RESEARCH ARTICLE

Evaluation of left ventricular function after sofosbuvir and daclatasvir regimen for chronic hepatitis C

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Abstract

Objectives: To assess left ventricular functions by echocardiography after 12 weeks of sofosbuvir-daclatasvir combination therapy.

Method: The prospective cohort study was conducted from December 2019 to December 2021 at Kafrelsheikh University Hospital, Egypt, and comprised adult patients of either gender who had been referred to the Cardiovascular Department for cardiac evaluation and were found to be eligible for sofosbuvir-daclatasvir combination therapy. The patients were classified into five groups according to cardiovascular risk factors. Group 1 had no risk factors; Group 2 had many risk factors; Group 3 had only hypertension; Group 4 had diabetes only; and Group 5 had smoking as the only risk. All patients were assessed at baseline and at the end of the 12-week of antiviral combination therapy sofosbuvir 400 mg once daily dose and daclatasvir 60 mg once daily dose. Parameters checked were left ventricular ejection fraction, global longitudinal strain, wall motion abnormalities and diastolic function. Data was analysed using SPSS 23.

Results: Of the 200 patients, 104(52%) were females and 96(48%) were males. The age range was 34-81 years, and 18(9%) patients were aged >70 years. There were 78(39%) patients in Group 1, 60(30%) in Group 2, 25(12.5%) in Group 3, Group 4 had 13(6.5%) and Group 5 had 24(12%) patients. There were no significant changes in mean ejection fraction, global longitudinal strain and wall motion abnormalities ($p>0.05$). Diastolic function had some significant parameters in each of the 5 groups ($p<0.05$).

Conclusion: Sofosbuvir-daclatasvir combination therapy did not affect or impair left ventricular systolic or diastolic functions.

Keywords: Stroke, Sofosbuvir, Antiviral, Hepatitis C, Chronic, daclatasvir, Coronary syndrome, Cardiovascular diseases, Echocardiography, Amiodarone, Recurrence, Smoking. **DOI: 10.47391/JPMA.EGY-S4-27**

Introduction

Chronic hepatitis C viral (HCV) infection is a systemic disease with increased morbidity and mortality burden.[1] In 2015, Egypt had the highest prevalence of this endemic disease, and a national health survey described a 4.5-6.7% prevalence of chronic HCV infection among those aged 15-59 years.[2]

Chronic HCV infection is not just a hepatotropic viral disease, it is also associated with extrahepatic manifestation involving cardiovascular system.[3] It complicates systemic atherosclerosis, myocardial cell injury, peripheral artery disease (PAD), cerebral and cardiovascular events with increased overall mortality.[4-6] During the past decade, direct-acting antivirals (DAAs) were incorporated in HCV treatment as an effective, tolerable and safe drug with lesser side effects compared to the traditional interferon regimens.[7,8]

Egypt included the DAAs in the national regimen as part of the 100 million Healthy Lives campaign, screening around 56 million Egyptians and 65,000 non-Egyptians free of charge.[9]

Despite this breakthrough therapy, safety concerns about DAAs' cardiac complications have surfaced. The Food and Drug Administration (FDA) of the United States warned about serious bradycardia if sofosbuvir-based regimen is administrated with amiodarone in documented cases of pacemaker insertion.[10] Ahmad et al.[11] reported severe myocardial dysfunction during therapy with BMS-986094 (an HCV nucleotide polymerase (non-structural 5B) inhibitor molecule, formerly known as INX-189) with severe congestive heart failure (CHF). Evidence of left ventricular (LV) global longitudinal strain (GLS) affection with further worsening after sofosbuvir-based regimens was reported by Mazetelli et al.[12] The reason behind DAA-induced cardiac events is not fully understood, but it may be related to cardio-toxic effect.[12]

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The current study was planned to assess LV functions by echocardiography after 12 weeks of sofosbuvir-daclatasvir combination therapy.

Patients and Methods

The prospective cohort study was conducted from December 2019 to December 2021 at Kafrelsheikh University Hospital, Egypt. After approval from the institutional ethics review committee, the sample was raised from among adult patients of either gender who had been referred randomly by the Hepatology outpatient clinic to the Cardiovascular Department for cardiac evaluation and fitness for antiviral combination therapy sofosbuvir 400 mg once daily dose and daclatasvir 60 mg once daily dose for 12 weeks in the light of the National Committee recommendations.[13]

Those excluded were patients with cardiomyopathy (ejection fraction [EF] <40%), recent myocardial infarction (MI) or amiodarone intake within the preceding 3 months, and patients with history of antiviral therapy relapse.

After taking informed consent from all the subjects, detailed medical history was obtained, stressing on cardiac symptoms (dyspnoea, angina, palpitations), current medications, particularly antihypertensive, antiarrhythmic, negative chronotropic, antiplatelet, anticoagulant and endothelin receptor antagonist drugs. Besides, full general and local cardiac examinations were conducted. Standard 12-lead electrocardiogram (ECG) was done to calculate heart rate (HR) and to detect arrhythmias or ischaemic ST-T wave changes. Echocardiography was performed using S5-1 probe (Philips Epic 7c), according to the of American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) guidelines.[14] EF was assessed by M-mode using Teicholz equation and biplane Simpson method.[14] Regional wall motion abnormalities (RWMA) were evaluated in 17-model segments in all views. Early to late diastolic transmitral flow velocity (E/A), and early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity (E/e')values were calculated using pulse-wave Doppler (PWD) of trans-mitral flow velocities and tissue Doppler sample volume at septal and lateral localisations of the mitral annulus, peak tricuspid regurgitation (TR) velocity was calculated using continuous-wave Doppler (CWD) at TR signal, and left atrial volume index (LAVI) was measured according to area-length formula.[14] Diastolic dysfunction (DD) was classified into grades I to IV, according to (ASE) and (EACVI) guidelines.[14] GLS was assessed using software on two-dimensional (2D) grayscale images of LV, and average GLS of 17 segments was calculated from standard apical 4, 3 and 2 views.

The subjects were classified into 5 groups according to cardiovascular risk factors. Group 1 had patients with no risk factor; Group 2 had patients with many risk factors; Group 3 had patients with hypertension (HTN) alone; Group 4 had patients with diabetes mellitus (DM) only; and Group 5 had patients with smoking as the only risk. All patients were assessed at baseline and at the end of the 12-week therapy.

Data was analysed using SPSS 23. Qualitative variables were expressed as frequencies and percentages. Marginal homogeneity test was used for pre-post comparisons of ordinal variables. McNemar test was used for pre-post comparison of dichotomous variables. Paired t test was used for quantitative continuous variables. Wilcoxon signed rank test was used for the comparison of non-parametric continuous variables. P<0.05 was considered statistically significant.

Results

Of the 200 patients, 104(52%) were females and 96(48%) were males. The age range was 34-81 years, and 18(9%) patients were aged >70 years. Overall, 10(5%) patients had atrial fibrillation (AF) and one patient had dual-chamber pacemaker. Mean HR was 69.5±9.9bpms (range: 45-117bpm).

There were 78(39%) patients in Group 1, 60(30%) in Group 2, 25(12.5%) in Group 3, Group 4 had 13(6.5%) and Group 5 had 24(12%) patients. Group 1 had 20(25.6%) males and 58(74.4%) females with mean age 54.4±10.45 years. Group 2 had 40(66.7%) males and 20(33.3%) females, with mean age 59.5±9.1 years. Group 3 had 3(12%) males and 22(88%) females, with mean age 61.4±7.8 years. Group 4 had 10(77%) males and 3(23%) females, with mean age 55.4±10.4 years. Group 5 had 24(100%) male patients having mean age of 60.7±5.7 years.

The sofosbuvir-daclatasvir combination therapy had no negative inhibitory effect on systolic or diastolic function in any group (Tables 1-3). At end of the therapy there was no significant changes in mean EF, GLS or WMA in any of the groups (p>0.05). Diastolic dysfunction showed significant changes in mean E/e` in Group 1 ($p$< 0.001), mean E/A ratio ($p$= 0.001) and mean E/e` (p< 0.001) in Group 2, mean E/e` (p=0.009) in Group 3, mean E/A ratio (p=0.04) in Group 4, and mean E/A ratio (p= 0.03) in Group 5 but in all these instances, diastolic function grades did not change.

Table 1: Studied variables before and after therapy in groups 1 and 2.

Variables	Group 1 Before start therapy (n=78)	At 12 weeks (n= 78)	*p-value*	Variables	Group 2 Before start therapy (n=60)	At 12 Weeks (n=60)	*p-value*
Mean EF	68±5.4	67.9±5.6	0.3	**Mean EF**	65.7 ±7.08	65.4±6.8	0.1
Diastolic function				**Diastolic function**			
Normal	49(62.8)	49(62.8)	1.0	**Normal**	19(31.6)	19(31.6)	1.0
Grade I	20(25.6)	20(25.6)		**Grade I**	32(53.3)	32(53.3)	
Grade II	9(11.5)	9(11.5)		**Grade II**	9(15)	9(15)	
Parameters				**Parameters**			
E/A	1.03±0.20	1.04±0.21	0.3	**E/A**	0.91±0.23	0.95±0.23	0.001
E/è	8.17±1.8	8.4±1.9	0.3	**E/e`**	9.1±2.3	9.3±2.3	<0.001
TR velocity	2.47±.49	2.48±0.51	<0.001	**TR velocity**	2.497±0.392	2.496±0.38	0.9
LAVI	33.5±1.6	33.3±2.3	0.2	**LAVI**	34.18±0.97	34±1.66	0.2
GLS	-22.07 ±2.3	-22.05±2.3	0.8	**GLS**	-21.2 ±2.3	-21.3±2.2	0.3
WMA				**WMA**			
Absent	77(98.7)	76(97.4)	1.0	**Absent**	57(95)	57(95)	1.0
Present	1(1.3)	2(2.6)		**Present**	3(5)	3(5)	

EF: Ejection fraction, GLS: Global longitudinal strain, LAVI: Left atrial volume index, TR: Tricuspid regurge, WMA: Wall motion abnormality.

Table 2: Studied variables before and after therapy in groups 3 and 4.

Variables	Group 3 Before start therapy (n=25)	At 12 weeks (n= 25)	*p-value*	Variables	Group 4 Before start therapy (n=13)	At 12 Weeks (n=13)	*p-value*
Mean EF	64±7.8	64.3±7.6	0.2	**Mean EF**	66.3±5.3	65.2±5.7	0.1
Diastolic function				**Diastolic function**			
Normal	9(36 %)	9(36 %)		**Normal**	11(84.6)	11(84.6)	1.0
Grade I	12(48%)	12(48%)	1.0	**Grade I**	1(7.6)	1(7.6)	
Grade II	4(16 %)	4(16 %)		**Grade II**	1(7.6)	1(7.6)	
Parameters				**Parameters**			
E/A	0.93±0.16	0.94±0.15	0.7	**E/A**	0.86±0.19	0.9±0.17	0.04
E/e`	8.6±1.9	8.8±1.9	0.009	**E/e`**	8.5±2.5	8.7±2.3	0.08
TR velocity	2.5±0.34	2.5±0.34	0.5	**TR velocity**	2.60±0.56	2.64±0.55	0.1
LAVI	34.1±1.3	34.1±1.3	1.0	**LAVI**	34.26±1.20	34.30±1.26	0.2
GLS	-21.48 ±2.5	-21.43 ±2.4	0.6	**GLS**	-21.4 ±1.7	-21.5±1.6	0.2
WMA				**WMA**			
Absent	24(96)	24(96)	1.0	**Absent**	12	12	1.0
Present	1(4)	1(4)		**Present**	1	1	

Ejection fraction, GLS: Global longitudinal strain, LAVI: Left atrial volume index, TR: Tricuspid regurge, WMA: Wall motion abnormality.

Table 3: Studied variables before and after therapy in group 5.

Variables	Group 5 Before start therapy (n=25)	At 12 weeks (n= 25)	*p-value*
Mean EF	66.3±5.3	65.6±5.7	0.18
Diastolic function			
Normal	10(41.6)	10(41.6)	
Grade I	8(33.3)	8(33.3)	1.0
Grade II	6(25)	6(25)	
Parameters			
E/A	0.86±0.19	0.90±0.17	0.03
E/e`	8.5±2.5	8.7±2.3	0.08
TR velocity	2.6±0.56	2.6±0.55	0.1
LAVI	34.2±1.2	34.3±1.3	0.2

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Discussion

Chronic HCV has multiple systemic effects with increased burden of cardiovascular complication.[15] Historically, HCV treatments had included peginterferon-alpha (PEG-INF) and ribavirin (RBV), but these agents were intolerable and had frequent side effects. DAAs were approved for HCV treatment with high therapeutic efficacy, more tolerability and less side effects, but with safety concerns involving cardiac toxicity.[16]

Table 3: *continued from previous page*

Variables	Group 5 Before start therapy (n=25)	At 12 weeks (n= 25)	*p-value*
GLS	-21.4 ±1.7	-21. 5±1.6	0.2
WMA			
Absent	24(100)	24(100)	-------
Present	0(0)	0(0)	

Ejection fraction, GLS: Global longitudinal strain, LAVI: Left atrial volume index, TR: Tricuspid regurge, WMA: Wall motion abnormality.

In 2014, Egypt started treatment with DAAs at 1% of its international price and provided it free of charge in national regimen of the 100 million Healthy Lives campaign.[9] There have been suggestions that DAAs might cause cardiac adverse events, including cardiotoxicity and CHF. Ahmad et al. reported that results of retrospective evaluation of the clinical and pathological outcomes of BMS-986094 that had led to trial abortion due to suspected cardiotoxicity, showed that 14 of the 34 patients who had received treatment had acute myocardial systolic impairment, but recovered within 20 days of drug withdrawal, suggesting drug-induced toxic cardiomyopathy.[11]

Mazzitelli et al. studied 109 patients receiving sofosbuvir-based regimen, including daclatasvir, and divided the patients into two groups. Group A received DAAs for 3 months and Group B received DAAs for 6 months. There were no significant EF changes in both the groups. There was significant worsening of GLS in Group A. This discrepancy was explained by the authors, arguing that Group B patients were older and had co-morbidities, and they suggested that DAA and prolonged exposure to DAAs may have direct cardiac toxic effect on the myocardium which may worsen EF later, but they did not recommend discontinuation of these combinations.[12] Farag et al. included100 patients with mildly reduced EF (40-50%) and 20 patients with EF >55%, and noted significant worsening of GLS in both the groups, with more impairment in patients with mildly reduced systolic function.[17]

In the present study, patients were followed for symptoms of progressive dyspnoea and echo parameters of EF, GLS, diastolic function (DF) and RWMA. The patients were divided into 5 groups, according to risk factors, to assess the effect of DAA therapy in each group.

Regarding systolic function, there were no significant changes in mean EF or GLS values before and after therapy in any of the groups. The study included 4 patients with mildly reduced EF; 1 patient each in groups 2, 3, 4 and 5.

Regarding DF, 98 patients had normal DF at baseline. DF showed significant changes only in certain parameters in each of the 5 groups, mainly related to E/A and E/e` values. There was no worsening of DF grades. No patient in the current study complained of progressive dyspnoea or heart failure symptoms.

Also, the current study had 6 patients with baseline RWMA. In Group 1 the single patient had left anterior descending (LAD) artery territory WMA, and had a LAD stent for 3 years In Group 2, there were 3 patients; 1 had coronary artery bypass graft (CABG) 5 years previously with multiple WMAs, 1 patient' echo showed WMA of inferolateral walls and on coronary angiography showed marked ectasia, while 1 patient had EF 45% with global hypokinesia. In Group 3, there was 1 patient with global hypokinesia and EF 47%. In group 4, 1 patient had EF 43%, global hypokinesia and paradoxical septal motion with normal coronary angiography. In Group 5, there was no patient with RWMA The patients with RWMAs tolerated the therapy well with no complaints or echo documentations of systolic impairment

These findings match those reported earlier, but differed in terms of GLS.[12,17]

Also, study findings as well as sampling, clinical and echo parameters match well with several studies.[18-20]

Finally, recent studies have suggested that eradication with DAA regimens is not only safe and tolerable with no major cardiac events, but also significantly reduces cardiovascular adverse events and overall mortality.[21,22]

The current study has its limitations. The sample size was not calculated, which could have had an adverse effect on the power of the study. The sample did not include patients receiving different DAA protocols as majority of patients infected with genotype 4 HCV virus receive the sofosbuvir-daclatasvir combination therapy as part of the national regimen. Also, it did not include patients with relapse of either interferon or DAA therapy, and, therefore, could not predict the cumulative effect of different protocols. The study did not include patients with cardiomyopathy or recent MI as there was no relevant data about DAA safety in such cases. Future studies should include all such patients, especially in the era of angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 (SGLT2) inhibitors which have given great hope to such patients.

Conclusion

The sofosbuvir-daclatasvir combination therapy did not affect LV systolic or diastolic functions and was found to be safe and tolerable in cardiac patients.

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Conflict of Interest: None.

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