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Effect of Direct Acting Anti-Hepatitis C Drugs on the Heart

Mohamed Mahmoud Ahmed[1], Muhammad Abdel-Gawad[2], Mahmoud Ahmed Abd elbaset[1], Assem Elkady *[1]

Departments of [1]Cardiology and [2]Hepatology, Gastroenterology & Infectious Diseases, Faculty of Medicine, Al-Azhar University, Assiut

***Corresponding author:** Assem Abd elraheim Ahmed Abd elraheim, **Mobile:** (+20) 01125715555, **E-Mail:** assemqadi21@gmail.com

ABSTRACT

Background: The introduction of direct acting antiviral agents (DAAs) for its treatment represents a major advance in terms of sustained virologic response (SVR) rates and adverse effect profiles; however, few data are available on cardiac side effect.

Objectives: We aimed to study the effect of DAA on echocardiographic changes.

Patients and Methods: One hundred and fifty (150) patients with HCV were divided into 3 groups according to type of treatment given: Group 1 included 50 patients received dual therapy (Sofosbuvir plus Daclatasvir), group 2 included 50 patients received triple therapy (Sofosbuvir, Daclatasvir and Ribavirin), and Group 3 included 50 patients received Qurevo ± Ribavirin. All participants went through a cardiac assessment for detection of development of cardiovascular changes after 3 months of treatment.

Results: In compare to baseline values, no significant difference regarding echocardiographic findings and the mean changes in values of QT & QTC interval among all patients' groups. Dual therapy produced a significant lower serum levels of Albumin (Alb), prothrombin time (PT) and a significant increase in the serum levels of alkaline phosphatase, hemoglobin. Triple therapy produced significant lower serum levels of ALT, AST, total bilirubin, hemoglobin concentration, WBCs, RBCs and platelets, while a significant increase was observed in the mean values of the Alb and alkaline phosphatase. In the third group, there was a significant decrease in serum levels of PT while a significant increase was observed in serum values of alkaline phosphatase.

Conclusion: DAAs are safe drugs to use in non-cardiovascular patients and in cardiac patients with caution and avoidance of some drugs.

Keywords: Anti-Hepatitis C Drugs, HCV, Heart, DAAs, hepatitis C virus, interferon free regimens.

INTRODUCTION

Hepatitis C virus (HCV) is considered one of the major public health problems all over the world [(1)]. Egypt has the highest prevalence of HCV infection in the world. HCV genotype 4 is the most predominant isolated genotype from 90% of the HCV-infected patients in Egypt [(2)].

The main objective of the treatment for chronic HCV infection is to attain a sustained virologic response (SVR), defined as undetectable HCV-RNA, 12 weeks after completing the treatment course. Long-term follow-up studies reported by **Backus *et al.*** [(3)], they showed that sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C.

The development and improvement of the HCV treatments were continuing. The use of interferon in the treatment proved to cause health issues and consequently was excluded from the treatment. However, the use of DAAs has raised some concerns about the possibilities of cardiac toxicity which could result in toxic cardiomyopathy [(4)].

Harvoni is a tablet in which there is combination of two DAA: Ledipasvir (NS5A inhibitor) and Sofosbuvir (NS5B Nucleotide Polymerase Inhibitor). It was approved by the FDA (Food and Drug Administration, USA) in October, 2014 for the treatment of naïve and treatment-experienced patients suffering from chronic hepatitis C genotype 1 4, 5 and 6. Most of the patients tolerate this medication very well [(3)]. Concerning, the new DAAs, FDA recently announced a change in labeling for the hepatitis C antiviral LDV/SOF (Harvoni) and SOF (Sovaldi) after the manufacturers reported bradycardia, pacemaker intervention, and even death in patients who took the medications along with amiodarone [(5)].

Advances in trans-thoracic echocardiography with the application of strain analysis and speckle tracking provide sensitive assessment of cardiac function that may predict clinical outcomes in various heart diseases, including those with HCV infection [(6)]. The aim of the study was to assess cardiac side effects of direct acting anti hepatitis C drugs.

PATIENTS AND METHODS

One hundred and fifty (150) patients with chronic hepatitis C virus infection attending to Sohag Center of Cardiac and Digestive system & Al-Azhar Assiut University Hospital were enrolled in this study. The study was conducted through the period from February 2018 to September 2018. The infection with hepatitis C virus in the studied cohort was confirmed by the positivity of HCV antibodies using ELISA and further confirmed by Real time PCR for quantitative measurement of the HCV RNA.

Ethical and patients' approval: The study protocol was approved by the Institutional Ethics Committee

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of Al-Azhar University. The study was explained to all participants and only those who gave informed written consent were included in the study.

According to the type of the regimen that was received by the patients, the studied cohort was classified into three groups*:*

1) **Group 1:** Included 50 non-cirrhotic patients with chronic hepatitis C received dual therapy (sofosbuvir 400 mg once daily plus daclatasvir 60 mg once daily) for 12 weeks.
2) **Group 2:** Included 50 compensated cirrhotic patients with chronic hepatitis C virus infection and received triple therapy (sofosbuvir 400 mg once daily, daclatasvir 60 mg once daily plus ribavirin 400 mg twice daily) for 12 weeks.
3) **Group 3:** Included 50 non-cirrhotic or compensated cirrhotic patients with chronic hepatitis C virus infection and received Qurevo, which is formed of ombitasvir 12.5 mg, paritaprevir 75 mg, and ritonavir 50 mg and is given twice daily for 12 weeks

All patients were receiving direct acting anti-hepatitis C treatment for 12 weeks. In addition, all patients in the three groups were subjected to full history taking including age, smoking, alcohol, hypertension, diabetes mellitus, cerebrovascular stroke, medications and peripheral artery disease. Full clinical examination with special emphasis on the following data: pulse, blood pressure, heart and neck examination, upper and lower limb examination, chest and heart examination, and BMI measurement.

All patient groups were followed up for 12 weeks after end of treatment to confirm sustained virological response and to detect any delayed onset cardiac side effects.

Inclusion criteria

We used the inclusion criteria of the Egyptian National Committee for Control and Prevention of Viral Hepatitis (NCCVH) according to the most recent Egyptian Protocol at the time of the study. We only included adults above age of 18 years of both sexes with no concomitant HBV or HIV infection.

Exclusion criteria:

1. Patients with autoimmune hepatitis, combined infection with hepatitis C, hepatitis B virus and coinfection with HIV.
2. Patients with advanced renal impairment.
3. Patients with history of cardiac disease or abnormal clinical or electrocardiographic findings (ECG) at baseline of the study.
4. Patients with psychiatric disorders.
5. Pregnant women patients.
6. Patients with non-sinus rhythms.

Laboratory Investigations:

From each patient whole blood and serum samples were obtained for further laboratory investigations at base line before the start of anti-HCV treatment and 6 months after the start of treatment. Whole blood samples were investigated for complete blood picture (Hgb concentration, RBCs count, WBCs count and platelet count). Serum samples were examined for amino alanine transferase (ALT), aspartate amino transferase (AST), serum bilirubin, serum Albumin (Alb), alkaline phosphatase (ALP), blood urea and creatinine and lipid profile including high-density lipoprotein (HDL), low-density lipoprotein (LDL), cholesterol and Triglyceride (TG).

Twelve leads ECG: ECG was conducted before commencing in treatment and within one month after ending the three months therapeutic period, resting 12 lead ECG was performed by ECGMAC device, EM-301 model made in Shenzhen, China at a paper speed of 25 mm/s and amplification of 10 mm/mV. heart rate was calculated from the ECG strip. Using magnifying lens, The QT interval was corrected by using Bazett's formula: QTc = QT/square root of R-R interval in seconds).

Evaluation of Cardiac Function:

All patients enrolled in the study were subjected to the followings:

- Trans-thoracic echocardiography (performed by Simens, Forcheim Germany using 3.5 MHz transducers) for assessment of left ventricular systolic function by motion mode, diastolic function and wall motion abnormalities. Complete transthoracic echocardiographic examination including conventional echocardiography. All echocardiographic examinations performed after 20–30 min of rest with the patient in quiet respiration in the partial left lateral decubitus position, and accompanied by recording resting electrocardiography. All measurements obtained online and Echocardiographic parameters measured according to the American Society of Echocardiography. Values for each parameter were obtained by averaging measurements from three successive cardiac cycles [(7)].

Statistical Analysis

Data are presented as mean ± SD. Continuous variables were expressed as the arithmetic mean ± SD and were compared between the enrolled patients using Student's t test, or Wilcoxon Rank Sum Test, as appropriate with a significance value at $p \leq 0.05$. The ANOVA test was used to examine the difference between groups of the enrolled subjects, as appropriate. All statistical analyses were completed with the help of Graph Pad Prism 8 Software (San Diego, California, USA).

RESULTS

Table (1): Laboratories characterization of chronic HCV-infected patients treated with dual therapy (Group 1) (n=50)

		Baseline	After 3 months of treatment	P-value
Liver function tests	ALT (U/L)	39.36 ± 2.40	32.19 ± 1.37	0.3
	AST (U/L)	43.37 ± 9.77	37.90 ± 5.23	0.2
	Albumin (g/L)	4.42 ± 0.72	4.22 ± 0.44	**0.03**
	Total bilirubin (µmol/L)	0.80 ± 0.04	0.81 ± 0.26	0.4
	Alkaline phosphatase (IU/L)	2.76 ± 0.10	3.52 ± 0.07	**0.02**
	Prothrombin Time	12.98 ± 0.67	12.77 ± 0.61	**0.006**
CBC	Hemoglobin (g/dL)	12.92 ± 1.41	13.55 ± 1.22	**0.007**
	RBCs (mcL)	4.86 ± 0.52	4.85 ± 0.37	0.98
	WBC (mcL)	7.54 ± 1.43	7.50 ± 1.60	0.93
	Platelets (mcL)	229.1 ± 8.07	228.4 ± 6.46	0.72
Renal function tests	Creatinine (mg)	0.95 ± 0.03	0.94 ± 0.03	0.97
	Urea (mg/dL)	23 ± 4.31	22.18 ± 3.78	0.74
	Uric acid (mg/dL)	5.05 ± 1.25	4.82 ± 0.85	0.51
Lipid profile	Triglyceride (mg/dL)	146.5 ± 18.07	142.80 ± 13.68	0.4
	Cholesterol (mg/dL)	198.60 ± 19.03	191.80 ± 13.29	0.1
	HDL (mg/dL)	61.10 ± 5.35	60.16 ± 4.43	0.1
	LDL (mg/dL)	137.0 ± 22.50	131.7 ± 14.51	0.3
	RBS (mg/dL)	97.08 ± 8.73	93.53 ±13.76	0.4

ALT: alanine aminotransferase, **AST**: aspartate aminotransferase, **CBC**: complete blood count, **RBCs**: red blood cells, **WBC**: white blood cells. Bold mean significant when P-value < 0.05. HDL**: high-density lipoprotein,** LDL**: low-density lipoprotein,** RBS**: random blood sugar.**

The mean age of group 1 was (55.90 ± 11.60) and 42% were males (n = 21) and 58% were females (n = 29) (data not shown). Table (1) showed that there was significant decrease in the mean values of the albumin and prothrombin time, after treatment (P = 0.03, 0.006 respectively). However, level of alkaline phosphatase was significantly higher in group (1) after the start of treatment (P = 0.02). In addition, there was significant increase in hemoglobin level after start of treatment (P = 0.007). However, there were no significant differences in baseline and after treatment regarding renal function tests. Concerning lipid profile in group (1), results showed that there were no significant differences in baseline and after treatment.

Table (2): Echocardiographic findings of chronic HCV infected patients treated with dual therapy (group 1)

Echocardiography			
	Baseline	**After 3 months of treatment**	**P-value**
EF%	66.56 ± 5.5	66.10 ± 5.82	0.9
Diastolic function			
Normal	2	2	0.5
DD Grad 1	48	48	
DD Grad 2	0	0	
Wall motion abnormality			
Yes	0	2	0.1
No	50	48	
Mitral valve affection			
Yes	1	3	0.6
No	49	47	
Aortic valve affection			
Yes	6	6	0.9
No	44	44	
Pericardial effusion			
Yes	0	0	0.9
No	50	50	
QT	384.5 ± 23.46	387.5 ± 22.55	0.4
QTc duration m/s	436.6 ± 15.34	435.2 ± 10.75	0.4

EF: ejection fraction.

Table (2) showed that there were insignificant differences in baseline and after treatment regarding echocardiographic findings. In addition, there was no significant difference in the mean change values of QT and QTc intervals among chronic HCV infected patients treated with dual therapy. (P = 0.4) for both respectively.

Table (3): Laboratories characterization of chronic HCV infected patients (group 2) treated with triple therapy

		Baseline	After 3 months of treatment	P-value
Liver function tests	ALT (U/L)	62.92 ± 8.24	55.04 ± 4.01	**0.007**
	AST (U/L)	72.31 ± 5.92	62.40 ± 2.92	**0.04**
	Albumin (g/L)	3.04 ± 0.30	3.08 ± 0.43	**0.03**
	Total bilirubin (µmol/L)	1.37 ± 0.05	1.26 ± 0.09	**0.04**
	Alkaline phosphatase (IU/L)	1.45 ± 0.43	2.91 ± 0.80	**0.01**
	Prothrombin Time	14.16 ± 1.34	14.11 ± 1.44	**0.4**
CBC	Hemoglobin (g/dL)	13.75 ± 1.14	11.14 ± 1.43	**<0.0001**
	RBCs (mcL)	4.82 ± 0.34	4.36 ± 0.28	**<0.0001**
	WBC (mcL)	7.66 ± 1.48	6.55 ± 1.20	**<0.0001**
	Platelets (mcL)	167.6 ± 9.84	145.40 ± 8.53	**0.01**
Renal function tests	Creatinine (mg)	0.97 ± 0.36	0.91 ± 0.22	**0.3**
	Uric acid (mg/dL)	4.61 ± 0.77	4.66 ± 0.92	**0.1**
Lipid profile	Triglyceride (mg/dL)	143.1 ± 16.27	139.4 ± 11.43	**0.4**
	Cholesterol (mg/dL)	194.70 ± 14.13	190.83 ± 7.55	**0.4**
	HDL (mg/dL)	61.23 ± 5.02	60.98 ± 3.89	**0.4**
	LDL (mg/dL)	133.32 ± 16.20	129.83 ± 8.19	**0.6**
	RBS (mg/dL)	103.25 ± 12.48	102.95 ± 9.71	**0.7**

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CBC: complete blood count, RBCs: red blood cells, WBC: white blood cells. Bold mean significant when P-value < 0.05 HDL: high-density lipoprotein, LDL: low-density lipoprotein.

Table (3) showed that there were 50 chronic HCV patients who received triple therapy with 48% (n = 24) male and 52% (n = 26) female and mean age was 57.96 ± 11.59 (data not shown). This table showed that there was significant decrease observed in the studied cohort after the start of treatment in mean values of ALT, AST, and total bilirubin (P = 0.007, 0.04, and 0.04 respectively), while a significant increase was observed in the mean values of albumin and alkaline phosphatase (P = 0.03 and 0.01 respectively). Moreover, the results showed that there was significant decrease in the mean levels of the hemoglobin concentration, WBCs, RBCs and platelets (P < 0.0001, P < 0.0001, P < 0.0001 & P = 0.01 respectively). This table showed that there were insignificant differences in baseline and after treatment regarding renal function tests. In addition, the results showed that there were insignificant differences in baseline and after treatment regarding renal function test. There were insignificant differences in baseline and after treatment with triple regarding lipid profile.

Table (4): Echocardiography of chronic HCV infected patients treated with triple therapy (group 2)

Echocardiography			
	Baseline	**After 3 months of treatment**	**P-value**
EF%	68.9 ± 4.46	68.13 ± 4.72	0.4
Diastolic function			
Normal	20	19	0.5
DD Grad 1	30	30	
DD Grad 2	0	1	
Wall motion abnormality			
Yes	0	2	0.1
No	50	48	
Mitral valve affection			
Yes	17	17	0.9
No	33	33	
Aortic valve affection			
Yes	2	2	0.9
No	48	48	
Pericardial effusion			
Yes	0	0	0.9
No	50	50	
QT	385.4 ± 25.1	384.5 ± 28.09	0.7
QTc duration m/s	431 ± 13.65	429.3 ± 12.42	0.2

EF: ejection fraction.

Table (4) showed that there were insignificant differences in baseline and after treatment with triple therapy regarding echocardiographic findings. This table showed that there was no significant difference in the mean change values of QT and QTc intervals among chronic HCV infected patients treated with triple therapy. (P = 0.7 and P = 0.2 respectively).

Table (5): Laboratories characterization of chronic HCV infected patients (group 3) treated with qurevo

	Baseline	After 3 months of treatment	P-value
Liver function tests			
ALT (U/L)	39.36 ± 2.40	32.19 ± 1.37	**0.3**
AST (U/L)	43.37 ± 9.77	37.90 ± 5.23	**0.2**
Albumin (g/L)	4.42 ± 0.72	4.22 ± 0.44	**0.03**
Total bilirubin (µmol/L)	0.80 ± 0.20	0.81 ± 0.26	**0.4**
Alkaline phosphatase (IU/L)	2.76 ± 0.10	3.52 ± 0.07	**0.02**
Prothrombin Time	12.98 ± 0.67	12.77 ± 0.61	**0.006**
CBC			
Hemoglobin (g/dL)	12.92 ± 1.41	13.55 ± 1.22	**0.007**
RBCs (mcL)	4.86 ± 0.52	4.85 ± 0.37	**0.98**
WBC (mcL)	7.54 ± 1.43	7.50 ± 1.60	**0.93**
Platelets (mcL)	229.1 ± 8.07	228.4 ± 6.46	**0.72**
Renal function tests			
Creatinine (mg)	0.95 ± 0.26	0.94 ± 0.22	**0.97**
Urea (mg/dL)	23 ± 4.31	22.18 ± 3.78	**0.74**
Uric acid (mg/dL)	5.05 ± 1.25	4.82 ± 0.85	**0.51**
Lipid profile			
Triglyceride (mg/dL)	146.5 ± 18.07	142.80 ± 13.68	**0.4**
Cholesterol (mg/dL)	198.60 ± 19.03	191.80 ± 13.29	**0.1**
HDL (mg/dL)	61.10 ± 5.35	60.16 ± 4.43	**0.1**
LDL (mg/dL)	137. ± 22.50	131.7 ± 14.51	**0.3**
RBS (mg/dL)	97.08 ± 8.73	93.53 ± 13.76	**0.4**

ALT: alanine aminotransferase, **AST**: aspartate aminotransferase, **CBC**: complete blood count, **RBCs**: red blood cells, **WBC:** white blood cells. **Bold mean significant when P-value < 0.05 HDL**: high density lipoprotein, **LDL**: low density lipoprotein. **RBS**: random blood sugar.

Table (5) showed that there was significant difference was observed in mean level of prothrombin time as it decreased and alkaline phosphatase as it increased before and after the treatment. Moreover, the results showed significant increase that was observed in mean level of hemoglobin before and after the treatment. The results showed that there were insignificant differences in baseline and after treatment regarding renal function tests. There were insignificant differences in baseline and after treatment with qurevo regarding lipid profile.

Table (6): Echocardiography of chronic HCV infected patients treated with qurevo (group 3)

	Baseline	After 3 months of treatment	P-value
Echocardiography			
EF%	66.56 ± 5.5	66.10 ± 5.82	**0.9**
Diastolic function			
Normal	15	15	**0.9**
DD Grad 1	35	35	
DD Grad 2	0	0	
Wall motion abnormality			
Yes	0	2	**0.1**
No	50	48	
Mitral valvular affection			
Yes	7	9	**0.7**
No	43	41	
Aortic valvular affection			
Yes	5	5	**0.3**
No	45	45	
Pericardial effusion			
Yes	0	2	**0.1**
No	50	48	
QT	384.4 ± 37.52	380.85 ± 27.9	**0.7**
QTc duration m/s	435.5 ± 10.47	434.6 ± 9.66	**0.4**

Table (6) showed that there were insignificant differences in baseline and after treatment regarding echocardiographic findings. Also, there was no significant difference in the mean change values of QT and QTc intervals among chronic HCV infected patients treated with qurevo (P=0.7 & P=0.4 respectively).

Table (7): PCR of chronic HCV infected patients in three group before and after treatment

	Baseline	After 3 months of treatment	P-value
Dual therapy (Group 1)			
Positive	50	2	
Negative	0	48	**0.0001**
Trible therapy (Group 2)			
Positive	50	4	
Negative	0	46	**0.0001**
Qurevo therapy (Group 3)			
Positive	50	3	
Negative	0	47	**0.0001**

Table (7) showed that among infected 50 cases in each group with positive PCR after treatment only negative patients were 2, 4 & 3 in dual therapy, triple therapy and qurevo therapy groups respectively.

DISCUSSION

Regarding the new DAAs, Food and Drug Administration (FDA) recently announced a change in labeling for hepatitis C antiviral LDV/SOF (Harvoni) and SOF (Sovaldi) after the manufacturers reported bradycardia, pacemaker invention, and even death in patients who took the medications along with amiodarone. As the prevalence of HCV in Egypt is high, and the new treatment combined with therapy involving oral DAAs either with or without PEG-IFN is extensively used. Therefore, in the current study we aimed to assess cardiac side effects of directly acting anti hepatitis C drugs. Significant decrease in the hemoglobin concentration was observed in the three groups included in the present cohort 3 months after treatment with direct acting anti-HCV treatment. Hemolytic anemia is the most important ribavirin side effect generally limits dose escalations. Anemia is likely due to a ribavirin-associated dose-dependent hemolytic anemia, which may be worsened by the myelosuppressive action of peginterferon. Ribavirin-induced anemia has also been observed even in trials of interferon-free and in ribavirin-containing regimens in development for chronic HCV.

Kuntzen *et al.* [8] demonstrated a significant higher rates of hemoglobin decline > 3 mg/dl were observed with higher ribavirin concentrations (p = 0.015), illustrating that optimal drug levels for maximum antiviral efficacy must be balanced with drug toxicity. In the same study, it was conducted that although hemoglobin decline was on average more pronounced in patients with higher ribavirin levels, hemoglobin remained relatively stable in a significant proportion of these indicating that ribavirin levels alone are insufficient to predict anemia. Further, this support that ribavirin treatment should be based on serum levels instead of purely weight-based dosing in combination with pegylated interferon.

In the current study we found that in dual therapy group, significant decrease in the mean values of albumin and prothrombin time, which was observed after the start of the treatment (P= 0.03, 0.006 respectively). However, level of alkaline phosphatase and hemoglobin were significantly higher in group 1 after the start of treatment. On the other hand, **Babatin *et al.*** [9] showed that the combination of SOF/DCV with or without RBV significantly decreased the elevated liver transaminases (ALT and AST). Such improvement was accompanied with significant amelioration in liver fibrosis, which was confirmed by a marked decrease in the FIB-4 score and AFP level. Improvement in liver enzymes occurred early during treatment, as most of the patients achieved normal ALT by week 2. At week 24, all patients in the DCV/SOF group had normal values. Moreover **Abdel-Moneim *et al.*** [10] **and Ahmed *et al.*** [11] reported that sofosbuvir plus daclatasvir, with or without ribavirin achieved high efficacy and safety in HCV genotype 4 patients. Their effect was accompanied with attenuation of liver fibrosis. In **Ahmed *et al.*** [11] study, non-cirrhotic naïve patients were treated with sofosbuvir plus daclatasvir for 12 weeks. Ribavirin was added to this regimen when treating cirrhotic patients and/ or treatment of experienced patients. The adverse event was anemia in (5.67%) of patients. **Kutala *et al.*** [12] reported about safety profile of different SOF combination that the mean change in hemoglobin level associated with regimens that contained RBV versus those that did not contain RBV. It was -2.4g/dl versus -0.4g/dl after 12 weeks of therapy, and this agrees with our study that showed that the mean change in hemoglobin level was 1.284 ± 1.431. **Attia *et al.*** [13] in his retrospective multicenter study, found adverse events in 5 patients out of 101 who received PTV/OBV/r/RBV regimen, mean age was (61 ± 5 years old) one had anemia, one had hyperbilirubinemia and 3 patients had non-specific side effects. SOF / DCV / RBV also showed hepatobiliary complications in 31% of the developed side effects, and were 92/45188 (0.2%) in the treated patients' group. Hematological complications were 96/45188 (0.2%) in treated patients with anemia being the most common one [76/45188 (0.16%)] in treated patients.

In the current study, we found that in the second group there was significant decrease in the studied cohort after the start of treatment in mean values of ALT, AST, total bilirubin, Hemoglobin concentration, WBCs, RBCs and platelets while a significant increase was observed in the mean values of the albumin and akaline phosphatase (P= 0.03, 0.01 respectively). This is in agreement with **Abdel-Moneim *et al.*** [10] who showed that group 2 (SOF/DCV with RBV) in their study was characterized mainly by decreased hemoglobin concentration (14%) and hyperbilirubinemia (4%), which were mainly due to RBV administration. In consistence with our result,

Othman *et al.* [14] showed that (17/50) 34% of patients receiving sosfsbuvir, daclatasvir and ribavirin regimen developed anemia with p value <0.001. **Herzer *et al.* [15]** showed that among 62 cases received DCV + SOF and 25 cases received DCV + SOF + RBV, anemia was more frequent in those patients who received treatment with RBV [nine patients (36%) versus two patients (3%) without RBV]. Three additional patients reduced RBV dose for other reasons; median platelet counts, ALT, total bilirubin, and albumin, which showed improvements between baseline and post- treatment week 12. ALT levels decreased by a median of 28 IU/l [(IQR) 47], total bilirubin decreased by a median of 2.9 μmol/l (IQR 7.7) while, albumin increased by a median of 2.0 g/l (IQR 4.0) and platelet counts increased by a median of 14×10^9/l. On the other hand, **Welzel *et al.* [16]** showed that after uses of DCV+SOF+RBV, laboratory parameters associated with liver function were assessed at baseline and post-treatment week 12. Among 272 patients with samples at both time points, total bilirubin and ALT decreased while albumin increased and platelets increased.

In the current study, we found that in all groups there was insignificant effect on lipid profile, renal function and echocardiography. This is confirmed by **El-Adawy *et al.* [17]** who showed that DAAs proved its efficacy in management of chronic HCV in Egyptian patients as standard of care for hepatitis C treatment. Also tested its safety on the heart with most of its applied regimens. A Japanese study of 200 individuals infected with HCV reported an improvement in myocardial injury in patients who achieved a sustained viral eradication after PEG-IFN plus ribavirin therapy, a transitory improvement in those who relapsed, and no improvement in nonresponse [18]. A Taiwanese community-based study of 18,541 anti-HCV seronegative and 1095 anti-HCV seropositive subjects reported an increase in mortality from circulatory diseases compared to uninfected subjects in patients with anti-HCV and detectable HCV-RNA, but not in those with undetectable HCV-RNA [19]. These two last studies provide indirect evidence of a potential positive impact of viral eradication on cardiovascular outcomes. Another Taiwanese study of 23,665 residents reported that the risk of lethal cerebrovascular events progressively increased from patients who were anti-HCV-positive with undetectable HCV RNA, to patients with a low viral load, and further to those who were highly viremic, compared to anti-HCV-negative patients [20]. Two other Taiwanese cohort studies in individuals infected with HCV found a significant reduction in the occurrence of acute coronary syndrome, stroke, and end-stage renal disease among those who underwent PEG-IFN-based antiviral therapy compared to those who did not receive these treatments. These findings are further confirmed in a subgroup of diabetic patients [21].

Importantly in this study, we found that DAAs used in the national Egyptian protocol for HCV infection treatment did not have effect on QTc interval. As mentioned, QTc interval did not change after treatment in this study. Moreover, **Biomy *et al.* [5]** investigated the cardiovascular effects of DAAs in 170 patients with HCV infection. They divided their patients into two groups: group 1 (n= 100) received pegylated interferon alfa, sofosbuvir, and ribavirin while group 2 (n = 70) received sofosbuvir and simeprevir. After 6 to 12 months of follow-up, their results showed that there was no change in the QTc interval. Additionally, no arrhythmias were observed throughout the study and during follow-up visits. In addition, **Lawitz *et al.* [22]** examined the ECG of 39 HCV infection patients treated with either a sofosbuvir (n = 26) or a non-sofosbuvir-based treatment (n = 13). ECG tracings were obtained on the first day of treatment then after 7, 14, and 28 days. Their results showed that for the sofosbuvir group, QTc interval significantly increased at 1 week (p = 0.013) then returned to baseline values later during therapy until the end of treatment.

In the current study, we found that in qurevo group there was significant decrease in the studied cohort after the start of treatment in mean level of prothrombin time while a significant increase was observed in the mean values of the alkaline phosphatase and hemoglobin. In contrast, **Othman *et al.* [14]** showed that occurrence of hyperbilirubinemia (6/50) 12% of patients was not significant in this regimen (p value 0.238). 29/50 (58%) of patients receiving qurevo and ribavirin regimen developed anemia with p value 0.001. There was increased incidence of anemia more with qurevo and ribavirin regimen with p value 0.014. In case of comparison of hyperbilirubinemia, although p value was 0.938 (nonsignificant), the significant increase with qurevo and ribavirin regimen was due to increased bilirubin before treatment with sosfsbuvir, daclatasvir and ribavirin regimen (p value before treatment was 0.007). **Okubo *et al.* [23] and Menon *et al.* [24]** reported that during treatment with ombitasvir, paritaprevir, and ritonavir with or without ribavirin, mild to moderate increase in serum bilirubin concentration, has been reported in some cases. **Liu *et al.* [25]** documented that in patients receiving paritaprevir, 23% had elevation in total bilirubin (> 2.25 mg/ dl), mainly indirect (unconjugated) bilirubin levels, without elevation in liver enzymes.

In the current study, as regards PCR we found that among infected 50 cases in each group with positive PCR after treatment only negative patients were 2, 4, 3 in dual therapy, triple therapy and qurevo therapy group respectively. This is confirmed by **Babatin *et al.* [9]** who revealed that SOF/DCV with or without RBV was highly effective in HCV GT4 treatment by achieving SVR12 100% in experienced and cirrhotic patients. Similarly, **Fontaine *et al.* [26]** in a study of a small group, 47 patients, reported that SOF/DCV in treatment of HCV GT4 for 12 weeks achieved SVR12 89% and reached 100% with SOF/DCV ± RBV regimen. Also, in a large real world cohort of HIV/HCV-coinfected patients with advanced liver disease, **Medeiros *et al.* [27]** concluded that DCV/ SOF ± RBV achieved SVR12 rate of 92% overall, 90% of patients with cirrhosis, and 95% of patients without cirrhosis in patients infected with HCV

genotypes 1, 3, and 4. Another study by **Othman *et al.*** [14] showed that cure rate of about 94%, 96% achieved SVR with (sofosbuvir daclatasvir and ribavirin regimen) and (qurevo and ribavirin regimen) respectively. Patients treated with sosfsbuvir, daclatasvir and ribavirin regimen showed efficacy of 94% and this is matched with **Attia *et al.*** [13] study, that included >18,000 Egyptian patients with HCV infection, about 95% achieved SVR 12. It was concluded that sofosbuvir plus daclatasvir with or without ribavirin regimen is safe and effective for the treatment of Egyptian patients with chronic hepatitis C genotype 4 [16]. In addition, our result is in agreement with a study, which documented that the combination of sofosbuvir and daclatasvir with or without ribavirin had high antiviral potency, with > 90% SVR rate in patients with chronic HCV infection [27]. This study agrees with **Fontaine *et al.*** [26] study, which concluded that the combination of sofosbuvir and daclatasvir was associated with a high rate of SVR in treatment of genotype 4 HCV. SVR was 86%-100%, according to patients' baseline characteristics and therapeutic regimen. Patients treated with qurevo and ribavirin regimen showed efficacy of 96 % and this is matched with **Crespo *et al.*** [29] study that reported high SVR rates of 96.2% in HCV GT4 infected patients treated with OBV/PTV/r (n=122) with or without RBV. This study shows little differences with **David and Nina** [30] study that examined the efficacy of a 12-week course of ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in adults with chronic HCV genotype 4 infection. For the 86 treatment naïve recipients of ombitasvir plus paritaprevir plus ritonavir without ribavirin, an SVR12 was achieved in 91% (40 of 44) compared to an SVR12 rate of 100% (42 of of 42) in participants treated with ombitasvir plus paritaprevir plus ritonavir with ribavirin. The study, showed an excellent treatment response with a 24-week regimen of ombitasvir plus paritaprevir plus ritonavir for genotype 4 infection, particularly if ribavirin is added to the regimen. **Schnell *et al.*** [31] study reported that SVR12 rate of 100% were observed among GT4- infected treatment naïve and treatment experienced patients receiving ombitasvir plus paritaprevir with RBV.

CONCLUSION

DAAs are safe drugs to use in non-cardiovascular patients and in cardiac patients with caution and avoidance of some drugs.

RECOMMENDATIONS

A future systemic multicenter study with large sample size should be conducted for accurate monitoring of the cardiac toxicity of DAAs. In addition, a careful and prospective monitoring of patients should be done to identify early changes in cardiac functions, which require the inclusion of tissue Doppler and speckle tracking study with echocardiograph.

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