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Assessment of Renal Function in Egyptian HCV Patients Treated with Combination Therapy of Sofosbuvir and Daclatasvir

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Abstract

BACKGROUND: According to the most recent Egyptian demographic health census, the estimated Hepatitis C virus (HCV) prevalence in the 15–59 age range was 14.7%. Globally, the incidence of renal impairment in HCV-positive individuals is 40% higher than in HCV-negative patients. HCV-induced renal impairment can range from mild-to-severe, and it frequently complicates the treatment outcome of HCV infection.

AIM: This study aimed to explore the changes in renal function in Egyptian HCV patients treated with a combination of Sofosbuvir (SOF) and Daclatasvir (DCV).

METHODOLOGY: Six hundred and eleven chronic HCV patients treated with SOF-DCV were enrolled. Patients were classified into three groups according to their baseline renal function: unimpaired group (estimated glomerular filtration rate [eGFR] ≥ 90 ml/min/1.73 m^2), mildly impaired group (eGFR of ≥60–89 ml/min/1.73 m^2), and moderately impaired group (eGFR of ≥30–59 ml/min/1.73 m^2). Every month during treatment and at 24 weeks after treatment (sustained virological response 24), the eGFR level was evaluated.

RESULTS: Our findings indicated that the eGFR level was significantly increased ($p < 0.001$) in all groups during the treatment but subsequent decline ($p < 0.001$) in all groups was documented after 6 months of treatment. Multivariate analysis identified baseline renal impairment (<90 ml/min/1.73 m^2, $p < 0.001$) and baseline anemia ($p < 0.001$) as independent risk factors for renal function deterioration at the end of treatment.

CONCLUSION: Clinical physicians should closely monitor renal function in patients treated with SOF-DCV. Furthermore, anemia therapy prior to SOF-DCV treatment should be recommended.

Introduction

Hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease worldwide, with approximately 130–150 million infected patients, of whom 15–30% develop cirrhosis with 3–5% of annual risk for hepatocellular carcinoma. In Egypt, according to the last demographic health survey in Egypt, An estimated HCV prevalence was 14.7% among the 15–59 years age group. Accordingly, Egypt has the highest HCV prevalence in the world. Globally, the incidence of renal impairment is 40% higher in HCV-positive patients compared to HCV negative [1], [2], [3]. HCV-induced renal impairment ranges from mild to end-stage renal disease, and it commonly complicates the treatment outcome of HCV infection. With the sustained virological response (SVR) rate that exceeds 95%, sofosbuvir (SOF) and daclatasvir (DCV) have become the main line of therapy adopted by the national hepatitis C treatment program in Egypt [4]. SOF and DCV are generally well-tolerated and reported a few adverse effects, including fatigue, nausea, headache, and insomnia. SOF is eliminated through the kidney, and its concentrations increase in patients with severe renal dysfunction. These drug levels in patients who pose estimated glomerular filtration rate (eGFR(≥30 ml/min/1.73 m^2 is similar to those in people with normal renal function [5]. Accordingly, Lim and Ahn reported that these drugs can be utilized without dosage modifications in moderately impaired renal function. Few studies have investigated the long-term renal outcomes after treatment with direct-acting antivirals [6]. The present study aimed to explore the changes in renal function in HCV patients treated with SOF-DCV combination through measures eGFR levels every month during the treatment and after 24 weeks of treatment (SVR24).

Methodology

Patients and study design

In this retrospective cohort study carried out in a single hospital serving a low-income community in Cairo, Egypt, all patients admitted to the Ahmad Maher Teaching Hospital with HCV between January 2018 and December 2019 were examined. HCV infection has been diagnosed dependent on clinical manifestations and a positive consequence of real-time PCR for blood specimens. The ethical committee of the General Organization of Teaching Hospitals and Institutes in Egypt has endorsed this research (GOTHI; IRB number HAM00104). The study was in compliance with the Helsinki Declaration. Six hundred and eleven HCV patients who were treated with SOF-DCV combination therapy and met the following criteria were enrolled in the present study: (1) infected with HCV; (2) negative for hepatitis B virus, human immunodeficiency virus and cytomegalovirus; (3) no severe renal function impairment (eGFR <30 ml/min/1.73 m^2) and end-stage renal disease; (4) no pregnancy; (5) no alcohol use; (6) no malignancy; (7) no hypertensive patients with renal impairment; (8) Patients with controlled diabetes mellitus were included; (9) SOF-DCV combination therapy prescribed according to the recommendation of the recent guidelines [5]. A total of 611 patients were treated with SOF, (400 mg/day)/DCV, (60 mg/day) for 12 weeks ending with SVR at 24 weeks post-treatment (SVR24).

Clinical data

The medical records of all patients were manually reviewed to determine eligibility based on the previous criteria. Baseline and follow-up analysis including complete blood count, liver enzymes, and serum creatinine was recorded by the outpatient department at baseline (initiation of treatment), at the end of first and second month of treatment, at end of treatment (EOT) and at 24 weeks after treatment, ending with undetected HCV-RNA quantitative PCR (SVR24). According to the World Health Organization criteria, anemia was defined as Hb <13 g/dL in men or Hb <12 g/dL in women [7]. eGFR was calculated using the Cockraft-Gault formula [8], [9]. Patients were stratified into three groups according to their baseline renal function: unimpaired (eGFR ≥90 mL/min/1.73 m^2), mildly impaired (eGFR of ≥60–89 mL/min/1.73 m^2), and moderately impaired (eGFR of ≥30–59 mL/min/1.73 m^2). Renal function progression was defined as a change in the eGFR category combined with a minimal percentage of decrease in eGFR by 25% or greater [10].

Statistical analysis

Data are presented as means ± SD or proportions. The differences in continuous and categorical variables across groups were assessed using *t*-test, ANOVA and Chi-square, as appropriate. Changes in eGFR from baseline to SVR24 were analyzed using the repeated-measures ANOVA. To identify factors associated with renal function deterioration multivariate logistic regression was used. $p < 0.05$ was considered as statistically significant. Statistical analysis was performed using SPSS 13.0.

Results

A total of 611 individuals were treated at Ahmed Maher Teaching Hospital and met the study's inclusion criteria. They were all given the SOF-based direct-acting antivirals SOF and DCV. Overall, 73.6% of the individuals were male, 6.9% were cirrhotic, and 22.9% had type-2 diabetes (DM). According to their baseline renal function and eGFR, all patients were categorized into three groups: 69% (n = 422) had unimpaired renal function (eGFR 116. 25 ml/min/1.73 m^2), 27 % (n = 164) had mild impairment (eGFR 76.89 ml/min/1.73 m^2; CKD stage II), and 4 % (n = 25) had moderate impairment (eGFR 55.14 ml/min/1.73 m^2; CKD stage III). Patients with moderate renal impairment were older than those in the other groups, and the unimpaired group had greater ALT and platelet levels (Table 1). Following that, there was a considerable drop in eGFR from baseline, 1st and the 2nd month to SVR24, and EOT to SVR24 (Figure 1).

Table 1: Baseline characteristics of the study population

Variables[1]	Unimpaired group (n = 422)	Mild group (n = 164)	Moderate group (n = 25)	p-value
Age, years	51.52 ± 11.98	62.85 ± 8.61	67.44 ± 8.66	0.01
Male, n (%)	314 (74.41)	119 (72.56)	17 (68)	0.73
Diabetes mellitus, n (%)	93 (22.04)	41 (25)	6 (24)	0.74
Cirrhosis, n (%)	31 (7.35)	8 (4.88)	3 (12)	0.35
INR	1.06 ± 0.1	1.05 ± 0.1	1.06 ± 0.1	0.87
Total bilirubin (mg/dl)	0.56 ± 0.22	0.59 ± 0.23	0.53 ± 0.21	0.30
Serum Albumin	4.14 ± 0.39	4.13 ± 0.41	4.06 ± 0.36	0.65
AST (U/L)	43.54 ± 31.48	38.85 ± 24.53	53.4 ± 40.88	0.05
ALT (U/L)	49.32 ± 36.54	41.27 ± 27.52	41.92 ± 31.75	0.03
Hemoglobin (g/dl)	13.99 ± 1.66	13.98 ± 1.38	13.69 ± 1.28	0.65
Anemia, n (%)	91 (21.56)	31 (18.9)	6 (24)	0.72
Platelets *10^3/μ L	268 ± 80	247 ± 72	233 ± 62	0.01
TLC *10^3/μ L	6.69 ± 1.77	6.56 ± 1.73	6.31 ± 1.71	0.46
Serum creatinine (mg/dl)	0.89 ± 0.14	1.03 ± 0.13	1.14 ± 0.14	0.01
eGFR (ml/min/1.73 m^2)	116. 25 ± 22.95	76.89 ± 7.65	55.14 ± 4.22	0.01

Continuous variables are presented as means ± SD, and categorical data as proportions. INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TLC: Total leucocytic count.

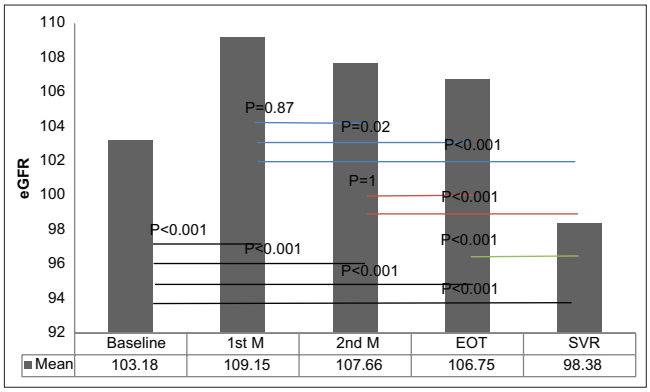

Figure 1: Estimated glomerular filtration rate (eGFR) comparison among all patients Using ANOVA with repeated measures. A bar chart with bars represents mean levels of the eGFR till 24 weeks after treatment (SVR24). A significant increase in eGFR from baseline to the end of first and second month and to the EOT, and a significant decline in eGFR from baseline to SVR24 are representing in black lines with their corresponding p values. While blue lines represent the decline from 1st month to 2nd month, EOT and SVR24 with their p values. The red lines represent the decline in eGFR from 2nd month to EOT and SVR24, and the green line represents the significant decline from EOT to SVR24

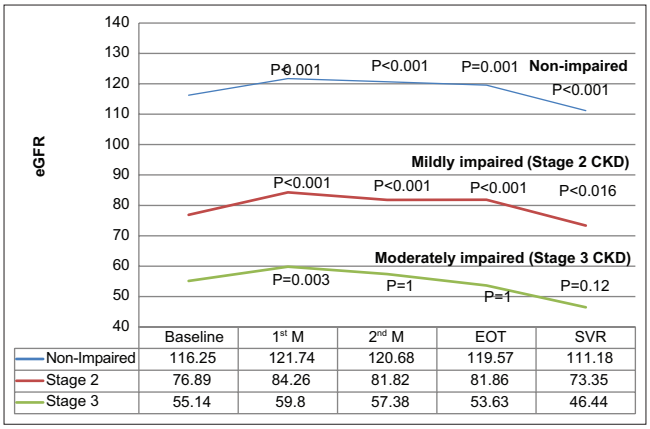

Figure 2: eGFR comparison within renal impairment subgroups using ANOVA with repeated measures. Each trendline represents the mean eGFR value for that subgroup from baseline to SVR24, with the mean value shown in the underlying table as well. The represented p value indicates pairwise comparison from baseline to that time where p value is shown adjacent

The graph depicts the mean eGFR levels from baseline to SVR24 (Figure 2). The pattern of eGFR rise is similar for all patients, although it tends to decrease steadily during the SVR 24 period. There was a substantial rise in eGFR from baseline to EOT (p = 0.001) and a significant drop from baseline to SVR (p = 0.001) and from EOT to SVR (p = 0.001) in the unimpaired group. In the mildly impaired renal function group, eGFR from baseline to EOT (p = 0.001). On the contrary, there is a substantial decrease in eGFR from baseline to SVR (p = 0.02) and EOT to SVR (p = 0.001). In the moderately impaired renal function group, there was no significant decrease in eGFR from baseline to EOT (p = 1), a significant decrease from baseline to SVR (p = 0.12), and a considerable decline from EOT to SVR (p < 0.001).

Renal function deterioration was defined as a change in the eGFR category with a 25% drop in eGFR from baseline to EOT and SVR24. At SVR24, 33 patients (5.4%) showed renal function impairment; out of these, 10 (2.4%) were in the unimpaired group, 15 (9.1%) in the mildly impaired group, and 8 (32%) in the significantly impaired group (p = 0.001). According to univariate analysis, baseline factors such as mild and moderate renal impairment (p = 0.001), anemic patients (p = 0.001), older age (p = 0.03), and platelet level (p = 0.001) were significant predictors of renal function degradation at SVR24. For multivariate analysis, any variables with a p < 0.2 were included. Baseline renal impairment (p =0.001) and baseline anemia patients (p = 0.001) were identified as independent risk variables for renal function deterioration at EOT and SVR24, according to multivariate analysis (Tables 2 and 3). In addition, no patients with cirrhosis experienced additional worsening of renal function from EOT to SVR24. However, when comparing renal function degradation from EOT to SVR24 in both groups, this was not significant (Table 4).

Table 2: Univariate and multivariate analysis of predictive factors for renal function deterioration at EOT

Variables[2]	No Deterioration (595 pts)	Deterioration (16 pts)	Univariate P-value	Multivariate P-value
Baseline kidney impairment, n (%)				
Non-impaired	417 (98.8)	5 (1.2)		
Mild-impairment	153 (93.3)	11 (6.7)		
Moderate-impairment	25 (100)	0 (0)	0.002	0.002
Diabetes mellitus, n (%)				
No	459 (97.5)	12 (2.5)		
Yes	136 (97.1)	4 (2.9)	0.84	
Liver cirrhosis, n (%)				
No	556 (97.7)	13 (2.3)		
Yes	39 (92.9)	3 (7.1)	0.057	0.054
Anemia, n (%)				
No	477 (98.8)	6 (1.2)		
Yes	118 (92.2)	10 (7.8)	0.0003	0.0003
Age, years	55.2 ± 12.4	55.56 ± 12.5	0.909	
Body weight, Kg	82.69 ± 10.28	85.62 ± 9.2	0.259	
Baseline INR	1.06 ± 0.1	1.05 ± 0.1	0.873	
Baseline total bilirubin (mg/dl)	0.56 ± 0.22	0.62 ± 0.22	0.283	
Baseline serum Albumin (g/dl)	4.13 ± 0.39	4.14 ± 0.51	0.925	
Baseline AST level (U/L)	42.65 ± 30.46	44.00 ± 25.68	0.860	
Baseline ALT level (U/L)	46.73 ± 34.24	51.5 ± 37.55	0.584	
Baseline TLC level (*10^3/mm^3)	6.65 ± 1.75	6.13 ± 1.94	0.242	
Baseline platelets level (*10^3/mm^3)	262 ± 78	225 ± 50)	0.062	0.155

[2]Continuous variables are presented as means ± SD, and categorical data as proportions. INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TLC: Total leucocytic count.

Table 3: Univariate and multivariate analysis of predictive factors for renal function deterioration at SVR24

Variables[3]	No Deterioration (578 pts)	Deterioration (33 pts)	Univariate P-value	Multivariate P-value
Baseline kidney impairment, n (%)				
Non-impaired	412 (97.6)	10 (2.4)		
Mild-impairment	149 (90.9)	15 (9.1)		
Moderate-impairment	17 (68)	8 (32)	<0.001	<0.001
Diabetes mellitus, n (%)				
No	442 (93.8)	29 (6.2)		
Yes	136 (97.1)	4 (2.9)	0.14	0.18
Liver Cirrhosis, n (%)				
No	539 (94.7)	30 (5.3)		
Yes	39 (92.9)	3 (7.1)	0.72	
Anemia, n (%)				
No	467 (96.7)	16 (3.3)		
Yes	111 (86.7)	17 (13.3)	<0.001	<0.001
Age, years	54.9 ± 12.3	59.8 ± 12.5	0.03	0.7
Body weight, Kg	82.9 ± 10.2	80.8 ± 11.8	0.25	
Baseline INR	1.1 ± 0.1	1.1 ± 0.1	0.9	
Baseline total bilirubin (mg/dl)	0.6 ± 0.2	0.6 ± 0.2	0.86	
Baseline serum Albumin (g/dl)	4.1 ± 0.4	4.2 ± 0.5	0.2	
Baseline AST level	42.3 ± 30	48.5 ± 36.1	0.26	
Baseline ALT level	46.9 ± 34.2	46.5 ± 36.7	0.9	
Baseline TLC level (*10^3/mm^3)	6.7 ± 1.7	6.2 ± 1.8	0.15	0.44
Baseline Platelets level (*10^3/mm^3)	263 ± 79	225 ± 50	<0.001	0.56

[3]Continuous variables are presented as means ± SD, and categorical data as proportions. INR: International normalized ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TLC: Total leucocytic count.

Discussion

This study revealed a significant drop in eGFR at SVR24 even in participants with normal renal function at the start. Chiu *et al*. [11] reported the effect of SOF-based regimens on SVR24 recently, demonstrating a drop in eGFR from SVR12 to SVR24 and SVR48 in their patients. In contrast, other studies have shown that HCV cure is associated with a considerable improvement in eGFR post-treatment [12], [13]. Furthermore, Chiu *et al*. [11] observed an initial reduction in eGFR toward EOT, followed by a transient spike at SVR12, followed by a further decline in eGFR between SVR24 and SVR48 [11], [14]. The current study found that eGFR improved significantly over the first few months of DAA treatment. Patients with unimpaired or mild renal impairment continued to demonstrate a substantial improvement in eGFR until EOT, but those with severe renal impairment had a non-significant decline in eGFR. The initial improvement in renal functions observed in this study, as well as those observed by Chiu *et al*. [11], at SVR12, can be explained by HCV clearance with the elimination of their harmful effect on renal tissues, whereas subsequent eGFR decline in both studies should raise concerns about the renal safety profile of SOF-based regimens and the effect of DAA therapy on proteinuria should be evaluated.

Table 4: Comparing the renal function deterioration between Cirrhotic and non-cirrhotic groups

Groups	No deterioration	Deterioration	%	p-value
Non-Cirrhotic, n	552	17	93.10%	
Cirrhotic, n	42	0	6.90%	p = 0.5

Another possible explanation for the long-term eGFR reduction after SOF-DCV therapy is an increase in muscle mass in cured HCV patients [15], [16]. This study found a practically significant decrease in eGFR among cirrhotic patients at EOT (p = 0.054), but no difference at SVR24 (p = 0.72). This quicker reduction in eGFR in cirrhotics (at EOT) compared to non-cirrhotics (at SVR24) could be related to an improvement in their muscle mass following HCV eradication.

Assessment of tubular damage extent and its effect on the GFR by measuring the neutrophil gelatinase-associated lipocalin and cystatin C-based may be more relevant to assessing renal function, particularly in cirrhotic patients [17], [18]. Renal function worsening was defined as a drop in eGFR of more than 25% from baseline to EOT and SVR24. According to multivariate analysis, baseline renal impairment and baseline anemia were indicative of renal function decline at SVR24. Our findings are fall in with other previously published reports [19], [20]; that found decreasing renal function was more likely in intermediate renal impairment (32%) than in mild impairment (9.1%).

Conclusion

Treatment of patients with renal impairment with SOF-based regimens necessitates continuous close monitoring. In addition, prior to SOF-DCV therapy, anemia should be corrected and additional long-term studies with various DAA regimens are still needed.

Limitations

The study has certain drawbacks. It is a retrospective study, and the effect of DAA therapy on proteinuria was not studied because the majority of patients were not evaluated for proteinuria. Finally, individuals who did not receive or failed the SOF-DCV regimen were excluded from the trial.

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Authors' Contributions

HM and AH were involved in the conception and design of the study. EE and HT involved in data collection. HE involved in data analysis and methodology. AH involved in writing the article and revising it critically for important intellectual content. MM involved in final reviewing and approval the version for submission.

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