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STUDY OF THE EFFECT OF SOFOSBUVIR BASED THERAPY ON ESTIMATED GLOMERULAR FILTRATION RATE IN EGYPTIAN CHRONIC HEPATITIS C PATIENTS

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ABSTRACT:
Introduction: Recent Hepatitis C virus (HCV) treatments, direct-acting antiviral agents (DAAS), have shown >90% efficacy in hepatitis C virus treatment and achieving the goal of a sustained virological response (SVR).Sofosbuvir acts as an inhibitor of viral RNA synthesis through suppression of "NS5B protein of the virus. Thus, it appears to have a high barrier to develop resistance. Sofosbuvir is only administered orally and mainly excreted renally. **The aim of the work** was to study the effect of sofosbuvir based therapy on the estimated glomerular filtration rate (eGFR) of Egyptian chronic hepatitis C patients with normal kidney function or mild renal dysfunction. **Subjects and methods:** This study was carried out on 100 chronic hepatitis C patients with eGFR ≥ 60 ml/ min/1.73 m2 .Before starting treatment with DAAS, all patients were subjected to full history taking, clinical examination and laboratory investigations, including: HCV PCR, HBsAg, liver function tests, complete blood picture, prothrombin activity, alfa fetoprotein, fasting blood sugar,HBA1c and renal functions. eGFR was calculated by using the Chronic kidney disease- Epidemiology Collaboration equation (CKD-ECI).All tests were repeated at the end of treatment. Also abdominal ultrasound was performed before and after treatment. **Results:** There were no statistically significant differences in either renal function tests or eGFR before and after treatment. There were improvements in the liver enzymes, liver functions tests and Alfa fetoprotein. **Conclusions:** Sofosbuvir based therapy is safe and effective in treating chronic hepatitis C patients even in patients with mild chronic kidney diseases (CKD).

Keywords: DAAS, CHC, eGFR, CKD.
Abbreviations: (DAAs) Direct-acting antiviral agents, (CHC) Chronic hepatitis C, (eGFR) estimated glomerular filtration rate, (HCV) Hepatitis C virus,(CKD) Chronic kidney diseases,(NS5B) Non-structure protein 5B

1. INTRODUCTION

Hepatitis C viral infection is endemic in Egypt with the highest prevalence rate of HCV Ab in the world (14.7%). [1] Direct-acting antiviral agents (DAAs) are molecules that target specific non-structural proteins of virus C and result in disruption of viral replication and infection. [2] There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. They are; non-structural proteins NS 3/4A protease inhibitors (Simiprevir, paritaprevir), NS5B nucleoside polymerase inhibitors (Sofosbuvir), NS5B non-nucleoside polymerase inhibitors (Dasabuvir), and NS5A inhibitors (Daclatasvir). [3] National protocol of HCV treatment used in Egyptian patients infected with HCV (genotype 4) is a combination of daily sofosbuvir and any other DAAs. Compared to previously used treatments, sofosbuvir-based regimens provide a higher cure rate (>90%), fewer side effects, and a two- to four-fold reduction in duration of therapy.[4, 5]It allows most people to be treated successfully without the use of peglated interferon.[6,7]. Sofosbuvir is only administered orally. The peak concentration after oral administration is 0.5–2 hours post-dose, regardless of initial dose.[8&9] It is a prodrug. It is metabolized to the active metabolite antiviral agent GS-461203 (2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-triphosphate) in the liver. GS-461203 serves as a defective substrate for the NS5B protein, which is the viral RNA polymerase, thus acts as an inhibitor of viral RNA synthesis.[10] It appears to have a high barrier to develop resistance .Following a single 400mg oral dose of sofosbuvir 80٪ is excreted in urine; 14٪ is excreted in faeces, and 2.5٪ in expired air.[11]
Sofosbuvir in patients with HCV infection and mild to moderate renal impairment (eGFR ≥30 ml/ min/1.73 m2) should be given according to the general recommendations. No dose

adjustment is needed, but those patients should be carefully monitored. On the other hand, Sofosbuvir should be used with caution in patients with an eGFR<30 ml/min/1.73 m^2 or with end-stage renal disease because no dose recommendation can currently be given to these patients. [3]If HCV treatment is urgently needed in patients with severe renal impairment (eGFR<30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis, they may receive sofobuvir free regimen (Ombitasvir and Paritaprevir). [3]

The aim of the work was to study the effect of sofosbuvir based therapy on the estimated glomerular filtration rate of Egyptian chronic hepatitis C patients with normal kidney function or mild renal dysfunction

Patients and methods:

Study design

This prospective study was conducted on100 chronic hepatitis C patients who were treated using sofosbuvir (400 mg/day) and Daclatasvir(60mg/day)with [in difficult to treat patients(Peg-IFN treatment experienced patients with total bilirubin >1.2 mg/dl, serum albumin < 3.5g/dl, INR >1.2, platelet count < 150.000/mm3and Child score< 8 {Child A})] or without [in easy to treat patients(Treatment naïve patients with total bilirubin ≤1.2 mg/dl, serum albumin ≥3.5g/dl, INR ≤1.2, platelet count ≥150.000/mm3 and non cirrhotic)] weight based ribavirin(<70 kg took 1000mg /day, ≥70 kg took 1200 mg/ day) for 12 weeks. They were recruited from outpatient Hepatology Clinic in Medical Research Institute, Alexandria University. For sofosbuvir; Gratisovir® (Pharco Pharmaceuticals, Alexandria, Egypt) or Soflanork® (Mash Premiere, Cairo, Egypt) or Heterosofir® (Pharmedhealthcare, Cairo, Egypt) was used, while for daclatasvir; Daktavira®(European Egyptian Pharmaceutical Industries, Amreya, Egypt) or Daclavirocyrl® (Marcyrl Pharmaceutical Industries, Cairo, Egypt) was used. For ribavirin; we used Ribavirin ® 200, 400 mg capsules (Minapharm Pharmaceuticals, Cairo, Egypt).

Inclusion criteria , according to the National Protocol for the Treatment of CHC Patients in Egypt, included chronic HCV infected patients (either cirrhotic or non-cirrhotic), who Fulfilled the criteria for treatment with antiviral therapy (positive PCR for HCV RNA and age ≥18 years) with eGFR ≥ 60ml/ min/1.73 m^2.

The exclusion criteria for the treatment , according to the National Protocol for the Treatment of CHC Patients in Egypt, included any of the following: Child's C cirrhotic patients, platelets count lower than 50,000/mm^3, hepatocellular carcinoma HCC(except 6 months after curative intervention with no evidence of activity by CT or MRI), extra hepatic malignancy (except after 2 years of disease free interval), pregnancy or inability to use effective contraception, inadequately controlled diabetes mellitus (HbA1c >8٪) or hypertension ,patients with collagenic diseases, patients with HCV related CKD and co infection with HBV or HIV.

All selected patients provided a written informed consent before enrolment in the study. The study was approved by the Ethical Committee of Medical Research Institute, Alexandria University, Egypt.

.**Data and samples collection:**

All selected patients were subjected to the following before treatment: medical history of the patients, including history of renal impairment or any nephrotoxic medication, complete physical examination(to detect signs of hepatic dysfunction)and laboratory investigations, including: complete blood picture. Fasting blood glucose level and HbA1c. Liver function tests included: serum albumin, serum bilirubin (total and direct), the international normalized ratio (INR), liver enzymes (ALT and AST) and alpha-fetoprotein (AFP).Renal function tests included blood urea and serum creatinine. Baseline eGFR was calculated before starting treatment with DAAs using the CKD Epidemiology Collaboration equation (CKD-EpI):i.e., $eGFR = 141 \times \min(Scr \times 0.0113/k, 1)^{\alpha} \times \max(Scr \times 0.0113/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, $^{\alpha}$ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1.[12] Viral markers [HCV- PCR, hepatitis B surface antigen (HBs Ag) &HIV antibodies], ECG and echocardiography for patients >65 years old and abdominal ultrasound (U/S) were also performed.

Most of the entire above mentioned laboratory investigations and U/S abdomen were repeated for all patients at the end of the treatment (12weeks).PCR for HCV was repeated for all patients after three months from the end of the treatment (24weeks from the start of the treatment)

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**. (**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, standard deviation and median. Significance of the obtained results was judged at the 5% level

The used tests were

1- **Paired t-test:** For normally distributed quantitative variables, to compare between two periods.
2- **Wilcoxon signed ranks test:** For abnormally distributed quantitative variables, to compare between two periods

RESULTS

Demographic data of the patients:

36% of patients were male and 64% were female. Mean age was (53.36 ± 11.10year).Mean body mass index (BMI) was (32.04 ± 5.67Kg/m^2).

Patients were distributed according to medical past history:

Twelve patients had controlled diabetes mellitus, six patients had controlled hypertension, while four patients had both controlled diabetes mellitus & hypertension.

Child Pugh Class and values of PCR HCV before and after treatment in the studied patients:

All patients were Child Pugh Class A (72% were score 5 & 28% were score 6).The values of PCR HCV ranged between 0.2 – 1000.0 x 10^4 with mean value 140.3 ± 203.4 x 10^4 before therapy. At the end of the treatment all patients (100%) were negative for PCR HCV. After three months from the end of treatment (24 weeks from the start of treatment), ninety six patients (96%) achieved sustained virological response (SVR) with negative PCR for HCV RNA.

Abdominal U/S findings before and after treatment in the studied patients: (Table1).

Neither of the patients had ascites nor any hepatic focal lesions. All the patients had normal kidneys. There was no change in the ultrasound findings before and after therapy.

Comparison of the laboratory investigations before and after treatment in the studied patients: (Table 2)

As regard the haemoglobin (Hb) level, there was a statistically significant decrease in Hb after treatment (p=0.026). On the other hand the white blood cells (WBC) and platelet (plat) count didn't change significantly before and after treatment. ALT, AST, serum bilirubin, AFP and INR showed statistically significant reduction after treatment (p=0.001), while the serum albumin showed statistically significant increase after treatment (p=0.001).Comparison between the blood urea level and serum creatinine level before and after treatment showed no statistically significant difference (p=0.061and 0.221, respectively).

The change in the eGFR before and after treatment in the studied patients:

(Table 3)

Before treatment fifty patients (50%) showed normal kidney function (eGFR ≥90 ml/min/1.73m^2),while fifty patients (50%) showed mild CKD (90>eGFR≥60 ml/min/1.73m^2).After therapy, five out of fifty patients (10%) with normal kidney function deteriorated to mild CKD, while two out of fifty patients (4%)with mild CKD deteriorated from mild to moderate CKD (60>eGFR≥45 ml/min/1.73m^2).So ,only 7(7%) patients out of 100 show deterioration of kidney function after treatment compared to 93(93%) patients who showed no deterioration of kidney function after treatment .

Comparison of eGFR before and after treatment in the studied patients : (Table 4) The mean eGFR before and after treatment showed no statisticaliy significant difference (p=0.069). **(Figure 1)**.

DISCUSSION

There is no doubt that the advent of direct-acting antiviral agents (DAAs) in the few recent years has revolutionized HCV treatment.[13] Reports of possible hepatotoxicity have emerged in patients with decompensated cirrhosis [14] and also possible concerns about potential nephrotoxicity have been raised, particularly in patients with pre-existing CKD[15].

The aim of the work was to study the effect of sofosbuvir based therapy on estimated glomerular filtration rate and liver profile in Egyptian chronic hepatitis C patients.

In the present work, 96% of patients achieved sustained virological response (SVR) and there was a relapse in only 4% of patients. This high result of SVR was comparable to many previous results.[14, 16-20].

There has been a concern about serious adverse effects with the use of sofosbuvir in patients with renal impairment. The area under the concentration-time curve (AUC) of GS-331007(which reflects the actual body exposure to drug after administration of a dose of the drug) is a statistical test which depends on the rate of elimination of the drug from the body. In the case of GS-331007,it is increased by 56% in mild, 90% in moderate and 456% in severe renal impairment subjects, compared to normal subjects according to a study by Cornprost MT et al.[21] A high GS-331007 level was seen in patients with ESRD caused by lack of renal clearance, and a four hour haemodialysis session removed nearly 18% of the circulating GS-331007.This might explain why sofosbuvir therapy needs an ultimate caution in patients with renal impairment and especially the severe type or the ESRD on haemodialysis.[15, 22]

EASL guidelines of 2016[3] preferred to use sofosbuvir free regimens in patients with renal impairment with adequate follow up, while the guidelines of EASL 2018[23] put restrictions on the use of sofosbuvir in CHC patients with renal impairment(severe impaired renal functions; eGFR<30 ml/min/1.73 m^2).

By following up our 100 CHC patients who included patients with normal kidney functions and early stage CKD we found that there was no significant decline in the level of serum creatinine or any significant decline in the eGFR after treatment with sofosbuvir combination therapy.

This result agreed with both EASL guidelines (2016and2018) [3, 23]regarding safety of sofosbuvir in patients with normal kidney functions or starting therapy with minimal decline in eGFR.

Our result is compatible with Hepatitis C Virus Therapeutic Registry and Research Network (HCV-TARGET) database which showed that episodes of worsening kidney function (defined by AKI diagnosis) were more common in patients with eGFR ≤ 45ml /min per 1.73 m2 compared with a reference group with eGFR >45 ml/min per 1.73 $m^{2[15]}$.

Another study by Sise et al.,[24] detected that patients with lower eGFR, on average, tended to have smaller declines in eGFR on therapy compared with patients with eGFR≤45 ml/min per 1.73 m2.

Shin et al.[25] in a Korean study demonstrated that SOF-based regimens resulted in high SVR12 rates without serious adverse events in patients with moderately impaired renal function. Both CKD stage 3A and CKD stage 3B patients can be considered for treatment with a SOF-based regimen. However clinicians should be cautious and monitor for worsening of renal functions during treatment.

As regards liver enzymes; AST and ALT, which are known to have clinical significance in viral hepatitis and other forms of liver disease associated with hepatic necrosis, there was a significant decline in ALT and AST .This finding in our study indicates the significant role of DAAs in improving hepatic necro-inflammatory changes induced by viral infection. This constitutes one of the goals of therapy of chronic HCV as stated in the EASL guidelines published in

2018.[23] Also, when considering liver function tests including serum albumin, serum bilirubin and INR there was a statistically significant rise in the serum albumin level with significant reduction in the level of total serum bilirubin and level of INR after treatment with DAAS. Also there was significant decrease in the level of alpha-fetoprotein after the end of treatment.

Those results were matching with the clinical study published in March2018 by Ahmed et al., which showed that there is a statistically significant reduction in ALT and AST in responders to therapy following 12weeks of treatment.[26] Also, in the study done by Menoufia University (both Faculty of Science and Faculty of Medicine), the biochemical findings revealed a significant improvement in the levels of ALT and AST in patients after treatment with SOF-based therapy regimens as compared to the corresponding pre-treatment recorded data, while no significant differences were detected on the levels of total bilirubin or creatinine.[27]

In an European study done on 34 patients to assess the possibility of delisting of liver transplant candidates with chronic hepatitis C after viral eradication, results showed that all oral DAAs were able to reverse liver dysfunction and favoured the inactivation and delisting of about one patient out-of-three and one patient out-of-five in 60 weeks, respectively.[28].

CONCLUSION

Sofosbuvir based therapy is safe and effective in treating chronic hepatitis C patients even in patients with mild CKD.

Limitation of the study:

- Small sample size, so further study with large sample size will be needed
- Follow up of kidney function after treatment stoppage was not done due to lack of patient's adherence.
- Patients with mild to moderated or moderate to severe CKD were not included in the study, as we were following the inclusion and exclusion criteria of the National Protocol for the Treatment of CHC patients in Egypt.

Conflict of interests

The authors declare that there are no conflicts of interests.

Table (1):Distribution of the studied patients according to U/S findings (N=100).

U/S	No.	%
Normal	28	28.0
Coarse Liver	64	64.0
Fatty liver	8	8.0

Table (2):Comparison of the laboratory investigations before and after treatment in the studied patients (N=100).

Lab tests	Before Mean ± SD	After Mean ± SD	Test of Sig.	P
WBCs (10^3/ cmm)	5..90 ± 2.41	5.60 ± 1.84	Z= 1.597	0.110
HB (g/dl)	12.67 ± 1.39	12.34 ± 1.41	t= 2.266*	0.026*
Plat (10^3/cmm)	177.7 ± 95.76	174.7 ± 66.99	Z =1.836	0.066
AST (IU/ml)	66.06 ± 49.15	27.92 ± 11.25	Z=7.961	<0.001*
ALT (IU/ml)	60.54 ± 47.58	28.36 ± 13.40	Z=6.571*	<0.001*
Albumin (g/dl)	3.79 ± 0.47	3.99 ± 0.51	t=6.750*	<0.001*
T.Bilirubin (mg/dl)	0.92 ± 0.38	0.68 ± 0.28	Z =5.599	<0.001*
AFP(ng/ml)	15.45 ± 26.75	12.01 ± 21.31	Z =6.338*	<0.001*
INR	1.14 ± 0.13	1.10 ± 0.09	t= 5.089*	<0.001*
Creatinine (mg/dl)	0.81 ± 0.12	0.83 ± 0.12	t=1.895	0.061
Urea (mg/dl)	35.96 ±11.64	36.62±10.48	t=1.22	0.221

t: Paired t-test Z: Wilcoxon signed ranks test

p: p value for comparison between the two studied periods *: Statistically significant at $p \leq 0.05$.

(WBC) White blood cells . (Hb) Haemoglobin (plat) platelets

(INR) The international normalized ratio (AFP).Alpha-fetoprotein

Table (3): The change in the eGFR before and after treatment in the studied patients (N=100):

eGFR		AFTER TREATMENT		
		(Normal)	(Mild CKD)	(Mild to Moderate CKD)
BEFORE	(Normal) N=50(50%)	45(90%)	5(10%)	0(0%)
TREATMENT	Mild CKD) N=50(50%)	0(0%)	48(96%)	2(4%)

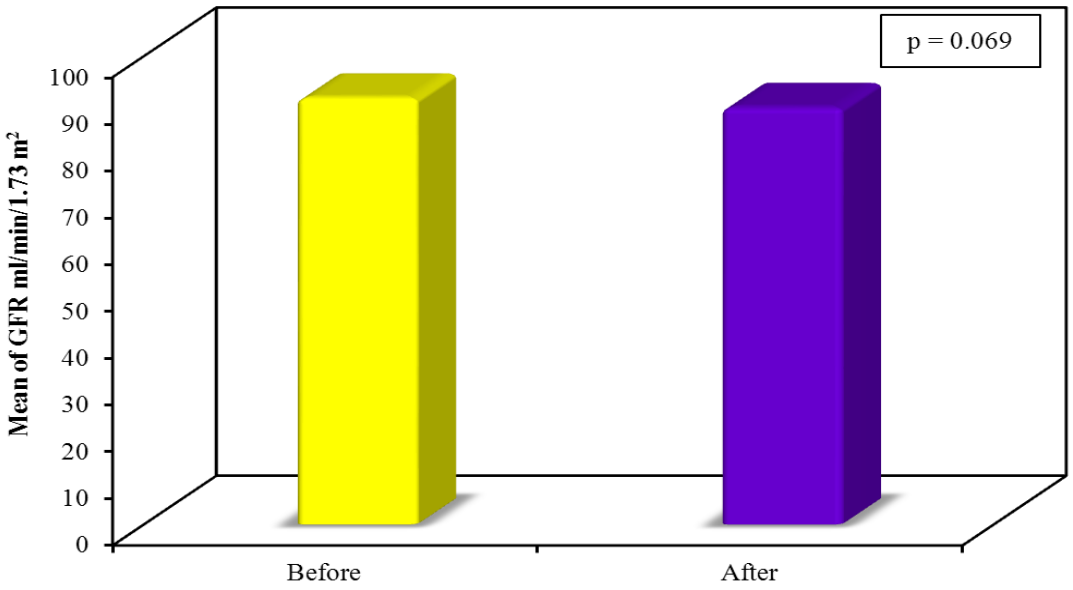
eGFR: Estimated glumerular filtration rate. CKD: Chronic kidney disease
Normal: (eGFR≥90ml/min/1.73m^2). Mild CKD: (90>eGFR≥60ml/min/1.73m^2
Mild to Moderate CKD: (60>eGFR≥45ml/min/1.73m^2)

Table (4): Comparison of eGFR before and after treatment in the studied patients group: (N = 100)

	Before	After	t	p
eGFR(ml/min/1.73m^2)				
Min. – Max.	65.20 – 129.70	55.90 – 134.90	1.836	0.069
Mean ± SD.	91.05 ± 15.30	89.01 ± 16.31		

t: Paired t-test
p: p value for comparison between the two studied periods *: Statistically significant at p ≤ 0.05
eGFR: Estimated glumerular filtration rate

Figure (1):Comparison of eGFR before and after treatment in the studied patients group:(n = 100)



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