKI) was uncommon; it occurred in three (3%) patients, out of them, two patients showed complete recovery. Adverse events were common (43%), but serious adverse events were uncommon (2%).

Conclusion: DAA regimens were effective and well-tolerated for HCV infected patients with stage 3-4 CKD, where viral clearance caused improvement in eGFR and proteinuria.

Implication for health policy/practice/research/medical education:
HCV infection might be associated with CKD. Direct-acting antiviral therapy is effective in CKD patients. Serious adverse effects and treatment discontinuations are rare. Improvement of kidney function occurs with viral clearance.

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Original Article

Introduction

Worldwide, more than 170 million persons have hepatitis C virus (HCV) infection, of whom 71 million have chronic infection and Egypt has one of the highest prevalence of HCV in the world (1). A unique relationship exists between HCV infection and chronic kidney disease (CKD). HCV infection complicates the course and alters the management of kidney disease in patients who suffer from both. Chronic HCV infection is associated with a 23% higher risk of presenting with CKD with an accelerated progression, the risk of end-stage renal disease (ESRD) is seven times higher in HCV-infected patients when compared to uninfected patients, and a higher morbidity and mortality (2). HCV infection can cause CKD through several mechanisms, including cryoglobulinemic vasculitis and immune complex-mediated glomerulonephritis (eg, membranous nephropathy) also chronic HCV infection is significantly associated with a higher risk (1.5–2.5-fold) of diabetes and (cardio- or cerebro-) vascular disease, which may itself participate in the deterioration of renal function (3).

Despite the significant link between HCV and CKD

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progression, most of the patients with CKD infected with HCV remain untreated, because they have historically been difficult to treat due to common adverse effects associated with interferon, ribavirin (RBV), and first generation protease inhibitors (4,5). Recently, there have been major advancements in the treatment of HCV with the development of new direct-acting antivirals (DAAs). Among the currently approved DAAs, sofosbuvir (a pangenotypic NS5B inhibitor). Sofosbuvir and its metabolites (GS-331007) are excreted by the kidney; available data support its use when GFR is > 30 mL/min (6). Additionally, therapy with ombitasvir/paritaprevir/ritonavir plus dasabuvir ± RBV is currently approved for the treatment of HCV in advanced stages of CKD as the metabolism of these compounds is mediated predominantly by the liver (7). A regimen without dasabuvir (OMV/PTV/RTV) can be used in HCV genotype 4 for 12 weeks with RBV-free and RBV-containing combinations of treatment-naïve and treatment-experienced patients (8).

Despite recent advances, little is known about the effect of HCV treatment with DAAs on short and long-term kidney function. Whether or not the CKD progression can be slowed by HCV treatment has not been established. Therefore, we aimed to evaluate the impact of those two different DAA regimens on HCV infected patients with CKD.

Objectives

The objective of this study was to assess the safety and efficacy of two different DAA regimens and investigate whether HCV clearance contributes to the improvement of overall kidney functions.

Patients and Methods

Setting

This study included CKD patients recruited from Nephrology and Hepatology outpatient clinics at Ain Shams University Hospitals and received treatment for HCV at MASRI (Faculty of Medicine Ain Shams University Research Institute) in Ain Shams University Hospital.

Study population

This is a prospective, observational study included 100 CKD patients stages 3-4, aged ≥18 years at the time of starting treatment. CKD was identified by two occasions of eGFR<60 mL/min per 1.73 m^2 that are >90 days apart. Proteinuria was identified by >200 mg proteinuria per 1 g creatinine. CKD was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for CKD as follows: Stage 3a: GFR (45-59 mL/min/1.73 m^2); Stage 3b: GFR (30-44 mL/min/1.73 m^2); Stage 4: GFR (15-29 mL/min/1.73 m^2) (9). Diagnosis of HCV infection confirmed by HCV RNA PCR. All patients were treatment-naive. Comorbid conditions were determined by chart review. Hypertension was defined as blood pressure >140/90 mm Hg on at least two visits in the year before treatment initiation or the use of antihypertensive medication. Diabetes was defined by hemoglobin A1c value >6.5% or the use of anti-diabetic medication. We excluded patients with eGFR<15 mL/min/1.73 m^2 at baseline, patients infected with HIV and /or hepatitis B virus, patients with decompensated liver cirrhosis, or patients with hepatocellular carcinoma.

Study procedures

A thorough systemic physical examination was conducted. Detailed drug history was obtained from patients and drug interaction with DAAs was checked using Liverpool Hep-drug interaction site (https://www.hep-druginteractions.org/). Nephrotoxic drugs (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs or vancomycin) were suspended during the DAAs treatment course. As a part of the pretreatment evaluation, baseline symptoms were carefully reviewed and recorded. Close attention was paid to pretreatment presence and severity of symptoms such as nausea, fatigue, headache, pruritus, and insomnia, as these commonly seen in patients with CKD, and have been described as common side effects of DAAs. At baseline, serum alpha fetoprotein, HbA1c, urine analysis, and abdominal ultrasonography were conducted. During and after treatment; complete blood count, liver function tests including serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, international normalized ratio (INR), and serum creatinine were followed monthly and estimated GFR was calculated monthly using the Modification of Diet in Renal Disease Study equation(MDRD) that requires age, gender, race and serum creatinine. Protein/creatinine ratio was tested for patients before, 3 months, and 6 months after initiation of treatment. Serum HCV RNA concentration was measured before and 12 weeks after treatment, using the HCV RNA TaqMan real-time PCR test (AmpliPrep/COBAS TaqMan 48 set; Roche). A value of <15 IU/L was considered negative. In some selected patients (with autoimmune manifestations, unexplained renal impairment, AKI or unexplained proteinuria), C3 and C4 fractions of the complement and serum cryoglobulins were tested. The follow up time was 24 weeks from the start of treatment.

Treatment plan

Selection of the DAAs regimen was based on the baseline eGFR; CKD patients with estimated GFR > 35 mL/min/1.73 m^2 received a sofosbuvir/daclatasvir regimen

with or without RBV. While patients with eGFR of <35 mL/min/1.73 m^2 received ritonavir-boosted paritaprevir/ombitasvir (OMV/PTV/RTV) with RBV. Patients were classified according to the type of direct acting antiviral drugs used into two groups: Group I: 45 patients received ombitasvir, paritaprevir, and ritonavir (OMV/PTV/RTV) (25/150/100 mg) daily with RBV (200 mg) daily. Group II: 55 patients received full dose sofosbuvir (400 mg) daily and daclatasvir (60 mg) daily with or without RBV. RBV was added in 19 (34%) (Difficult to treat patients) out of this group who have one or more of the following; total serum bilirubin higher 1.2 mg/dL, serum albumin lower than 3.5 g/dL, INR higher than 1.2, platelet count lower than 150 000/mm^3. RBV was only added when the baseline hemoglobin level was >10 g/dL. The dose of RBV was decided and adjusted according to body weight, eGFR, and hemoglobin level. During the HCV treatment period, RBV was stopped when hemoglobin level became <8.5 g/dL. DAA treatment duration was three months.

Outcome

Outcomes of interest included (1) change in serum creatinine and eGFR from baseline, (2) change in proteinuria from baseline (3) development of side effects and (4) sustained virologic response after 12 weeks of ending treatment (SVR12).

Definitions

Cirrhosis: Liver biopsy was not conducted in any of the patients. The presence of two of the following criteria was taken as indicative of cirrhosis; platelets count <140 000 per µL, presence of esophageal varices, evidence of cirrhosis, and/or portal hypertension and/or ascites by imaging studies or transient elastography (FibroScan) results compatible with Metavir stage 4 fibrosis.

Treatment-induced anemia: Defined as hemoglobin drop >2 g/dL from baseline, new administration, or increasing the dose of erythropoiesis stimulating agents (if already on such drugs before the start of therapy) or need for blood transfusion.

On the treatment of AKI: A rise in serum creatinine 1.5 times the baseline within a month was indicative of AKI on top of CKD. Causes other than DAAs were excluded (hepatic decompensation and prerenal azotemia).

Sustained virologic response (SVR12): (cure of HCV) was defined as an undetectable HCV RNA at least 12 weeks after the completion of therapy (10).

Adverse effects: Adverse events were any new or worsening complaints from the time of treatment initiation until 4 weeks after treatment completion. Clinical symptoms were considered severe adverse effects if they indicated admission to the hospital.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The research was approved by the Ethics Committee of Faculty of Medicine of Ain Shams University (reference number; FWA 000017585). Informed consent was obtained from all patients who participated in this study.

Statistical analysis

Data were revised for its completeness and consistency. Double data entry on IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA) was done. Baseline characteristics of patients were described using mean and SD or percentage. Baseline and follow-up eGFRs were compared using paired samples t-tests. A logistic regression model was used to determine baseline factors associated with changes in eGFR during therapy; odds ratios and 95% confidence intervals were used to summarize the results of this model. One way analysis of variance (ANOVA) test was used to compare quantitative data between more than two groups. Chi-square test was used to compare qualitative data between different groups. Repeated measure ANOVA test was used to compare quantitative data for the same group at different time points and the Friedman test was used for qualitative data. Logistic regressive analysis and linear regression analysis: were used to measure the independent effect of different variables on some outcomes. A *P* value of less than 0.05 was considered statistically significant.

Results

A total of 100 patients were identified with HCV and stage 3–4 CKD. The mean age was 57.41 ± 12.23 years and most patients (66%) were males. 18 patients were stage 4 and 82 patients were stage 3 (37 patients 3a and 45 patients 3b). Co-morbidities were common and included diabetes mellitus in 48%, hypertension in 69%, ischemic heart disease in 2%. Liver cirrhosis was found in 8 patients. At baseline mean serum creatinine was 1.82 ± 0.57 mg/dL, corresponding to mean eGFR 40.62 ± 11.15 mL/min per 1.73 m^2. Regarding the incidence of proteinuria, we found 70 patients had baseline proteinuria, out of which five patients had heavy proteinuria (>3.5) and 21 patients had proteinuria less than 0.5. Other patients' characteristics and laboratory results are described in Tables 1 and 2. Upon classification of patients according to DAA regimens, we found that in SOF/DAC regimen, mean serum creatinine was 1.54 ± .16 mg/dL with estimated GFR of 47.97 ± 6.43 mL/min/1.73 m^2, while in OMV/PTV/RTV regimen, mean serum creatinine was 2.16 ± .70 mg/dL with estimated GFR of 31.62 ± 8.85 mL/min/1.73 m^2; shown in Table 3 along with other baseline investigations.

Table 1. Demographic data of study population (N = 100)

	Mean ± SD or No. (%)
Age (y)	57.41±12.23
Gender	
Male	66 (66)
Female	34 (34)
Stage of CKD	
Stage 3a	37 (37)
Stage 3b	45 (45)
Stage 4	18 (18)
DM	48 (48)
HTN	69 (69)
Cirrhosis	8 (8)
Child-pugh class	
A5	82 (82)
A6	18 (18)

DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease

Table 2. Baseline investigations of study population

	Mean ± SD
eGFR (mL/min/1.73 m^2)	40.62 ± 11.15
Creatinine (mg/dL)	1.82 ± 0.57
Protein/creatinine ratio	1.16 ± 1.50
Albumin (g/dL)	3.92 ± 0.53
HGB (g/dL)	13.07 ± 2.05
Platelets (10^3/µL)	230.78 ± 84.30
AST (U/L)	37.91 ± 30.40
ALT (U/L)	36.92 ± 38.23
Total bilirubin (mg/dL)	0.73 ± 1.76
INR	1.21 ± 1.00
HCV RNA PCR (IU/L)	927 655 ± 15 486

eGFR, estimated glomerular filtration rate; HGB, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

Efficacy

Sustained virological response (SVR) was achieved in 100% of the patients in our study. HCV load dropped to below the detection limits when measured 12 weeks after finishing the treatment.

Effect of direct-acting antiviral therapy on kidney function

As regards the effect on kidney function, we found significant improvement during follow up of serum creatinine, eGFR, and proteinuria in both groups as described in Table 4. Comparing between the two groups as regards the pattern of improvement in eGFR, it was more remarkable in SOF/DAC group (+15 mL/min/1.73 $m^{2)}$ compared to OMV/PTV/RTV group (+8 mL/min/1.73 m^2). However, no significant difference was found as regards proteinuria in both groups; shown in Table 5 and Figure 1. Improvement of eGFR was negatively influenced by age and DM (Table 6). All CKD stages showed improvement of eGFR during and after the treatment course, more in stage 3a (+15 mL/min/1.73 m^2) in comparison to stages 3b and 4 (+11 and +5 mL/min/1.73 m^2 respectively), but with no statistically significant difference between the stages as shown in Table 7 and Figure 2.

Effect of DM on the study outcome

We examined the effect of diabetes on the change in eGFR and proteinuria. In non-diabetic CKD patients, eGFR improved on average from (41.65 to 56.45 mL/min/1.73 $m^{2)}$ in comparison to (39.50 to 47.34 mL/min/1.73 $m^{2)}$ in diabetic patients, but with no statistical significance (Table 8, Figures 3 and 4).

Adverse events

Adverse events were common during treatment; 43 patients (43%) reported at least one new or worsened symptom while on direct-acting antivirals. The most common non-hematological adverse events were itching, headache, diarrhea, nausea, and fatigue. We found a significant difference between the two groups as regards

Table 3. Comparison between baseline investigations in both groups

	Type of Antiviral drugs		t*	*P* value
	(OMV/PTV/RTV) (n=45)	Sofosbuvir/Daclatasvir (n=55)		
	Mean ± SD	Mean ± SD		
Albumin (g/dL)	3.85± .48	3.98 ±.56	1.253	0.213
eGFR (mL/min/1.73 m^2)	31.62± 8.85	47.97 ± 6.43	10.680	<0.001
Creatinine (mg/dL)	2.16± .70	1.54 ±.16	5.789	<0.001
Protein/creatinine ratio	1.39± 1.62	0.98 ± 1.39	1.83	0.07
HGB (g/dL)	12.63± 1.92	13.44 ± 2.09	1.993	0.049
Platelets (10^3 /µL)	232.8± 68.78	229.1 ± 95.74	0.213	0.832
AST (U/L)	38.07± 41.53	37.78 ± 16.99	0.046	0.963
ALT (U/L)	34.58± 43.18	38.84 ± 33.95	0.552	0.582
Bilirubin (mg/dL)	0.61±0 .30	0.83 ± 2.37	0.610	0.543
INR	1.12±0 .20	1.29 ± 1.34	0.876	0.383

eGFR, estimated glomerular filtration rate; HGB, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

*Student *t* test, significant at 0.05 level.

Table 4. Change in kidney functions and proteinuria in both groups

	(OMV/PTV/RTV) (n=45)			Sofosbuvir/Daclatasvir (n=55)		
	Mean ± SD	F*	P value	Mean ±SD	F*	P value
eGFR baseline	31.62[a] ± 8.85			47.97[a] ± 6.43		
eGFR 1 month	33.74[a] ± 16.43			50.21[a] ± 16.70		
eGFR 2 months	34.19[a] ± 14.54			49.72[a] ± 17.40		
eGFR 3 months	34.41[a] ± 15.22	4.79	<0.001	51.30[a] ± 17.49	19.17	<0.001
eGFR 4 months	36.05[a] ± 13.27			56.43[b] ± 21.43		
eGFR 5 months	35.49 ± 14.71			59.81[b] ± 16.76		
eGFR 6 months	39.09[b] ± 15.06			62.71[b] ± 16.87		
Creatinine baseline	2.16 ± 0.70			1.54[a] ± .16		
Creatinine 1 month	2.20[a] ±0 .89			1.56[a] ± 0.36		
Creatinine 2 months	2.17[a] ± 0.95			1.59[a] ±0.37		
Creatinine 3 months	2.20[a] ± 1.01	4.62	<0.001	1.55[a] ± 0.39	16.50	<0.001
Creatinine 4 months	2.03 ± 0.85			1.44[b] ±0 .37		
Creatinine 5 months	2.03 ±0 .89			1.33[b] ±0 .29		
Creatinine 6 months	1.93[b] ± 0.91			1.27[b] ± .28		
Protein/creatinine baseline	1.39[a] ± 1.62			0.98[a] ± 1.39		
Protein/creatinine 3 months	1.19 ± 1.13	3.27	0.04	1.07[a] ± 2.41	3.61	0.03
Protein/creatinine 6 months	1.15[b] ± 1.12			0.73[b] ± 1.32		

*Repeated measure ANOVA test (a,b….post hoc test).

eGFR, estimated glomerular filtratio.

insomnia (P=0.03) and headache (P=0.02) as shown in Table 9. Anemia was common in our study (41%). It was more common in OMV/PTV/RTV group compared to the SOF/DAC group; this may be attributed to RBV in the former group (Table 9). RBV was given to 64 patients in our study, 19 patients with SOF/DAC and 45 patients with OMV/PTV/RTV. We found a significant difference regarding anemia between patients who received RBV and patients who did not (P=0.015; Table 10). It was managed with iron, erythropoietin (either adding erythropoietin or increasing its dose), reducing RBV dose in 14 patients, or discontinuing in 13 patients (when hemoglobin dropped < 8.5 g/dL). A blood transfusion was done in one patient. As regard hepatic decompensation (elevated liver enzymes, INR, jaundice, and newly developed lower-limb edema or ascites), occurred in 10 patients in OMV/PTV/RTV group and six patients in SOF/DAC group as shown in Table 11. Hepatic decompensation resolved spontaneously or at the end of treatment. Only one patient was admitted to the hospital and OMV/PTV/RTV was discontinued.

Table 5. Comparison between two groups regarding change in kidney function

		F*	*P* value
eGFR	Time	20.681	<0.001
	Time * Drug	4.594	<0.001
	Drug	49.608	<0.001
Protein/creatinine ratio	Time	4.433	0.013
	Time * Drug	2.045	0.132
	Drug	1.111	0.294

eGFR, estimated glomerular filtration rate.
*Repeated Measure ANOVA test.

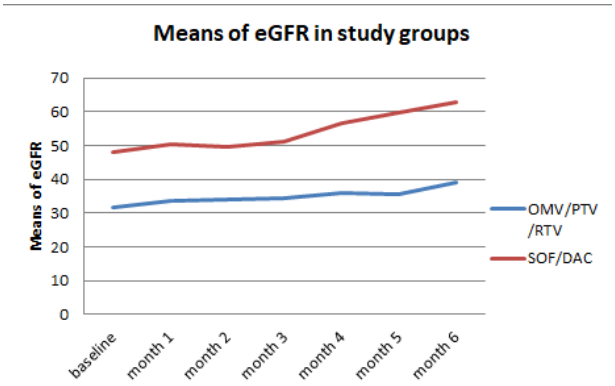

Figure 1. Improvement in eGFR in (SOF/DAC) group compared to (OMV/PTV/RTV) group, being more remarkable in (SOF/DAC) group.

Incidence of AKI

The incidence of AKI was uncommon in the study, which occurred in three patients (3%) and all among SOF/DAC group. All were diabetic and had baseline proteinuria. During follow up, AKI resolved in two patients (End of follow up serum creatinine = 0.3 mg/dL from baseline) without cessation of DAAs and none of them needed hemodialysis.

Modification of treatment during the study

During follow up; treatment was discontinued in two patients. One patient was on OMV/PTV/RTV with RBV due to hepatic decompensation in the picture of jaundice and generalized edema and needed temporary hospital

Table 6. Linear regression analysis for predictors of change in eGFR

	Unstandardized Coefficients		Standardized Coefficients	T	P	95% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	17.783	9.132		1.947	0.05	-.352	35.918
Drug type	4.784	3.123	0.167	1.532	0.13	-1.417	10.985
Age	-.260	0.128	-0.221	-2.028	0.05	-.514	-.005
Gender	1.740	3.256	0.058	0.534	0.59	-4.726	8.206
DM	-6.016	2.768	-0.210	-2.173	0.03	-11.513	-.519
HTN	3.275	3.324	0.106	0.985	0.33	-3.326	9.876
Baseline PCR	5.003E-7	0.000	0.078	0.796	0.43	0.000	0.000

DM, diabetes mellitus; HTN, hypertension; PCR, polymerase chain reaction.

admission, however on doing PCR for HCV it showed viral clearance. The second patient was on SOF/DAC and developed on treatment AKI after one month, drugs were suspended for a 2-week till recovery of kidney function, half dose sofosbuvir and full dose daclatasvir reinitiated again with weekly follow up.

Cryoglobulinemia in the study

Cryoglobulins were found in five patients out of 57 patients tested, (four males and one female), only one of them was cirrhotic. Three patients had sub-nephrotic range proteinuria, four patients had consumed C3 and five patients had consumed C4. Renal biopsy was conducted in two patients having extra-renal manifestation, showed a picture of MPGN; those two patients received pulse steroid and six sessions of plasmapheresis with DAAs. Four patients received SOF/DAC regimen and one received OMV/PTV/RTV/RBV. Proteinuria improved, C3 and C4 were normalized and extra-renal manifestation (skin rash) disappeared gradually.

Renal biopsy was conducted in two patients other than the two cryoglobulinemic patients. One diabetic patient had heavy proteinuria, renal biopsy showed diabetic nephropathy and proteinuria slightly improved after DAAs. While the other patient had an unexplained renal

Table 7. Comparison between CKD stages regarding change in eGFR and serum creatinine

		F*	*P* value
eGFR	Time	17.08	<0.001
	Time * Stage	1.05	0.40
	Stage	48.89	<0.001
Creatinine	Time	18.29	<0.001
	Time * Stage	1.45	0.14
	Stage	50.94	<0.001

eGFR, estimated glomerular filtration rate.
*Repeated Measure ANOVA test.

Table 8. Comparison between diabetics and non-diabetics regarding kidney function

		F*	*P* value
eGFR	Time	21.73	<0.001
	Time * DM	1.97	0.07
	DM	3.84	0.05
Creatinine	Time	16.94	<0.001
	Time * DM	1.36	0.23
	DM	0.50	0.48
Protein/creatinine	Time	4.66	0.01
	Time * DM	0.13	0.88
	DM	9.72	0.002

eGFR, estimated glomerular filtration rate.
*Repeated Measure ANOVA test.

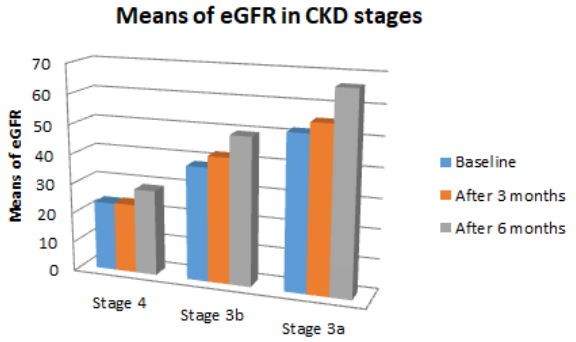

Figure 2. Comparison between CKD stages 3a , 3b and 4 regarding values of eGFR at baseline, after 3 months and after 6 months of therapy with no statistically difference as regard pattern of improvement.

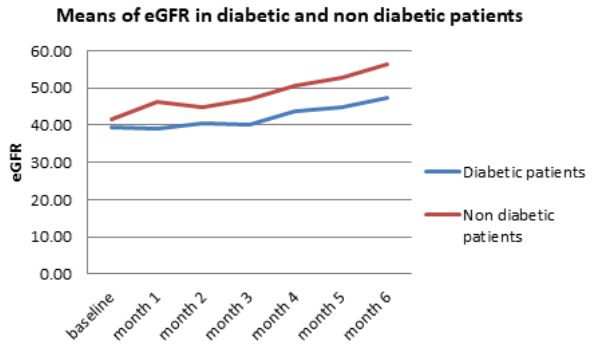

Figure 3. Improvement in eGFR in diabetic compared to non-diabetic CKD patients, showing no statistical difference.

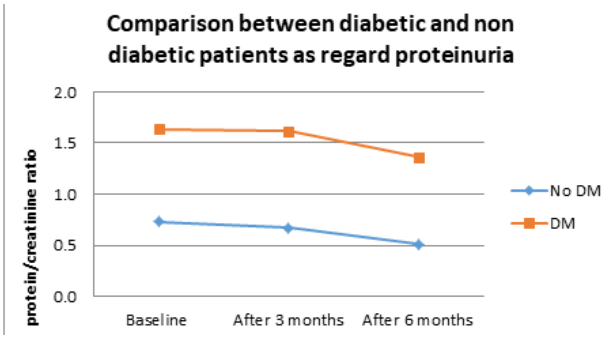

Figure 4. Improvement of protein/creatinine ratio in diabetic compared to non-diabetic CKD patients at baseline, after 3 months and after 6 months, showing no statistical difference.

impairment and active urinary sediment, his renal biopsy showed a picture of post-infectious glomerulonephritis and glomerulosclerosis.

Discussion

The prevalence of HCV infection in Egypt is one of the highest in the world (11). The largest screening program in Egypt was done in 2018. By screening 49.6 million persons over a period of 7 months, 2.2 million HCV-seropositive persons were identified and referred for evaluation and treatment (12). CKD patients are a priority population for treatment as chronic HCV infection exacerbates renal dysfunction, resulting in ESRD and increases morbidity and mortality (13). The approval of DAAs revolutionized the treatment of HCV by leading to high rates of SVR12 with fewer side effects. However, current knowledge about the efficacy and safety of DAA-based regimens in patients with different stages of CKD is insufficient (14). According to the guidelines provided by European Association for the Study of the Liver (EASL) on Treatment of HCV published in 2018: Patients with HCV infection with mild to moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2) should be treated according to the general recommendations, while patients with severe renal impairment (eGFR ≤30 mL/min/1.73 m^2) could be treated with one of the three regimens: a combination of glecaprevir and pibrentasvir for 8 or 12 weeks, grazoprevir and elbasvir for 12 weeks or the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks. This leads us to the aim of our study which is to assess the safety and efficacy of two different DAA regimens among Egyptians HCV patients (genotype 4 predominant) with stages 3 and 4 CKD. In the present study, we confirmed that the used DAAs regimens were effective in CKD patients. All patients achieved SVR and HCV load dropped to below the detection limits after 12 weeks in patients receiving both regimens in agreement with Singh et al (15) and Kumar et al (16) who studied Sofosbuvir-based direct-acting antiviral therapy. Besides, high SVR12 among CKD patients receiving OMV/PTV/RTV for 12 weeks with or without RBV was also described by the PEARL-I (8) and the AGATE-II (17) studies (100% and 94% respectively). Regarding proteinuria, significant improvement was found in both study groups which goes in hand with Medeiros et al (18) and Goetsch et al (19). This finding may be explained that a substantial number of patients with HCV infection who have non-diabetic CKD may have undiagnosed HCV-related glomerular disease which resolves after viral clearance. These results were not in agreement with the study by Elmowafy et al (11) who found that there was no statistical difference regarding proteinuria before or after treatment. Comparing between diabetic and non-

Table 9. Comparison between side effects in both groups

	Type of Antiviral drugs		χ^{2*}	*P* value
	(OMV/PTV/RTV) (n=45)	Sofosbuvir / daclatasvir (n=55)		
	No. (%)	No. (%)		
Diarrhea	2 (4.4%)	1 (1.8%)	0.59[a]	0.59
Insomnia	0 (0.0%)	6 (10.9%)	5.22[a]	0.03
Fatigue	8 (17.8%)	10 (18.2%)	0.003	0.96
Itching	10 (22.2%)	6 (10.9%)	2.36	0.13
Headache	0 (0.0%)	7 (12.7%)	6.16[a]	0.02
Anemia	21 (46.7%)	20 (36.4%)	1.09	0.30

*Chi square test; [a] Fisher exact test.

Table 10. Relation between patients received ribavirin and anemia

	Patients not on Ribavirin No. (%)	Patients on Ribavirin No. (%)	Test value	*P* value
Anemia	9 (25.0%)	32 (50.0%)	5.953	0.015

*Student *t* test, significant at 0.05 level.

Table 11. Comparison between hepatic decompensation in both groups

Group	Total number of patients	Elevated bilirubin (>1 mg/dL)	Elevated liver enzymes AST>39IU/L ALT>52 IU/L	Prolonged INR (>1.2)	Edema &ascites
OMV/PTV/RTV group	10 (22.2%)	5(11%)	3(6%)	2(6.6%)	1(2%)
SOF/DAC group	6 (10.9%)	3(5.4%)	1(1.8%)	2(3.6%)	0(0%)

diabetic patients as regard improvement in proteinuria we found more improvement in non-diabetic patients but with no significant difference between both groups, this disagrees with the study by Sise et al (20) who studied 1590 CKD patients received different regimens of DAA and found that albuminuria was significantly improved in non-diabetic CKD patients. We found that regarding eGFR, significant improvement was found in follow up during treatment course in SOF/DAC and OMV/PTV/RTV groups ($P < 0.001$), supporting the hypothesis that viral clearance contributes to improvement in kidney function, on comparing between both groups, an improvement was more remarkable in SOF/DAC group (15 mL/min/1.73 m^2) compared to OMV/PTV/RTV group (8 mL/min/1.73 m^2) this may be attributed to higher baseline eGFR in SOF/DAC group. Results regarding serum creatinine go in hand with findings concluded regarding eGFR, however, there was a mild elevation in serum creatinine in both groups in the first month. Our results were not in agreement with previous studies (11,16,21). Elmowafy et al (11) found that treatment of HCV among CKD patients with DAAs was associated with a rapid rise of serum creatinine in 46.67% of their patients, which may be explained by the higher number of patients with stage 4 (60%). Saxena et al (21) studied the effect of sofosbuvir in full dose in combination with other drugs and found that the use of SOF-based therapies given to patients with baseline renal function impairment (eGFR < 45 mL/min /1.73 m^2) was associated with a higher risk of worsening renal function. Moreover, Kumar et al (16) studied the safety of full-dose sofosbuvir in combination with RBV, ledipasvir, and daclatasvir on 71 CKD patients with HCV infection and described a decline in kidney function at three months after stopping treatment, however it was explained that this was because of a natural history for CKD. While Sise et al (22) found no change in kidney function during treatment course as patients experienced minor fluctuations in serum creatinine and did not change >0.3 mg/dL from baseline at any time during treatment. Other studies agree with our results and describe improvement in eGFR after viral clearance (18,20,23). Upon comparing diabetics and non-diabetics, we noted that non-diabetics showed more improvement in eGFR after treatment compared to diabetic patients however, this difference was statistically insignificant. Medeiros et al (18) and Sise et al (20) also reported more improvement in eGFR in non-diabetic patients.

In the cryoglobulinemic patients, improvement in eGFR, proteinuria, cryoglobulins disappeared, complement levels were normalized and any extrarenal manifestation disappeared gradually.

Similar results were found in numerous studies (13,24-27), as DAAs use caused the same improvement in most of the patients (50% to 70%) and complete clinical response in most of the patients. Our study brings further supporting evidence to the current recommendations of the KDIGO 2018 guidelines on the use of DAAs, which is now recommended as the first-line therapy in cryoglobulinemic glomerulonephritis. Immunosuppression is reserved for patients with severe manifestations or those who do not enter remission after achieving SVR with DAA treatment. As regards side effects of DAA on the kidney, AKI occurred in 3 (3%) patients in our study, all in SOF/DAC group; 2 patients showed complete recovery and none of them needed hemodialysis.

Our results agree with the study by Sise et al (20). They found that AKI events were rare, occurring in 29 patients (2.6%) in the overall cohort because the rate of AKI in patients receiving a sofosbuvir-containing regimen was higher than in those treated with non–sofosbuvir-based regimens (20). Elmowafy et al (11) had a higher AKI incidence (47%) there were only two independent risk factors for developing AKI cirrhosis and OMV/PTV/RTV. This may be explained by low-baseline eGFR (29.75 ± 14.06 mL/min /1.73 m^2).

The safety of new DAAs treatment was studied among the study population, 43 patients suffered from minor side effects. The most common adverse events were itching, headache, diarrhea, nausea, and fatigue. Regarding the OMV/PTV/RTV group, itching was the most common side effect after anemia. This was not in agreement with Iliescu et al (13) as the itching was not a significant complaint in patients with CKD who received OMV/PTV/RTV and dasabuvir. In SOF/DAC group, fatigue, headache, and insomnia were common side effects. These results were reported in many studies (16,28).

Generally, all side effects were tolerable, managed with symptomatic treatment, and improved dramatically after finishing therapy. None of the patients had to discontinue treatment because of side effects.

Anemia was the most common side effect reported in both groups, it was more common in OMV/PTV/RTV group (46.7%) that may be attributed to RBV. This agrees with the recent studies in which patients received RBV with different DAAs regimens (13,16,29).

Hepatic decompensation was seen in 16 (22.2%) patients among OMV/PTV/RTV group and six patients (10.9%) in the SOF/DAC group. All resolved after stopping treatment with no recurrence during follow up. Similar findings were found by Hsieh et al (30) regarding jaundice during OMV/PTV/RTV and dasabuvir treatment in HCV infected CKD patients. Recently Elmowafy et al (11) reported a higher incidence of decompensation in SOF/DAC group (16.6%) in comparison to (9.5%) in OMV/PTV/RTV group with recurrence of decompensation 2 or

3 months occurred after stopping treatment.

There were no deaths in any group while on treatment and for the 12 weeks after completion of treatment.

Conclusion

In conclusion, direct-acting antiviral therapy is effective in patients with stages 3-4 CKD. Although adverse effects are common, serious adverse effects and treatment discontinuations are rare. The kidney function improved on therapy. Significant AKI events were rare. Additionally, DAAs is an effective line of treatment in cryoglobulinemic patients who achieved sustained virologic response regarding clinical and laboratory improvement.

Limitations of the study

There are some limitations to our study. As our study was a "real life experience," we could not control other independent factors such as age, hypertension, or diabetes. Relatively short follow-up period to demonstrate the effect on natural history of CKD. Future studies are needed to confirm the long-term effects of HCV eradication on kidney function.

Authors' contribution

All authors contributed to design, management and review of the manuscript. WA and HH proposed the idea and conducted the clinical study. LK edited the paper. IS and OA managed and supervised the method, checked experiments and morphology of the tests. All authors have read approved the submitted version and agreed both to be accountable for the authors own contribution.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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