RESEARCH ARTICLE

Cardiovascular Risk Assessment after Sofosbuvir and Daclatasvir Regimen for Chronic Hepatitis C Virus Infection

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Abstract

Objective: To assess cardiovascular risk after sofosbuvir and daclatasvir antiviral combination therapy in chronic hepatitis C virus patients.

Methods: The prospective cohort study was conducted at the Kafrelsheikh University Hospital, Egypt, from December 2019 to December 2021, and comprised adult patients of either gender with chronic hepatitis C virus and with minimum ejection fraction 40%. They were classified into groups according to their cardiovascular risk. Group 1 had individuals with no risk factors, Group 2 had patients with many risk factors, Group 3 had patients with only hypertension, Group 4 had those with diabetes alone, and Group 5 comprised smokers. All the patients were evaluated for the risk of major cardiovascular events at baseline and at the end of 12-week of antiviral combination therapy of sofosbuvir 400 mg once daily dose and daclatasvir 60 mg once daily dose. Data was analysed with SPSS version 23.

Results: Of the 200 patients, there were 96(48%) males and 104(52%) females. The age ranged 34-81 years. There were 78(39%) patients in Group 1; 20(25.6%) males and 58(74.4%) females with mean age 54.4±10.45 years. Group 2 had 60(30%) patients; 40(66.6%) males and 20(33.3%) females with mean age 59.57±9.1 years. Group 3 had 25(12.5%) patients; 3(12%) males and 22(88%) females with mean age 61.4±7.8 years. Group 4 had 13(6.5%) patients; 10(77%) males and 3(23%) females with mean age 55.4±10.4 years. Group 5 had 24(12%) patients who were all (100%) males with mean age 60.7±5.7 years. There were non-significant changes in the incidence of angina, arrhythmias or progression of dyspnoea ($p>0.05$). Echocardiography follow-up results showed non-significant changes in mean ejection fraction, global longitudinal strain and pulmonary artery pressure ($p>0.05$).

Conclusion: Sofosbuvir and daclatasvir combination therapy was found to be safe in chronic hepatitis C virus patients regarding cardiac risks.

Keywords: Sofosbuvir**,** Daclatasvir**,** Stroke, Pulmonary**,** coronary syndrome, Cardiovascular, Hepatitis C, Ventricular dysfunction, Echocardiography, Amiodarone, Hypertension, Arrhythmias, Diabetes, Dyspnoea, Smoking.

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Introduction

Globally, about 70 million people are seropositive for hepatitis C virus (HCV), a condition which complicates chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).[1]

HCV infection is a systemic disease associated with multiple extrahepatic manifestations, including cardiovascular system.[2] A lot of studies proved higher incidence of HCV-induced major adverse cardiovascular events (MACEs), such as coronary artery disease (CAD), heart failure (HF), stroke and peripheral artery disease (PAD), with proposed mechanisms of HCV-induced atherosclerosis, including systemic inflammation, autoimmunity and increased levels of pro-atherogenic inflammatory markers.[3-5]

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Chronic HCV infection is endemic in Egypt, recording the highest prevalence rate in the world, and it is related to past history of anti-bilharzial therapy. In 2006, Egypt established the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) which started to treat patients using the interferon regimen.[6]

During the past decade, direct-acting antivirals (DAAs) were approved for HCV treatment of HCV infection with high efficacy and safety with less undesirable side effects compared to the interferon regimen.[7] DAAs improve liver-related outcomes, such as liver cirrhosis and HCC[8], with recent studies suggesting that DAAs have a significant reduction of major cardiovascular events.[9]

By October 2014, the NCCVH had introduced DAAs for nationwide treatment of HCV infection at 1% of its international price, which extended to the national regimen of the 100 Million Healthy Lives campaign free of charge.[9]

Although DAAs represented a breakthrough therapy, safety warnings and literatures suggested that DAAs had been

associated with significant bradycardia,[10-12] congestive heart failure (CHF)[13], myocardial infarction (MI)[14] and exacerbating pulmonary hypertension (PH).[15]

The current study was planned to assess cardiovascular risk after sofosbuvir and daclatasvir antiviral combination therapy in chronic HCV patients.

Patients and Methods

The prospective cohort study was conducted at the Kafrelsheikh University Hospital, Egypt, from December 2019 to December 2021. After approval from the institutional ethics review committee, the sample was raised from among the patients who had been referred randomly from the Hepatology Outpatient Department (OPD) to the Cardiology Department for cardiac evaluation and fitness before starting sofosbuvir and daclatasvir combination therapy, which is a recommended regimen for chronic HCV infection treatment under the Egyptian 100 Million Health Lives campaign.[9]

Those included were adult patients of either gender with chronic HCV infection and with minimum ejection fraction (EF) 40% who were eligible for antiviral combination therapy of sofosbuvir 400 mg once daily dose and daclatasvir 60 mg once daily dose for 12 weeks according to the NCCVH recommendations.[6,9] Those excluded were patients with cardiomyopathy (EF <40%), recent MI or amiodarone intake within the preceding 3 months, and patients with history of antiviral therapy relapse.

After taking written informed consent from the participants, they were classified into groups according to their cardiovascular risk. Group 1 had individuals with no risk factors, Group 2 had patients with many risk factors, Group 3 had patients with only hypertension (HTN), Group 4 had those with diabetes mellitus (DM) alone, and Group 5 comprised smokers.

Detailed medical history was obtained, with the focus on cardiac symptoms, like dyspnoea, angina and palpitations, current medications, especially anti-hypertensive, antiarrhythmic, negative chronotropic, anti-platelet, anticoagulant and endothlin receptor antagonist drugs. All the participants were then subjected to full general and local cardiac examination. Standard 12-lead electrocardiogram (ECG) was done to calculate heart rate (HR) and to detect arrhythmias or ischaemic ST-T wave changes. Dyspnoea was assessed in line with the New York Heart Association (NYHA) classification.[16] Echocardiographic (echo) examinations were performed using S5-1 probe machine (Philips Epic 7c) according to the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) guidelines.[17] EF was assessed by M-mode using Teicholz equation and biplane Simpson method.[17] Regional wall motion abnormalities (RWMA) were evaluated with 17-model segments in all views. Peak systolic pulmonary artery pressure was calculated from tricuspid regurgitation velocity using Bernoulli equation.[17]

The patients were evaluated before starting the therapy and after the 12-week at end of therapy .

Statistical methods: Data entry and analysis was done by statistical package of social sciences "spss" version 23. Qualitative variables are summarized in number & percentage. Marginal homogeneity test is used for pre-post comparisons of ordinal variables. Mc Nemar 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 comparison of non parametric continuous variables. Level of significance less than 0.05 is considered statistically significant.

Results

Of the 200 patients, there were 96(48%) males and 104(52%) females. The age ranged 34-81 years, with 18(9%) patients aged >70 years. There were 10(5%) patients with atrial fibrillation (AF) and 1(0.5%) patient had dual-chamber pacemaker.

There were 78(39%) patients in Group 1; 20(25.6%) males and 58(74.4%) females with mean age 54.4±10.45 years, while Group 2 had 60(30%) patients; 40(66.6%) males and 20(33.3%) females with mean age 59.57±9.1 years (Table 1). Group 3 had 25(12.5%) patients; 3(12%) males and 22(88%) females with mean age 61.4±7.8 years, while Group 4 had 13(6.5%) patients; 10(77%) males and 3(23%) females with mean age 55.4±10.4 years (Table 2). Group 5 had 24(12%) patients who were all (100%) males with mean age 60.7±5.7 years (Table 3).

There were non-significant changes in the incidence of angina, arrhythmias or progression of dyspnoea (p>0.05). Echocardiography follow-up results showed non-significant changes in mean ejection fraction, global longitudinal strain and pulmonary artery pressure (p>0.05).

Overall, 2(1%) patients developed ischaemic chest pain during therapy, but there was no worsening or improvement of their baseline dyspnoea NYHA class. There were 7(3.5%) patients with frequent ventricular ectopics, but there was no significant increase in frequency or symptomatology of ectopics. ST-T wave changes were fixed and related to non-ischaemic causes with no dynamics. There were 6(3%) patients with baseline RWMA, while post-intervention there were 7(3.5%%), with the lone addition noted in Group 1.

Table 1: : Clinical, electrocardiogram (ECG) and echocardiogram (echo) variables before and after therapy in Group 1 and Group 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*
Angina				**Angina**			
No angina	78(100)	77(98.7)	1.0	**No angina**	59(98.3)	59(98.3)	1.0
Anginal pain	0(0)	1(1.3)		**Anginal pain**	1(1.6)	1(1.6)	
Dyspnoea				**Dyspnoea**			
No dyspnoea	69(88.4)	69(88.4)	1.0	**No dyspnoea**	48(80)	48(80)	1.0
NYHA class 1	5(6.4)	5(6.4)		**NYHA class 1**	11(18.3)	11(18.3)	
NYHA class II	3(3.8)	3(3.8)		**NYHA class II**	1(1.6)	1(1.6)	
NYHA class III	1(1.2)	1(1.2)					
Palpitation				**Palpitation**			
Absent	68 (87.1)	70(89.7)	0.5	**Absent**	56(93.3)	56(93.3)	1.0
Present	10(12.8)	8(10.2)		**Present**	4(6.6)	4(6.6)	
HR	71.9 ±10.79	72.2±11.51	0.5	**HR**	68.3±9.29	68.5±10.52	0.2
Ectopics				**Ectopic beats**			
Absent	75 (96.1)	75(96.1)	1.0	**Absent**	48(80)	48(80)	1.0
Present	3(3.8)	3(3.8)		**Present**	12(20)	12(20)	
ST changes				**ST changes**			
No	78(100)	78(100)	-----	**No**	56(93.3)	56(93.3)	1.0
Present	0(0)	0(0)		**Present**	4(6.6)	4(6.6)	
Mean EF	68.2±5.4	67.9±5.6	0.3	**Mean EF**	65.7±7.08	65.4±6.8	0.1
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)	
Pulmonary Pressure				**Pulmonary Pressure**			
Normal	66(84.6)	66(84.6)	1.0	**Normal**	50(83.3)	50(83.3)	1.0
Mild pulmonary HTN	7(8.9)	7(8.9)		**Mild pulmonary HTN**	7(11.6)	7(11.6)	
Moderate pulmonary HTN	1(1.2)	1(1.2)		**Moderate pulmonary HTN**	3(5)	3(5)	
Severe pulmonary HTN	4(5.1)	4(5.1)					

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

Table 2: : Clinical, electrocardiogram (ECG) and echocardiogram (echo) variables before and after therapy in Group 3 and Group 4.

Variables	Group 2 Before start therapy (n=25)	At 12 weeks (n= 25)	*p-value*	Variables	Group 3 Before start therapy (n=13)	At 12 Weeks (n=13)	*p-value*
Angina				**Angina**			
No angina	25(100)	25(100)	----	**No angina**	13(100)	13(100)	-----
Anginal pain	0(0)	0(0)		**Anginal pain**	0(0)	0(0)	
Dyspnoea				**Dyspnoea**			
No dyspnoea	20(80)	20(80)	1.0	**No dyspnoea**	11(84.6)	11(84.6)	1.0
NYHA class 1	4(16)	4(16)		**NYHA class 1**	2 (15.3)	2 (15.3)	
NYHA class II	1(4)	1(4)					
Palpitation				**Palpitation**			
Absent	23(92	23(92	1.0	**Absent**	12(92.3)	12(92.3)	1.0
Present	2(8)	2(8)		**Present**	1 (7.69)	1 (7.69)	
HR	67.5 ±7.8	67.8±7.9	0.5	**HR**	65.2 ±9.1	65.1±10.7	0.5
Ectopics				**Ectopics**			
Absent	23(92 %)	23(92 %)	1.0	**Absent**	13(100)	13(100)	----
Present	2(8%)	2(8%)		**Present**	0(0)	0(0)	
ST changes				**ST changes**			
No	25(100 %)	25(100 %)	-----	**No**	13(100)	13(100)	----
Present	0(0)	0(0)		**Present**	0(0)	0(0)	

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Table 2: *: continued from previous page*

Variables	Group 2 Before start therapy (n=25)	At 12 weeks (n=25)	*p-value*	Variables	Group 3 Before start therapy (n=13)	At 12 Weeks (n=13)	*p-value*
Mean EF	64.0±7.8	64.3±7.6	0.2	**Mean EF**	66.3 ±5.3	65.2±5.7	0.1
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	
Pulmonary Pressure				**Pulmonary Pressure**			
Normal	19(76)	19(76)	1.0	**Normal**	12(92.3)	12(92.3)	1.0
Mild pulmonary HTN	6(24.0)	6(24.0)		**Mild pulmonary HTN**	1(7.6)	1(7.6)	

EF: Ejection fraction, GLS: Global longitudinal strain, HR: Heart rate, HTN: Hypertension, NYHA: New York Heart Association, WMA: Wall motion abnormality.

Table 3: Clinical, electrocardiogram (ECG) and echocardiogram (echo) variables before and after therapy in Group 5.

Variables	Group 5 Before start therapy (n=24)	At 12 weeks (n= 24)	*p-value*
Angina			
No angina	24 (100)	24 (100)	-----
Anginal	0(0)	0(0)	
Dyspnoea			
No dyspnoea	19(79.1)	19(79.1)	1.0
NYHA class 1	5(20.8)	5(20.8)	
Palpitation			
Absent	19(79.1)	19(79.1)	1.0
Present	5(20.8)	5(20.8)	
HR	65.2 ±9.1	65.1±10.7	0.8
Ectopics			
Absent	19(79.1)	20(83.3)	1.0
Present	5(20.8)	4(16.6)	
ST changes			
No	24(100)	24(100)	------
Present	0	0	
Mean EF	66.3±5.3	65.6±5.7	0.18
GLS	-21.4 ±1.7	-21. 5±1.6	0.2
WMA			
Absent	24(100)	24(100)	------
Present	0	0	
Pulmonary Pressure			
Normal	19(79.1)	19(79.1)	1.0
Mild pulmonary HTN	3(12.5)	3(12.5)	
Severe pulmonary HTN	2(8.3)	2(8.3)	

EF: Ejection fraction, GLS: Global longitudinal strain, HR: Heart rate, HTN: Hypertension, NYHA: New York Heart Association, WMA: Wall motion abnormality.

Discussion

Chronic hepatitis C disease represents a major health problem with high morbidity and mortality burden also involving the cardiovascular system.[18] Egypt started treatment with DAAs in the national regimen under the 100 Million Healthy Lives campaign.[6] Retrospective studies, case reports, and post-marketing reports suggest that DAAs might cause adverse cardiac events (ACEs). Ahmad et al. reported that results of retrospective evaluation of the clinical and pathological outcomes in a Phase 2 study had led to clinical discontinuation due to suspected cardiotoxicity[13] In 2015, the Food and Drug Administration (FDA) announced changes in the labelling of the Sovaldi (sofosbuvir) and Harvoni (sofosbuvir/ledipasvir) brands to warn about serious and significant bradycardia when either drug is taken with amiodarone, and it recommended that DAAs should not be started until 3 months after the last intake.[19] Also, Ucciferri et al. reported a single-centre experience about DAA-induced arrhythmias and MI.[14] Renard et al. reported 3 cases of newly diagnosed or worsened pulmonary arterial hypertension (PAH) in patients treated with sofosbuvir.[15]

In the current study, concerning these warnings, the patients were followed for symptoms of progressive dyspnoea, palpitation, angina, and, using diagnostic tools of standard 12-lead ECG and echo evaluation, HR variability and/or arrhythmia, EF, global longitudinal strain (GLS), RWMAs and systolic pulmonary pressure.

Regarding systolic function, there was no significant changes in mean EF or GLS values across the groups at baseline and post-therapy. The study included 4 patients with mild reduced EF; 1 patient each in groups 2, 3, 4 and 5. The higher baseline EF value 78% changed to 75 %; the lower 43% changed to 45%; the higher GLS -16.5 and improved to -17.9; and the lower GLS -30 declined to -29. Also, the 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's 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. Also, 3 patients were diagnosed with chronic coronary syndrome (CCS); 1 of them had LAD stent, second had CABG, and the third had proximal LAD ectasia. All of them tolerated the combination therapy well with no complaints. During therapy, 2 patients complained of angina; first was in group 1, a female aged 65 years, who complained after 2 months of limiting chest pain. The ECG showed no significant changes, stress echocardiography was non-conclusive and coronary angiography showed proximal LAD ectasia with slow flow and non-obstructive lesions. The second patient was in group B, a male aged 58 years who was hypertensive diabetic. He had average ECG with good systolic function and no WMA. He developed acute coronary syndrome (ACS). Coronary angiography at 10 weeks showed multivessel disease (MVD) for coronary bypass surgery. It is suggested that combination therapy was not definite a culprit for these attacks as the first patient had mostly chronic disease of coronary ectasia, and the second patient had MVD with chronic obstructive lesions. Regarding safety concerns about arrhythmia, the current study excluded patients on amiodarone therapy in the preceding 3 months, had 18 patients aged >70 years, 10 with permanent AF, 7 had frequent ventricular ectopics, and 15 had frequent atrial ectopics (Tables 1-3). Also, there were patients with beta blockers (BBs), calcium channel blockers (CCBs), digoxin and sotalol. These patients were followed carefully initially and at 12 weeks .Minimum HR was 45bpm, average was 68bpm, with maximum HR being 117bpm. Patients with baseline clinical and or ECG-documented ectopics and patients complaining of palpitations were evaluated and medications were revised and optimised for comorbidities with antiarrhythmic medications if needed. At follow-up, there was no significant increase in frequency or symptomatology of ectopics. The patients who were free of ectopics at baseline did not develop any significant arrhythmia, and there was no change in mean HR and no dynamic ST-T wave change. These results match well earlier studies (20-23), which concluded that different DAA protocols had no major cardiac events.

The current study had 156 patients with normal pulmonary systolic pressure, 24 mild, 4 moderate and 6 severe. Of these, 2 had severely dilated right-side and pulmonary artery, and 1 was diagnosed as hypoxic and 1 as bilharzial corpulmonale. The higher peak systolic pressure was about 90mmHg, and at follow-up, there was no worsening or improvement of pulmonary pressure values. The results are in contrast with a study[15] which reported 3 cases of severe haemodynamic deterioration after DAA therapy, and had more severe right-sided failure with worse baseline presentation. However, the current study agrees with the need for close follow-up of these patients. The current findings, however, are in line with another study[24] which did not observe any case of clinical, functional, echocardiographic or invasive worsening of pre-existing pulmonary hypertension. Ibrahim et al.[22] studied 100 patients receiving DAA therapy and concluded that at follow-up, right ventricular function and pulmonary pressure did not change, while right ventricular GLS showed significant decrease. Also, Schild et al.[25] followed 33 patients who received different DAA regimens for 16 weeks, and reported no significant changes in right ventricular function and pulmonary systolic pressure after therapy.

The current study has its limitations. It did not include patients receiving different DAA protocols, or patients with relapse of either interferon or DAA therapy. Also, the study did not include patients with cardiomyopathy or recent MI as it had no relevant data about DAA safety in such cases. Future studies should include all such patients, especially in the era of angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors which have given great hope to such patients.

Conclusion

Sofosbuvir and daclatasvir combination therapy was found to be safe for chronic HCV patients regarding cardiac risks, including patients with CCS, mild reduced EF and severe pulmonary HTN with no significant arrhythmogenic effect.

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