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Is the Treatment with Direct Acting Antiviral Agents (DAAs) Affecting Glomerular Filtration Rate (GFR)?

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ABSTRACT

Background: The kidney is a major component of extrahepatic manifestations of hepatitis C virus (HCV) clinical syndrome and the risk of chronic kidney disease (CKD) is more than 20% higher in patients with HCV infection than in seronegative individuals. Introduction of direct acting antivirals (DAA) represented a transforming point in the treatment of HCV.

Patients and Method: Retrospective cohort study of 118 adult HCV infected patients with normal baseline kidney functions and eGFR >60 ml/min were included. Patients coinfected with HBV and those with impaired kidney functions at beginning of treatment were excluded. Patients were divided into 3 groups according to their DAA-combination treatment regimen. Patients' eGFR were measured at baseline, at the end of treatment and one year later.

Results: Our results showed that patients who received sofosbuvir/daclatasvir/ribavirin, their pre-treatment eGFR mean±SD was (86.156±16.37). Post treatment eGFR showed an insignificant change after end of treatment (84.736± 17.41) and 1 year after treatment (82.06± 18.07). Those who received sofosbuvir/daclatasvir, their pretreatment eGFR mean ±SD was (94.606 ±19.32). Post treatment eGFR showed an insignificant change after end of treatment (89.396 ±18.39) and 1 year after treatment (89.176±20.27). As for patients who received sofosbuvir/simeprevir, their pretreatment eGFR mean ± SD was (92.716 ± 15.11). Post treatment eGFR showed an insignificant change after end of treatment (88.366 ±16.27) and 1 year after treatment (89.016± 15.72).

Conclusion: The new direct antiviral agents like sofosbuvir, daclatasvir and simeprevir are safe regarding glomerular filtration rate in patients with normal renal function. However, the treated patients need careful monitoring of kidney function tests during the period of treatment.

Keywords: Direct acting antiviral, GFR, HCV, Renal function

INTRODUCTION

In both chronic kidney diseases (CKD) patients and kidney transplant recipients, HCV infection raises the risk of end-stage renal disease (ESRD) and increases the rates of morbidity and death [(1)].

Different histological patterns of renal manifestations are reported in association with HCV infection such as membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), focal segmental glomerulosclerosis (FSGS), fibrillary glomerulonephritis, IgA nephropathy, immunotactoid glomerulopathy, interstitial nephritis and vasculitic renal involvement. The most common HCV-associated glomerulopathy is type I MPGN associated with type II mixed cryoglobulinemia [(2)].

HCV-associated CKD may be attributed to viral antigen- antibody complexes, cryoglobulinemia and possibility of a direct viral cytopathic effect [(3)]. Treating HCV decreases these complications and improves life span [(4)].

There is a very rapid advancement in the development of DAAs that made the pharmacological details of each DAA more difficult [(5)]. Nephrotoxicity has been reported after administration of sofosbuvir-containing antiviral regimen in HCV infected cases, especially in patients with underlying chronic kidney diseases [(6)].

Aim of the present study was to evaluate the effect of direct antiviral agents on glomerular filtration rate (GFR) in HCV positive patients with normal renal function after the full treatment period (12 weeks) and 1 year after the end of regimen.

PATIENTS AND METHODS

Our study was observational retrospective cohort study, conducted in Hepatology Unit in Sharque Elmadinah Hospital – Alexandria, at the period between January 2018 and December 2018. It included 118 patients adult >18 years who had received DAAs and attended hepatology clinic during the study period, they were recruited irrespective of their virological response.

Only patients with normal kidney functions at the beginning of the treatment were included in our study (eGFR> 60 ml/min, normal serum creatinine). We excluded: those with co-infection with HBV, patients with chronic kidney disease and those maintained on regular hemodialysis or transplant recipients and hard to treat patients (decompensated liver disease, hepatocellular carcinoma).

Patients were divided into 3 groups according to their treatment regimens as follows: Group 1: 61 patients received sofosbuvir 400 mg /daclatasvir 60 mg /ribavirin 600 mg for 12 weeks, **Group 2**: 35 patients received sofosbuvir 400 mg/daclatasvir 600 mg for 12 weeks, and **Group 3**: 22 patients received sofosbuvir

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400 mg /simeprevir 150 mg for 12 weeks.

All participants were subjected to:

History of patients' comorbid conditions extracted from their files, laboratory investigations (liver function tests (total bilirubin, serum albumin) liver enzymes (ALT, AST), complete blood picture, INR, PTT, HCV PCR serum creatinine level measured at baseline, at the end of treatment and one year later.

eGFR using EPI formula:

The CKD-EPI creatinine equation is [7]:

{GFR = 141 × min (Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] ─ 1.159 [if black]}. Where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1.

Patients' eGFR were measured at baseline, at the end of treatment and one year later.

Radiological studies: Abdominal ultrasound.

Ethical consent:

An approval of the study was obtained from Sharque Elmadinah Hospital Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 22.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean and standard deviation and were compared by ANOVA with repeated measures test for normally distributed quantitative variables. P value < 0.05 was considered significant.

RESULTS

Our patients were normotensive and non-diabetics with normal renal function tests. They started their HCV regimen in 2017 for 12 weeks and all of them reached sustained virological response (SVR). They have been followed up for renal functions (urea and creatinine) and eGFR measurement after full regimen (12 weeks) then after one year in 2018.

Demographic data of the studied cases are shown in table 1.

Table (1): Demographic data of the studies cases (n =118)

	No.	%
Sex		
Male	47	40.0
Female	71	60.0
Age (years)		
Min. – Max.	25.0 – 78.0	
Mean ± SD.	52.22 ± 11.44	
Weight (kg)		
Min. – Max.	45.0 – 126.0	
Mean ± SD.	82.47 ± 14.03	
Height (cm)		
Min. – Max.	149.0 – 191.0	
Mean ± SD.	163.4 ± 8.37	
BMI (kg/m^2)		
Min. – Max.	13.74 – 45.61	
Mean ± SD.	31.07 ± 5.79	

As regard liver appearance in ultrasound 38 of the cases had normal hepatic morphology while 80 cases had abnormal appearance of the liver (Table 2).

Table (2): Laboratory and radiological investigations of the studied patients

Investigations	Mean ± SD.
Hb (gm/dl)	12.74 ± 1.57
WBCs (x 10^3/ mm^3)	5.55 ± 1.12
Plat (x 10^3/ mm^3)	182.5 ± 38.32
ALT (U/L)	46.50 ± 7.81
AST (U/L)	48.50 ± 8.21
Albumin (gm/dl)	3.90 ± 0.81
Total Bilirubin (mg/dL)	0.80 ± 0.11
INR	1.12 ± 0.12
PCR of HCV (x10^3)	273.5 ± 57.34
U/S of liver	39 Normal (32.5%), 81 Abnormal (67.5%)

WBCs: white blood cells, ALT: alanine transaminase, AST: Aspartate Aminotransferase, INR: International Normalized Ratio and PCR: polymerase chain reaction.

Treatment protocol used in the 3 groups of patients is shown in table 3.

Table (3): Distribution of the studied cases according to treatment regimen

Treatment (12 weeks)	No.	%
Sofosbuvir/Daclatasvir/Ribavirin	61	50.8
Sofosbuvir/Daclatasvir	35	29.2
Sofosbuvir /Simeprevir	22	18.3

There was no significant change in eGFR after end of treatment and 1 year after treatment in group 1 (Table 4).

Table (4): Comparison of eGFR pretreatment and posttreatment (12w/1yr) in group 1 patients (SOF/DAC/ribavirin cases, n=61)

eGFR (ml/min)	Pre- treatment (n =61)	Post-treatment		F	P
		After full regimen (12 weeks) (n = 61)	After one year (n = 61)		
Min. – Max. Mean ± SD.	49.40–120.6 86.15±16.37	53.70–125.7 84.73±17.41	42.90–122.7 82.0±18.07	2.228	0.112
Δ change		**↓16.12± 1.42**	**↓17.79 ± 4.15**		

F: F test (ANOVA) with repeated measures

There was no significant change in eGFR after end of treatment and 1 year after treatment in group 2 (Table 5)

Table (5): Comparison of eGFR pretreatment and post- treatment (12w/1yr) in group 2 patients (SOF/DAC cases, n = 35)

eGFR (ml/min)	Pre- treatment (n =35)	Post-treatment		F	p
		After full regimen (12 weeks) (n = 35)	After one year* (n = 34)		
Min. – Max. Mean ± SD.	54.90–129.3 94.60±19.32	58.50–122.4 89.39±18.39	51.20–119.2 89.17±20.27	3.830	0.059
Δ change		**↓15.57 ± 5.21**	**↓16.13 ± 6.18**		

F: F test (ANOVA) with repeated measures

There was no significant change in eGFR after end of treatment and 1 year after treatment in group 3 (Table 6).

Table (6): Comparison of eGFR pretreatment and post- treatment (12w/1yr) in group 3 patients (SOF/SIM cases, n=22)

eGFR (ml/min)	Pre- treatment (n =22)	Post-treatment		F	p
		After full regimen (12 weeks) (n = 22)	After one year* (n = 21)		
Min. – Max. Mean ± SD.	60.30–117.2 92.71±15.11	59.0–113.3 88.36±16.27	60.80–111.7 89.01±15.72	1.565	0.225
Δ change		**↓14.9 ± 4.35**	**↓13.08 ± 3.57**		

F: F test (ANOVA) with repeated measures

DISCUSSION

Our results showed that the mean decrease in GFR in patients received SOF/DAC/Ribavirin were 16.12 ± 1.42 and 17.79 ± 4.1 after full 12-week regimen and after 1 year respectively. While the mean decrease in patients SOF/DAC were 15.57 ± 5.21 and 16.13 ± 6.18 after full 12-week regimen and after 1 year respectively. And the mean decreases in those who received SOF/SIM were 14.9 ± 4.35 and 13.08 ±3.57 after full 12-week regimen and after 1 year respectively. The decrease was not statistically significant in all 3 regimens.

Our results agreed with results by **Kawakami *et al.*** [8] study, which conducted on patients from multicenters in Japan. They compared daclatasvir (DCV) and asunaprevir (ASV) dual therapy for 24 weeks in normal kidney function patients (n: 54) versus hemodialysis patients (n: 18) infected with hepatitis C virus. At the end of the treatment, they found that both normal kidney function patients and patients on hemodialysis had no significant decrease in GFR.

Moreover, our results also agreed with the results by **Kao *et al.*** [9], in their meta-analysis conducted to systematically collect all the available clinical comparative studies for DAAs use in patients with different renal conditions. They specially focused on the efficacy and safety of DAAs for these populations. After comparing large number of studies, they found that the decrease in eGFR after direct antiviral therapy was limited only to patients with moderate to advanced CKD while those with normal kidney function had no risk of eGFR decrease.

Our study results also agreed with the results of **Medeiros *et al.*** [10] in their observational prospective study conducted to assess the safety of sofosbuvir based therapy (sofosbuvir with simeprevir, daclatasvir or ribavirin) on renal function conducted on 85 HCV infected patients with mean GFR ≥ 76.5 ± 15.2 mL/min/1.73 m^2 and mean serum creatinine 0.9 ± 0.17 mg /dl. At the end of the treatment there was an

increase of mean GFR to 84.2 ±15.1 and after one year to 90.5 ± 15.6, also there was decrease of mean serum creatinine to 0.76 ± 0.17 mg /dl after one year.

Another study supporting the benign effect of DAAs therapy on the GFR is the study conducted by **Sise *et al.* [11],** in Boston, a retrospective observational cohort study of HCV-infected patients received DAA therapies from 2013 to 2017. The patients were 115 HCV infected patients with baseline eGFR less than 60 mL/min/1.73 m^2. They compared the slope of GFR decline in the 3 years before DAAs therapy (sofosbuvir based regimen) to the slope of decline after therapy. They found that the annual decline in eGFR in the 3 years before the treatment was -5.98 ml/min per year that improved to – 1.32 ml/min per year after DAA therapy stating that DAA therapy for HCV treatment may slow CKD progression. **Sise *et al.*[11]** results did not prove DAAs to slow kidney disease progression- as they included patients with normal GFR- however their patients did not experience a significant decline in their GFR.

Kondo *et al.* [12], as well declared results similar to ours in their study conducted in Japan from 2014 to 2015 on 194 patients having HCV infection with normal kidney function (mean baseline eGFR≥ 60 ml/min/1.73 m^2) aiming to evaluate the impact of treatment of HCV with direct antiviral agents on the change of eGFR in these patients. The patients initiated daclatasvir and asunaprevir regimen for 24 weeks. They found that at the end of the treatment, there were no significant changes in the eGFR (P = 0.216), like patients in groups 1 and 2 in our study where daclatasvir containing regimens proved to be safe as regard GFR.

As for the study by **Sharma and his colleagues [13]**, that was done in India from 2015 to 2017 on a very special category of patients who were renal transplantation recipients with normal renal function and stable grafts. They aimed to evaluate efficacy and tolerability of direct antiviral agents in renal transplant recipients. Their study included 3 regimens: Sofosbuvir-ribavirin combination for 24 weeks (30 patients), ledipasvir-sofosbuvir combination (8 patients) and daclatasvir-sofosbuvir combination (7 patients). They declared the ledipasvir-sofosbuvir combination regimen to yield an excellent virological response and no significant decrease in GFR at the end of the treatment. While with the other two regimens there was significant decrease in the GFR at the end of the study. Our results disagreed with theirs as regard the daclatasvir-sofosbuvir combination regimen, as it was shown to be completely safe as regard GFR in our study (group 2 patients).

In contrast to our results, **Chen *et al.* [14],** study conducted in China from 2015 to 2017. They aimed to explore changes in hepatic and renal function indices in chronic hepatitis C patients treated with DAAs. They enrolled 43 patients treated with sofosbuvir (SOF)-containing regimens. They found a statistically significant decrease in GFR at the end of the treatment compared to the pretreatment value (eGFR: 86.7 ± 20.4 vs 80.5 ± 21.3 respectively).

Also, our results disagreed with the results of **Mallet *et al.* [15],** study, a retrospective cohort study conducted in France studied the effect of direct antiviral agents in 740 HCV infected patients with baseline GFR > 60 mL/min/1.73 m^2. The patients received sofosbuvir containing regimens, then assessed GFR post treatment and over a maximum 37 months post treatment. Mean eGFR decrease between first and last measure was 2.6 ($p < 0.001$).

CONCLUSION

The new direct antiviral agents like sofosbuvir, daclatasvir and simeprevir are safe regarding glomerular filtration rate in patients with normal renal function. However, the treated patients need careful monitoring of kidney function tests during the period of treatment.

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