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ASSESSMENT OF CARDIAC FUNCTIONS IN EGYPTIAN CHRONIC HEPATITIS C PATIENTS BEFORE AND AFTER TREATMENT WITH DIRECTLY ACTING ANTIVIRALS

By
MOHAMED G. TALKAHN[1], KHALED H. ABDEL MAGED[1], HESHAM H. R. ELKILANY[1], ESLAM S. MOHAMED[1], HAITHAM G. MOHAMED[2], and AYMAN G. A. DAWOD[1]*
Department of Internal Medicine, Hepatogastroenterology and Endoscopy[1], and Department of Cardiology[2], Faculty of Medicine, Ain Shams University, Cairo 11566, Egypt (*Correspondence: Ayman.gamil@med.asu.edu.eg).

Abstract

Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease worldwide. It poses a serious health risk. Liver cirrhosis of is also linked to a variety of cardiovascular abnormalities. Nowadays, direct-acting antivirals (DAAs) for hepatitis C have the potential to reduce this disease burden, but their potential long-term cardiac effects are unknown. The aim of this work was to see how direct-acting antivirals affect the cardiac functions of naive Egyptians with chronic hepatitis C.

The 90 treatment-naive adult patients with chronic hepatitis C were divided into two groups (cirrhotic and non-cirrhotic). Only two patients within the non-cirrhotic group and a patient among cirrhotic patients showed nonspecific ST segment changes which remained unchanged after treatments. Two non-cirrhotic patients and four cirrhotic patients showed T wave inversion, which remained static post treatment, but without significant difference in corrected QT interval before & after treatment between groups.

Key words: Egypt, Patients, HCV, Liver cirrhosis, cardiac functions, Direct-acting antivirals (DAAs).

Introduction

HCV has a major impact on public health with over 170 million infected individuals. It was thought to be the cause of 25% of hepatocellular carcinoma (HCC) and 27% of cirrhosis cases worldwide. The death rate from HCV infection is very high, with approximately 350,000 people dying each year after becoming infected. Afridi *et al.* (2013) in Pakistan reported that to date, neither vaccine nor immunotherapy was available. HCV infection frequently results in extra-hepatic diseases involving innate immune and autoimmune pathogenic processes. Cirrhosis of liver is also linked to a variety of cardiovascular abnormalities, such as pulmonary vascular abnormalities, hyperdynamic circulation, and cirrhotic cardiomyopathy (Elgharably *et al,* 2017). Previous anti-HCV therapies based on interferons were poorly tolerated and had limited elimination efficacy in patients with advanced heart failure (Petta, 2016). The introduction of novel interferon-free, highly efficient and well tolerated anti-HCV combination therapies may finally resolve the issue of the causal relationship between HCV infection and cardiac disease (Kohli *et al,* 2014). But, retrospective studies of case reports, and post-marketing reports indicated that a novel polymerase inhibitor designed to treat chro-nic HCV infection could cause toxic cardiomyopathy (Sherman *et al,* 2013).

In Egypt, endemic HCV and its impact on liver cirrhosis & HCC reported (Madwar *et al,* 1999; Abdel-Bary *et al,* 2012; Abdelwahab *et al,* 2020). Anwar *et al.* (2021) reported that while HCV prevalence among patients decreased since the last survey done within ASU hospitals in 2008, but was still significantly higher than in general population.

The study aimed to evaluate the effect of direct-acting antivirals (DAAs) on cardiac functions in naive Egyptians with chronic hepatitis C.

Subjects and Methods

This is a prospective cohort study involved 90 treatment-naive adult patients with chronic hepatitis C infection randomly selected from the Ain Shams University Hospitals'

Center for viral hepatitis treatment (one of Cairo's National Committee for the Control of Viral Hepatitis (NCCVH) Centers) and the gastroenterology and hepatology unit at Ain Shams hospital. They were chosen based on the following: males and women over 18years old with HCV/PCR positive without chronic HCV treatment history. If a patient had any of the following criteria were excluded: men and women <18, pregnant females, patients with arrhythmia, cardiomyopathy, ischemic heart disease, organic vulvular heart disease, uncontrolled hypertension and/or diabetes, chronic HCV previous treatment, co-infection with HBV or HIV, chronic renal disease patients with a GFR < 30ml/min, and with autoimmune diseases or malignancy.

Patients were divided into: GI: 45 chronic HCV patients without liver cirrhosis. GII: 45 chronic HCV patients with liver cirrhosis (Child- Pugh score A& B). All patients were treated according to the national protocol for chronic HCV management: GI received Sofosbuvir 400mg + Daclatasvir60mg/day for 12 weeks. GII received Sofosbuvir 400mg + Daclatasvir 60mg + Ribavirin (RBV)/ day for 12 weeks (if RBV eligible) or Sofosbuvir 400mg + Daclatasvir 60mg/day for 24 weeks (If RBV ineligible). RBV started at a dose of 600mg daily and gradually increased based on patient tolerance.

Medical sheets were filled out on each patient, and thorough clinical examination with a focus on: age, marital status to assess contraception need, occupations as simeprevir containing regimens were avoided in those with frequent sun exposure. Residences to ensure patients' compliance with treatment and follow-up schedules, substance abuse as patients with substance abuse were co-managed by a psychiatrist, history of chronic liver disease and hepatic decompensating, diabetes, hypertension and cardiac diseases.

Laboratory examinations: All patients underwent CBC, liver profile (albumin, INR, total & direct bilirubin, ALT, AST, and alkaline phosphatase), HCV Ab & HBsAg, serum alpha-fetoprotein (AFP), kidney function tests (serum creatinine & blood urea), fasting blood sugar, and HbA1C. Pregnancy test was assessed for females in child bearing period and HCV/PCR pre-, post-treatment and followed up for12 weeks (SVR12), of NT-pro BNP serum level pre-treatment and post-treatment.

Abdominal U/S was done using GE LogiQ P5 ultrasound system and Fibroscan (Transient Elastography) was done before treatment using Echo sense device system.

Cardiac function was assessed pre and 12 weeks after treatment, including: a- 12 lead-ECG (with special comment on: ST segment abnormality, T wave changes and corrected QT interval), b- Transthoracic Echocardiography (TTE) using the GE vivid E 9 system, with special comments on: Left Ventricular (LV) diameter and systolic functions (by M-Mode & Simpson methods), Segmental wall motion abnormalities (SWMA) to exclude ischemic nature, Left Ventricular (LV) diastolic function (E-wave, A-wave, E/A ratio & é wave by tissue Doppler), The right ventricular systolic and diastolic functions, of cardiac valves assessment to exclude valvular heart diseases, pulmonary artery pressure (PAP) and left and right atrial sizes and pressures.

Ethics approval and patients consent: All procedures performed were in accordance with ethical standards of Ain Shams University Research Committee and with Helsinki declaration 1964, and its later amendments, Ethics's reference No. 000017585. An informed written consent was obtained from all patients

Statistical analysis: IBM SPSS software program version 20.0 (IBM Corporation, Armonk, NY) was used. For normal distribution, Kolmogorov-Smirnov test was used.

For quantitative data (minimum & maximum), mean, standard deviation, and median Chi-square test, Fisher's Exact or Monte Carlo correction & Student t-test were used. Significance level was expressed as $P \geq 0.05$: insignificant, $P < 0.05$: significant & P

<0.01: highly significant

Results

Demographic data in both groups was insignificant. A significant difference (P=.011) was in non-cirrhotic patients as to fibroscan features. In cirrhotic patients 45(100%) were classified as F3-4, without change after the treatment.

Details were given in tables (1, 2, 3 & 4).

Table 1: ECG findings among non-cirrhotic and cirrhotic groups treated with DAAs:

ST segment abnormality				
Basal		2 (4.4%)	1 (2.2%)	1.000
Week-12		2 (4.4%)	1 (2.2%)	1.000
P (before/After)		1.000	1.000	
T wave changes				
Basal		2 (4.4%)	4 (8.9%)	0.677
Week-12		2 (4.4%)	4 (8.9%)	0.677
P (before/After)		1.000	1.000	
Corrected QT interval (msec)				
Basal	M±SD	406.0±19.2	407.8±19.1	0.645
	Range	370.0–440.0	370.0–458.0	
Week-12	M±SD	408.5±13.8	404.1±22.8	0.271
	Range	378.0–436.0	304.0–444.0	
Change	M±SD	2.6±20.7	-3.7±26.0	0.210
	Range	-40.0–44.0	-116.0–32.0	
P (before/After)		0.408	0.347	

Two non-cirrhotic patients and one cirrhotic showed nonspecific ST segment changes after treatments. Two non-cirrhotic patients and 4 cirrhotic patients had T wave inversion that remained static after treatment. There was no significant difference between patients regarding corrected QT interval before and after treatment.

Table 2: Comparison between cirrhotic & non-cirrhotic as to NT-Pro BNP and LV function before & after DAAs treatment.

Time	Measures	Non-cirrhotic (N=45)	Cirrhotic (N=45)	P (NC/C)
NT-Pro BNP (pg./ml)				
Basal	M±SD	82.1±49.9	65.4±30.6	0.058
	Range	10.0–300.0	5.0–150.0	
Week-12	M±SD	114.3±48.3	99.6±34.2	0.099
	Range	40.0–260.0	40.0–180.0	
Change	M±SD	32.2±54.5	34.2±36.9	0.835
	Range	-175.0–118.0	-85.0–125.0	
#P (before/After)		<0.001	<0.001	
Ejection Fraction %				
Basal	M±SD	66.0±4.3	67.0±3.8	0.266
	Range	57.0–75.0	59.0–75.0	
Week-12	M±SD	67.5±3.4	66.3±4.9	0.169
	Range	59.0–74.0	58.0–72.0	
Change	M±SD	1.5±3.2	-0.7±5.5	0.241
	Range	-6.0–9.0	-27.0–7.0	
#P (before/After)		0.386	0.405	
Diastolic Time (msec.)				
Basal	M±SD	201.6±31.6	189.6±21.8	0.038
	Range	140.0–285.0	143.0–230.0	
Week-12	M±SD	203.7±26.4	191.8±21.7	0.022
	Range	162.0–320.0	152.0–250.0	
Change	M±SD	2.1±29.2	2.2±20.6	0.973
	Range	-65.0–98.0	-40.0–50.0	
#P (before/After)		0.638	0.470	

NT-Pro BNP significantly increased after DAA treatment in both groups (P = 0.001), but L.V. function of EF & DT didn't change significantly after treatment in both group.

Table 3: Comparison between groups (cirrhotic and cirrhotic) regarding left ventricular volumes.

Time	Measures	Non-cirrhotic(N=45)	Cirrhotic(N=45)	^P (NC/C)
LVESV (mL)				
Basal	M±SD	34.2±7.8	30.8±6.7	0.27
	Range	21.0–60.0	20.0–52.0	
Week-12	M±SD	33.1±6.3	31.5±5.6	0.205
	Range	20.0–52.0	20.0–50.0	
Change	M±SD	-1.1±6.9	0.7±5.8	0.173
	Range	-28.0–15.0	-11.0–10.0	
#P (before/After)		0.278	0.413	
LVEDV (mL)				
Basal	M±SD	99.8±20.7	93.5±19.0	0.137
	Range	54.0–139.0	53.0–132.0	
Week-12	M±SD	102.6±17.9	95.9±18.2	0.079
	Range	64.0–144.0	64.0–144.0	
Change	M±SD	2.9±13.3	2.4±13.5	0.863
	Range	-17.0–34.0	-28.0–21.0	
P (before/After)		0.156	0.245	

No significant difference changes were in left ventricular volumes in LVESV & LVEDV between groups before and after treatment.

Table 4: Comparison between groups (non-cirrhotic and cirrhotic) regarding left ventricular diameters.

Time	Measures	Non-cirrhotic (N=45)	Cirrhotic (N=45)	^P (NC/C)
LVEDD (mm)				
Basal	M±SD	47.2±3.5	48.2±2.9	0.158
	Range	39.0–53.0	42.0–53.0	
Week-12	M±SD	47.9±2.5	49.2±2.4	0.131
	Range	44.0–52.0	41.0–53.0	
Change	M±SD	0.6±3.2	1.0±2.6	0.559
	Range	-9.0–5.0	-4.0–6.0	
P (before/After)		0.193	0.141	
LVESD (mm)				
Basal	M±SD	29.9±3.0	29.8±2.4	0.969
	Range	24.0–37.0	25.0–34.0	
Week-12	M±SD	29.6±2.1	30.1±2.1	0.262
	Range	26.0–36.0	25.0–34.0	
Change	M±SD	-0.2±3.1	0.3±2.3	0.375
	Range	-10.0–5.0	-6.0–4.0	
P (before/After)		0.628	0.412	

No significant difference changes were in left ventricular diameters in LVESD & LVEDD between both groups before and after treatment.

Table 5: Comparison among groups (cirrhotic and non-cirrhotic) regarding RV functions.

Time	Measures	Non-cirrhotic (N=45)	Cirrhotic (N=45)	P(NC/C)
MPAP (mmHg)				
Basal	M±SD	15.0±3.5	14.5±3.4	0.466
	Range	8.0–21.0	8.0–23.0	
Week-12	M±SD	14.8±3.4	14.9±3.1	0.923
	Range	9.0–21.0	9.0–22.0	
Change	M±SD	-0.2±3.7	0.4±3.6	0.438
	Range	-8.0–6.0	-8.0–7.0	
P (before/After)		0.693	0.479	
Diastolic filling (abnormal diastolic filling %)				
Basal	17 (37.8%)	14 (31.1%)	0.506	0.466
Week-12	17 (37.8%)	20 (44.4%)	0.520	
P(before/After)	1.000	0.070		0.923
	Range	9.0–21.0	9.0–22.0	
Change	M±SD	-0.2±3.7	0.4±3.6	0.438
	Range	-8.0–6.0	-8.0–7.0	
#P (before/After)		0.693	0.479	

No significant differences in RV functions were between both groups as regards MPAP, and % abnormal diastolic filling before and after treatment.

Discussion

Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease worldwide, posing a serious health risk (CDC, 2020). Egypt's HCV prevalence rate in 2008 was reported to be 14.7%. Cirrhosis of the liver was also linked to a variety of cardiovascular abnormalities, such as pulmonary vascular abnormalities, hyper dynamic circulation, and cirrhotic cardiomyopathy (Elgharably *et al,* 2017). Direct-acting antivirals (DAAs) have the potential to reduce the disease burden and eliminate this bloodborne virus as a public health concern (WHO, 2017). The long-term cardiac effects of hepatitis C direct-acting antiviral treatment are unkn-own. One of the most crucial issues to addr- ess was to link between it and cardiovascular diseases (Renet *et al,* 2015).

In the present study, there was a significant difference in the transient elastography (FibroScan) in non-cirrhotic patients before and after treatment by DAAs (P= 0. 0.011), an increase in patients with F1-2 score from 31(68.9%) before treatment to 39 (86.7%) after treatment. This agreed with Mariusz and Robert (2018), who among 189 chronic HCV reported a significant improvement in liver stiffness after DAA.

In the present study, ECG characteristics showed that only two non-cirrhotic patients and one cirrhotic patient with nonspecific ST segment remained unchanged after treatments. Two non-cirrhotic patients & four cirrhotic ones had T wave inversion, which remained static after treatment. Also, there was no significant difference between patients groups regarding corrected QT interv- al before and after treatment. This agreed with Biomy *et al.* (2017), who didn't find significant changes in ST-T wave abnormalities or QT interval among 170 patients.

In the present study, in both patients groups, NT-Pro BNP level increased significantly after DAA treatment (P= 0.001). This agreed with El-Adawy *et al.* (2018) who rep-orted the occurrence of myocardial injury confirmed biochemically by elevation of cardiac enzymes including BNP and radiological by CMR after various SOF-contained regimens.

In the present study, an echocardiogram was done for patients prior to treatment with direct acting antiviral regimens and 3 months after treatment. There was no significant difference regarding cardiac chamber dimensions, including LVESV, LVEDV, LVESD & LVEDD between different non-cirrhotic and cirrhotic patients These agreed with Adinolfi *et al.* (2018**)** in Italy who showed static parameters regarding cardiac chambers before and after treatment.

In the present study, the L.V. function in form of EF & DT did not change significantly post treatment in both patients groups. However, Ahmad *et al*. (2015) reported the first incidence of cardiotoxicity related to the use of DAAs in the treatment of chronic HCV infection, with 34 individuals developping LV Systolic dysfunction and a reduction in LV EF. The discrepancies between the outcomes of the two studies can be traced to the fact that the latter used a different methodology to choose the research population, as the latter included high-risk patients for cardiovascular disease.

In the present study, there were no significant differences in RV functions between both groups as regards MPAP and abnormal diastolic filling% before and after treatment. This disagreed with Renard *et al.* (2016) in France among 3 patients only who reported severe PAH and RV dysfunction in three patients treated with a Sofosbuvir-based HCV treatment regimen.

Conclusion

Generally, the viral hepatitis endemics and pandemics have a heavy load on lives, communities and health authorities. DAAs in treating chronic HCV infection don't show clinical significant affect cardiac function. However, subclinical myocardial injury occurred by a significant increase in NT-Pro BNP after treatment warrants further investigation, which is ongoing and will be published in due time elsewhere.

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