Effect of Chronic Hepatitis C Virus Treatment by Combination Therapy on Cardiovascular System

Clinical Medicine Insights: Cardiology
Volume 11: 1–9

DOI: 10.1177/1179546817713204

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ABSTRACT:

BACKGROUND: The prevalence of hepatitis C virus (HCV) in Egypt is quite high, and the combined oral direct-acting antiviral agents (DAAs) may have impressive results.

OBJECTIVE: To assess the cardiovascular effects of DAAs in patients with HCV.

METHODS: A total of 170 patients with HCV were divided into 2 groups: first group (100 patients) received triple combination therapy (pegylated interferon alfa, sofosbuvir, and ribavirin, whereas the second group (70 patients) received dual combination therapy (sofosbuvir and simeprevir). Group 1 patients were followed up for 1 year more than 3 visits, whereas group 2 patients were followed up for 6 months more than 2 visits; and the end point of the study was the development of a major cardiovascular event (eg, congestive heart failure, echocardiographic evidence of left ventricular dysfunction, occurrence of significant arrhythmias, or acute coronary syndrome). The following parameters were accomplished: medical history and clinical examination, electrocardiogram, echo-Doppler study, and laboratory investigations.

RESULTS: No significant differences were found between the 2 study groups regarding demographic criteria. None of the both group patients had developed any major cardiac event. No significant changes were observed regarding ST-T wave abnormalities, arrhythmias, or QT interval. None of the both group patients developed echocardiographic regional wall motion abnormalities at baseline or at study end. Systolic function parameters showed minute nonsignificant changes over study visits. Diastolic function parameters showed nonsignificant changes between baseline and 6-month and 12-month visits.

CONCLUSIONS: The DAAs used in combination regimen with interferon or used orally in combination do not significantly affect the cardiovascular system.

KEYWORDS: Hepatitis C virus, oral direct antiviral agents, echocardiography

RECEIVED: December 10, 2016. **ACCEPTED:** April 16, 2017.

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 669 words, excluding any confidential comments to the academic editor.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Background

Hepatitis C virus (HCV) poses a real health threat being one of the most prominent causes of chronic liver diseases worldwide. According to Lavanchy[1] as stated in *The Global Burden of Hepatitis C*, about 170 to 200 million individuals, which accounts for 3% of the world's population, are chronically infected with HCV, with 3 to 4 million new cases annually. In Egypt, however, the situation is even more critical. Egypt has a higher prevalence for HCV than any of its neighboring countries or any other country in the world with a similar socioeconomic situation and hygienic conditions.[2]

The main objective of the treatment for chronic HCV infection is to attain a sustained virologic response (SVR), defined as undetectable HCV-RNA, 24 weeks after completing the treatment course. According to long-term follow-up studies reported by Backus et al[3] in "A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C" and Kanwal et al in "Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C," 97% to 100% of sustained responders retained undetectable HCV-RNA in serum, liver, and peripheral blood mononuclear cells which advocate the theory that SVR can be associated with eradication of HCV infection. There is also evidence that SVR can be attained at lower rates, in patients having extensive fibrosis or cirrhosis, decreasing the risk of HCC development and improving the survival rate altogether.[4]

Between the period of 2001 and 2011, the standardized treatment for chronic HCV infection was a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV).[5] The treatment showed an SVR of 40% to 50% in genotype 1 (G1) and 70% to 80% in genotypes 2 and 3 (G2/G3).[6] However, the effectiveness of the treatment was limited by frequent side effects and restricted efficacy as stated in "the American

Association for the Study of Liver Diseases. Diagnosis, management and treatment of hepatitis C: an update."[7]

The development of direct-acting antiviral agents (DAAs) has been a primary focus of the medical community for the past decade. The DAAs can block the activity of the viral enzymes targeting both NS3/4A serine protease, which blocks HCV polyprotein processing, and HCV replication. Another approach is using the nucleoside/nucleotide and nonnucleoside inhibitors of the RNA-dependent polymerase and inhibitors of the NS5A viral protein which has a regulatory role in HCV replication.[8]

In May 2011, the use the first-generation NS3/4A protease inhibitors, boceprevir and telaprevir, was approved for use in genotype 1 (G1), provided that they will be combined with PEG-IFN and RBV to prevent the development of resistance-associated variants.[9]

A second-generation NS3/4A protease inhibitor known as simeprevir was being developed and it was approved in December 2013 for the use in genotype 1 (G1) with PEG-IFN and RBV for 12 weeks after the surgery.[10]

Based on the data collected from *Quest 1, Quest 2*, and *Pillar*, clinical trials showed that the use of simeprevir with a combination of PEG-IFN and RBV in genotype 1 (G1) for 12 weeks and then followed by just PEG-IFN and RBV for 12 to 36 weeks attained an SVR of 80% to 81%, and consequently, simeprevir was approved in December 2013.[11–13]

However, the development of cross-resistance by first-generation and second-generation protease inhibitors remained an issue that led to the development of other DAA classes, such as nucleotide NS5B polymerase inhibitors which include sofosbuvir (SOF). Data showed that the use SOF in combination with PEG-IFN and RBV in genotype 1 (G1) for 12 weeks attained an SVR of 89% to 91% in genotype 1 treatment-naïve patients. The treatment also proved effective for genotype 4 (G4) infections.[13]

The limited safety and tolerability of interferon-based treatments encouraged the development of interferon-free treatments which proved to be a healthier alternative and an even more cost-effective treatment.[14]

In 2012, The study by Lok et al[15] showed that SVR could be achieved by an interferon free regimen whereby asunaprevir (NS3/4A protease inhibitor) and daclatasvir (DCV) (NS5A replication complex inhibitor) given for 24 weeks for to G1 previous null responders produced an SVR of 36%. Sofosbuvir was approved for use with RBV for 12 weeks in G2 and 24 weeks in G3. In G2 treatment-naïve patients, SOF and RBV for 12 weeks produced an SVR of 92% to 97% in noncirrhotics and 94% to 100% in cirrhotics in different clinical trials, namely, Fission,[16] Positron,[17] and Valence.[18] Following the success of simeprevir and SOF in COSMOS study,[19] several other SOF-based treatments in combination with another DAA have shown impressive results. In G1 treatment-naïve noncirrhotic patients, SVR with ledipasvir (LDV) (NS5A replication complex inhibitors) and SOF with or without RBV for 8 weeks were 93% to 100% in ION-3 study[20] and DCV (NS5A replication complex inhibitor) and SOF with or without RBV for 12 weeks were 95% to 100% in AI444040 study.[21] And GS-9669 (NS5B nonnucleoside polymerase inhibitor) and SOF with RBV for 12 weeks was 92% in Electron.[22] Regarding the new DAAs, Food and Drug Administration (FDA) recently announced a change in labeling for the 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.[23]

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, this work was conducted to study the cardiovascular effects of DAAs in combination with or without PEG-IFN in Egyptian patients with chronic HCV infection.

Patients and Methods

The study consisted of 170 patients diagnosed with chronic HCV infection, recruited from the outpatient clinics of Al-Sahel Teaching Hospital, located in Cairo, Egypt, starting from October 2014 till April 2016.

Inclusion criteria

The study includes patients who have chronic HCV infection and are candidates for combination therapy.

Patients were divided into 2 groups:

- *Group A* included 100 patients who received a triple combination therapy in the form of PEG-interferon alfa, SOF (Sovaldi), and RBV.
- *Group B* included 70 patients who received dual combination therapy in the form of SOF and simeprevir (Sovaldi and Olysio).

Exclusion criteria

The patients belonging to the following criteria were excluded from the study:

- Patients with advanced liver disease or decompensated liver cirrhosis (encephalopathy, ascites, and bleeding varices);
- Patients with autoimmune hepatitis, chronic hepatitis B, combined chronic hepatitis B and C;
- Patients with advanced renal impairment;
- Patients with uncontrolled thyroid dysfunction, poorly echogenic patients;
- Patients with previous history of cardiac diseases or with abnormal clinical or electrocardiographic (ECG) findings;

- Patients with severe psychiatric disorders;
- Patients with diabetes mellitus or hypertension;
- Pregnant patients.

Methods

Group A patients were followed up for 1 year more than 3 visits before initiating treatment and then followed up for 6 and 12 months after the treatment.

Group B patients were followed up for 6 months more than 2 visits before initiating the treatment, then 6 months after the treatment.

The objective of the study was to monitor whether the patients would complete the study without showing any cardiac complications or would the treatment cause a cardiovascular complication (eg, congestive heart failure, echocardiographic evidence of left ventricular [LV] dysfunction, occurrence of a significant arrhythmias, or acute coronary syndrome):

All patients who participated in the study filled a written informed consent.

The study protocol was reviewed and approved by the local ethics committee.

All participants went through a cardiac assessment and a thorough medical history check for premature coronary artery disease.

The *symptoms* were shortness of breath, chest pain, palpitations, dizziness, presyncope or syncope, orthopnea, or paroxysmal nocturnal dyspnea (PND).

The *signs* were systolic and diastolic blood pressure, heart rate, presence of gallop or any detected murmurs, or fine basal crepitation.

ECG, a standard 12-lead ECG, was recorded before the treatment and at a later follow-up visit to assess the presence of arrhythmias, ST-T wave changes, and corrected QT interval using the Bazett formula which states the following: QTc = QT interval/√PR interval.

Echocardiography includes a full 2-dimensional (2D), M-mode, Doppler and color flow mapping, and tissue Doppler echocardiography study performed before initiating the treatment and at a later follow-up throughout the treatment. Echo was used to estimate end diastolic dimension and end systolic dimension, interventricular septum thickness, posterior wall thickness, left atrial diameter, and mitral regurgitation. Ejection fraction (EF) was assessed by M-mode using Teicholz equation and 2D mode by the biplane Simpson method. Evidence of regional wall motion abnormalities (RWMA) was evaluated. Transmitral flow velocities were recorded using pulsed-wave Doppler with the sample volume placed at the tip of the mitral valve leaflets in the apical 4-chamber view. The following measurements were taken: peak E velocity (cm/s), peak A wave velocity (cm/s), and early to late (E/A) ratio with E wave deceleration time (ms). Diastolic dysfunction was assessed according to the American Society of Echocardiography Guidelines and the estimation of peak pulmonary artery systolic pressure from tricuspid regurgitation velocity using Bernoulli equation was applied.[24,25] Tissue Doppler was used to measure the systolic and diastolic mitral annular velocities. The tissue Doppler sample volume was applied on septal and lateral localizations of the mitral annulus in the apical 4-chamber view. Systolic (s) and diastolic (Ea and Aa) velocities, pulsed-wave Doppler–derived E wave velocity, and tissue Doppler Ea velocity ratio (e/Ea) were measured.

Full hepatological assessment

Liver function tests include the following: aspartate aminotransferase, alanine aminotransferase, serum bilirubin, serum albumin, alkaline phosphatase, prothrombin time, and international normalized ratio.

Blood tests include the following: serum creatinine, blood glucose (fasting and postprandial blood sugar), and complete blood count (hemoglobin, white blood cells, red blood cells, and platelets).

Enzyme-linked immunosorbent assay (ELISA) includes the following: viral markers for hepatitis A virus were screened using the ELISA technique. Also, thyroid-stimulating hormone, T3, T4, autoantibodies, antinuclear antibody, and alpha fetoprotein were studied using the ELISA technique.

Abdominal ultrasound was performed to check for liver cirrhosis, splenomegaly, and ascites and to check the kidneys and pancreas.

Statistical methods

Data are statistically described in terms of mean ± SD, range, or frequencies (number of cases) and percentages when appropriate.

Comparison of numerical variables of the study groups between the follow-up visits was done using Student *t* test/analysis of variance for independent samples.

Comparison of categorical data was done using the χ^2 test. Exact test was used instead when the expected frequency is less than 5.

P values less than .005 were considered statistically significant.

All statistical calculations were done using the following computer program: SPSS Inc., IL, USA, version 21 for Microsoft Windows.

Results

The included patients (170) were studied regarding the demographic criteria where no significant differences were found between the 2 study groups regarding age, gender breakdown, family history, and smoking practice. As an inclusion prerequisite, none of the recruited patients was diabetic (Tables 1–5).

Table 1. Demographic data of the studied groups.

	GROUP 1 (100)	GROUP 2 (70)	*P* VALUE
Age, y Mean ± SD	49.78 ± 7.11	47.54 ± 9.16	.0891
Gender Male:female, No. (%)	51 (51):49 (49)	37 (53):33 (47)	.8115
DM Yes:no, No. (%)	0 (0):100 (100)	0 (0):70 (100)	NA
Family history Yes:no, No. (%)	3 (3):97 (97)	2 (3):68 (97)	.9567
Smoking Yes:no, No. (%)	39 (39):61 (61)	25 (36):45 (64)	.6634

Abbreviation: DM, diabetes mellitus; NA, not applicable.

Table 2. Symptoms and signs at baseline and at 6 and 12 months after treatment initiation in group 1 patients.

	BASELINE (DAY 0)	MONTH 6	MONTH 12	*P* VALUE
Symptoms				
Chest pain Yes:no, No. (%)	0 (0):100 (100)	4 (4):96 (96)	3 (3):97 (97)	.1493
Shortness of breath Yes:no, No. (%)	0 (0):100 (100)	5 (5):95 (95)	2 (2):98 (98)	.0621
Palpitation Yes:no, No. (%)	0 (0):100 (100)	2 (2):98 (98)	0 (0):100 (100)	.1335
Signs				
Systolic blood pressure Mean ± SD	120.30 ± 7.91	121.45 ± 7.76	121.70 ± 5.65	.0592 (D0 vs M6) .7209 (M6 vs M12) .0540 (M6 vs M12)
Diastolic blood pressure Mean ± SD	75.8 ± 4.31	76.81 ± 6.46	76.86 ± 4.93	.0533 (D0 vs M6) .9296 (M6 vs M12) .0550 (M6 vs M12)
Heart rate Mean ± SD	74.69 ± 5.84	75.36 ± 5.19	74.58 ± 5.40	.0564 (D0 vs M6) .1246 (M6 vs M12) .8604 (M6 vs M12)

Group 1

In group 1 that received triple combination therapy, none of the patients developed any major cardiac complication, such as congestive heart failure, echocardiographic evidence of LV dysfunction, occurrence of a significant arrhythmias, or acute coronary syndrome, throughout the course of treatment. Shortness of breath has been reported in 5% of the patients 6 months after initiating the treatment. However, none of them has described orthopnea or PND. At the 12-month follow-up, only 2% of patients remained experiencing shortness of breath but with no signs of orthopnea or PND. Similarly, 4% of patients had reported chest pain at the 6-month follow-up which decreased to 2% at the 12-month follow-up with $P > .05$. Also, 2% had described palpations at the 6-month follow-up that disappeared at the 12-month follow-up. None of the patients has experienced any associated dizziness, presyncope, or syncope.

There was no significant increase in neither of the mean systolic nor the mean diastolic blood pressure recordings after 6 and 12 months into the course of triple combination therapy. However, abnormally elevated blood pressure of (160/95 and 150/100) was evident in 2 patients at the 6-month follow-up and a third patient (160/100) at the 12-month follow-up. Still, these instances were statistically nonsignificant ($P > .05$). Heart rate recordings did not show any significant alterations between baseline and follow-up visits (Table 2).

ECG findings

None of the group 1 patients developed prolonged QT interval at follow-up visits. There was no significant alterations in the mean-corrected QT interval at the 6-month and 12-month follow-up. No arrhythmias had been observed throughout the study follow-up visits apart from infrequent supraventricular

Table 3. Echocardiographic features in group 1 at baseline and at 6 and 12 months after treatment initiation.

	BASELINE (DAY 0)	MONTH 6	MONTH 12	*P* VALUE
Systolic function				
EDD Mean ± SD	4.77 ± 0.29	4.84 ± 0.34	4.82 ± 0.36	.0685 (D0 vs M6) .5099 (M6 vs M12) .1531 (D0 vs M12)
ESD Mean ± SD	2.87 ± 0.27	2.89 ± 0.35	2.88 ± 0.37	.6909 (D0 vs M6) .7517 (M6 vs M12) .9443 (D0 vs M12)
EF Mean ± SD	69.16 ± 3.60%	69.36 ± 5.06%	69.96 ± 4.74%	.6822 (D0 vs M6) .2211 (M6 vs M12) .0865 (D0 vs M12)
Tissue Doppler S-wave velocity, m/s Mean ± SD	0.0847 ± 0.02	0.0849 ± 0.019	0.0851 ± 0.02	.2057 (D0 vs M6) .0775 (M6 vs M12) .0514 (D0 vs M12)
Diastolic function				
Pulsed Doppler E velocity, m/s	0.821 ± 0.07	0.819 ± 0.07	0.820 ± 0.07	.7161 (D0 vs M6) .7734 (M6 vs M12) .9122 (D0 vs M12)
Pulsed Doppler A velocity, m/s	0.598 ± 0.06	0.610 ± 0.06	0.612 ± 0.06	.1471 (D0 vs M6) .8112 (M6 vs M12) .0734 (D0 vs M12)
E/A ratio Mean ± SD	1.386 ± 0.19	1.357 ± 0.19	1.350 ± 0.16	.1455 (D0 vs M6) .7165 (M6 vs M12) .0597 (D0 vs M12)
Deceleration time, ms Mean ± SD	190.826 ± 10.64	191.196 ± 8.34	192.143 ± 9.71	.7264 (D0 vs M6) .3713 (M6 vs M12) .2735 (D0 vs M12)
Tissue Doppler Ea velocity, m/s Mean ± SD	0.346 ± 0.02	0.345 ± 0.02	0.345 ± 0.01	.1519 (D0 vs M6) .7895 (M6 vs M12) .4293 (D0 vs M12)
E/Ea ratio	2.379 ± 0.25	2.380 ± 0.24	2.381 ± 0.22	.9471 (D0 vs M6) .9800 (M6 vs M12) .9342 (D0 vs M12)

Abbreviations: EDD, end diastolic dimension; ESD, end systolic dimension; EF, ejection fraction.

extrasystoles in 1% of the patients at the 6-month follow-up visit. There was no increase in the number of patients with ST-T wave changes over the follow-up visits.

Echocardiographic findings

None of the group 1 patients had or developed echocardiographic RWMA at baseline or the study follow-up visits. There was no significant increase in EF at the 6-month and the 12-month follow-up visits. Regarding the diastolic function parameters, there was no significant decrease in E/A ration and no significant increase in the deceleration time over the follow-up visits. Also, there was no significant increase in the E/Ea ratio (Table 3).

Group 2

None of the group 2 patients has developed any major cardiac complication, such as congestive heart failure, echocardiographic evidence of LV dysfunction, occurrence of significant arrhythmias, or acute coronary syndrome, throughout the course of the study. Even though none of the group 2 patients had chest pain at baseline, 3% had developed it at the 6-month follow-up visit with an insignificant $P > .05$. Similarly, 4% had developed shortness of breath 6 months after therapy initiation; still, this was not statistically significant. None of the patients had described orthopnea or PND. Also, 4% reported palpitations at the 6-month follow-up visit as a new symptom that was not evident at the beginning in the study ($P > .05$). None of the patients had described dizziness, presyncope or syncope. None of the patients had developed abnormally elevated blood pressure at the 6-month follow-up visit. In addition, mean value of blood pressure slightly and insignificantly changed from 119.5/75.29 at baseline to 119.36/75.57 beats per minute at both study visits ($P > .05$). None of the group 2 patients had or developed gallop or fine basal crepitations.

Table 4. Electrocardiographic changes in group 2 patients at baseline and 6 months after initiation of the treatment.

	BASELINE (DAY 0)	MONTH 6	*P* VALUE
ST-T wave changes Yes:no, No. (%)	0 (0):70 (100)	3 (4):67 (96)	.1543
Arrhythmia Yes:no, No. (%)	0 (0):70 (100)	2 (3):68 (97)	.0800
Corrected QT Mean ± SD	0.388 ± 0.024	0.387 ± 0.020	.8274

Table 5. Echocardiographic features in group 2 at the baseline and at 6 months after treatment initiation.

	BASELINE (DAY 0)	MONTH 6	*P* VALUE
Systolic function			
EDD Mean ± SD	4.88 ± 0.35	4.87 ± 0.39	.7190
ESD Mean ± SD	2.87 ± 0.37	2.86 ± 0.38	.8995
EF Mean ± SD	69.80 ± 4.02%	69.83 ± 3.29%	.8690
Tissue Doppler S-wave, m/s Mean ± SD	0.0844 ± 0.001	0.0846 ± 0.001	.2844
Diastolic function			
Doppler E velocity, m/s	0.848 ± 0.045	0.846 ± 0.043	.8359
Doppler A velocity, m/s	0.596 ± 0.066	0.595 ± 0.068	.9355
E/A ratio Mean ± SD	1.442 ± 0.182	1.439 ± 0.164	.9732
Deceleration time, ms Mean ± SD	191.647 ± 10.148	192.819 ± 8.231	.9812
Tissue Doppler Ea velocity, m/s Mean ± SD	0.348 ± 0.019	0.347 ± 0.019	.1269
E/Ea ratio	2.446 ± 0.189	2.445 ± 0.171	.9036

Abbreviations: EDD, end diastolic dimension; ESD, end systolic dimension; EF, ejection fraction.

Electrocardiography

No significant alterations regarding ST-T wave abnormalities or arrhythmias had occurred from the start of the treatment and the 6-month follow-up. None of the patients had developed prolonged QT interval at the follow-up visits. No significant alterations were evident in the mean values of corrected QT in group 2 patients over the study visits ($P > .005$) (Table 4).

Echocardiography

None of the group 2 patients had or developed echocardiographic RWMA at the baseline or at the end of the study. Systolic function parameters showed nonsignificant changes over the study visits ($P > .05$). Similarly, diastolic function parameters (E/A ratio, deceleration time, and E/Ea ratio) showed no significant alterations between the beginning and the 6-month follow-up visits ($P > .05$) (Table 5).

Discussion

More than 3% of the world's population, which accounts for 170 million individual, is infected with chronic HCV infection according to the study by Strader et al.[26] Hepatitis C virus infection, while a serious infection on its own, leads to more drastic complications; it is estimated that minimum 20% of chronic HCV-infected patients develop cirrhosis within the course of 10 to 20 years, whereas other patients develop liver cancer within the course of 20 to 40 years[27] (HCV is the cause of about half of the cases of primary liver cancer in the developed world).

In Egypt, about 12% of the over-90-million population is infected with HCV and it is considered to be the primary cause of hepatocellular carcinoma and chronic liver disease.[28]

Although PEG-IFN and RBV have always been included in HCV treatments, their limited efficacy and frequent side effects have encouraged the search for a better alternative.[8] Direct-acting antiviral agents, which have a different approach

in targeting the life cycle of HCV, have been developed and approved by the US FDA.[29,30]

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 and it became based on DAAs. However, the use of DAAs has raised some concerns about the possibilities of cardiac toxicity.

In this study, we research the potential cardiovascular toxicities in both interferon-based therapy using triple combination therapy on *Group 1* and interferon-free DAAs using dual combination therapy on *Group 2*.

First: group 1: PEG–interferon alfa, RBV, and SOF

Not so long ago, the treatment for chronic HCV infection solely depended on PEG-IFN in combination with RBV therapy which achieved an SVR in more than 50% of the patients with chronic HCV infection.[30] Pegylated interferon with triple combination therapy, however, achieved an SVR of 70% to 80%.[31]

Even though evidence of cardiotoxicity caused using interferon has been rarely reported, and often in isolated cases, according to Rechciński et al,[32] in the publication "Hepatitis C, stigma and cure," interferon alfa proved to be the most likely to cause cardiotoxicity followed by interferon beta and then interferon gamma. Interferon treatment is presumed to cause manifestation of ischemic heart disease, arrhythmias, and cardiomyopathy.[33] Interferon flu-like reaction which is a fever that results in an increased myocardial oxygen demand could cause ischemia in patients with previous history of coronary artery disease. The mechanism, however, of which interferon causes ischemia is still not accurately tracked.[34]

In this study, *Group 1* includes 100 cases with chronic HCV infection that were submitted to detailed medical history taking, clinical examination, 12-lead ECG, and transthoracic echocardiography.

Results showed no significant increase in shortness of breath, palpations, or chest pain after treatment in comparison with the beginning of the study. As for the heart rate and blood pressure, results showed no significant alterations in their values before and after the treatment.

In agreement with the study at hand, Erol et al[35] reported in their study that the interferon alfa therapy did not cause any significant alterations in the patients' heart rate or blood pressure throughout the course of therapy.

In another study by Friess et al, which included 20 patients who were assessed for cardiac rhythm disturbances, patients received DNA gene interferon. The results showed no significant alterations in average heart rate or in the frequency of ventricular or supraventricular ectopic beats throughout the course of therapy.[36]

Similarly, a study by Fukuhara et al[37] showed that chronic interferon therapy did not modulate the sympathetic activity of the heart or cause any alterations in the circadian variations in blood pressure and pulse rate, which further supports the results of this study.

Regarding the ECG findings, the corrected QT showed no significant alterations in their values before the treatment (0.391 ± 0.02), 6 months after the treatment (0.932 ± 0.02), and 12 months after the treatment (0.093 ± 0.02).

Patients with cirrhosis frequently experience QT interval prolongation regardless of the cause of the disease. Its prevalence can reach 45% according to the severity of the cirrhosis, which is drastically higher than the 5% prevalence in the general population.[38]

Alongside with QT interval prolongation, several electrophysiological abnormalities are common in patients with cirrhosis such as chronotropic incompetence and electromechanical uncoupling, as reported by Wong et al.[39] However, in this study, patients included are in the early stages of HCV infection with no evidence of cirrhosis. Therefore, there are very little data regarding the effects of interferon on QT interval.

The results of this study also showed no evidence of atrial or ventricular arrhythmias after the triple combination therapy.

The first to report atrial and ventricular arrhythmias in patients who received recombinant interferon alfa was based on a study done in 1984 by Kirkwood that involved 9 patients with cancer. However, most of these patients were already admitted with underlying heart disease and were receiving doxorubicin therapy, which is very known to cause cardiotoxicity.[40]

According to the echocardiography findings of the study, there was no significant alteration in the echocardiography parameters values before and after the treatment.

A study by Erol et al[35] in 2004 showed that the treatment with interferon alfa did not cause any alteration in values of systolic and diastolic functions before and after the treatment.

Another study by Kadayifci et al[41] done in 1997 further supports the claims of this study; the clinical examinations showed no significant alterations or adverse effects on the ECG and echocardiographic evaluations of HCV-infected patients before and after the interferon-based therapy.

Contradictory findings, however, were reported in a study by Kühl et al in 2003. The study showed a significant decrease in LV end diastolic diameter (LVEDD) and LV end systolic diameter (LVESD) from 59.7 ± 11.1 to 56.5 ± 10.0 mm ($P < .001$) and 43.2 ± 13.6 to 39.4 ± 12.1 mm ($P < .001$), and, accordingly, an increase in LV EF from 44.6 ± 15.5% to 53.1 ± 16.8% ($P < .001$). The treatment also resulted in the improvement of New York Heart Association functional class of these patients due to diminished angina pectoris, dyspnea, palpitations, and fatigue.[42]

The contradictions with this study could be attributed to the fact that the previous study monitored the alterations in patients already having myocarditis with no consideration to the underlying viral cause which is suggested by initially high values of LVESD and LVEDD. Also, these beneficial

effects were paralleled with the evidence of viral clearance through endomyocardial biopsy.

Another study findings by Sartor et al, in 1995, reported more than 10% decrease in LV EF in 5 of 11 patients with HCV infection using radionuclide angiography 1 month into the interferon-based therapy and that this effect disappeared 3 months after therapy cessation, which suggests that this effect is reversible.[43]

The contradictions could be attributed to the difference in patients' characteristics, number of patients, and the use of different techniques, such as echocardiography vs radionuclide angiography. In addition, there was no follow-up to the patients on the month into the interferon therapy.

Second: group 2: (SOF and simeprevir)

The development of interferon-free treatments was encouraged because of the limited safety and tolerability of interferon-based treatments which proved to be a healthier alternative and an even more cost-effective treatment.

Group 2 in this study includes 70 cases with chronic HCV infection that were submitted to detailed medical history taking, clinical examination, 12-lead ECG, and transthoracic echocardiography.

Study findings showed no significant alterations in patients' symptoms (shortness of breath, palpitations, and chest pain), signs (heart rate and blood pressure), or ECG recordings (arrhythmias, QT interval, or ST-T wave changes) before and after the treatment. In addition, there were no significant alterations in echocardiographic parameters regarding the systolic and diastolic functions before and after the treatment.

In agreement with the results of this study, a review of the FDA Adverse Event Reporting System quarterly reports, on DAAs that are available in the market since 2011, showed no reported cases of serious cardiac complications caused by these novel therapies.[44]

However, in 2015, a study by Ahmed et al has reported the first occurrence of cardiotoxic changes associated with the use of DAAs in the treatment of chronic HCV infection. Treatment with BMS-986094, which is a nucleotide analog HCV nonstructural 5B polymerase inhibitor, in interferon-free combinations with DCV and RBV, was terminated after 34 patients experienced rapidly progressive heart failure and expired. Further cases of cardiotoxicity were later identified.[45]

The 34 patients received interferon-free BMS-986094 treatment. Six patients had left ventricular ejection fractions (LVEFs) <30%, 8 patients had LVEFs of 30% to 50%, and 11 patients required hospitalization of suspected cardiotoxicity. Six patients with LVEFs <50% had a normal systolic function values within 20 days.

Electrocardiographic recording showed several abnormalities; 3 cases of nonspecific intraventricular conduction defect, 2 cases of sinus bradycardia, 2 cases of nonspecific ST abnormality, 1 case of nonspecific T-wave abnormality, and 1 case of borderline prolongation in QTc interval.

ST-segment abnormalities, such as ST depressions, T-wave inversions, or loss of T-wave amplitude, were also frequent with patients with LV dysfunction.

The contradictory results between the latter study and this study are attributed to the fact that the study by Ahmad et al. examined the effects of BMS-986094 treatment in combination with DCV, whereas in this study, we examine the effects of the SOF and simeprevir combination treatment. Also, RBV was included in their treatment contrary to the RBV-free treatment of this study. The conclusion of the study suggests that some individuals of the new investigational DAAs, such as BMS-986094, have cardiotoxic properties and could result in toxic cardiomyopathy.

In conclusion, the treatments for DAAs used in combination regimens with interferon or consumed orally in combination with other similar agents do not affect the cardiovascular system.

Study Limitations

The limitations of this study include the following: small sample size, exclusion of high-risk patients for coronary artery disease, and no stress study was done to objectively assess functional status and to more sensitively exclude myocardial ischemia.

Author Contributions

Thanks for GG, MA, AA, HA-E for conception and design, drafting of manuscript and final approval of manuscript.

REFERENCES

1. Lavanchy D. The global burden of hepatitis C. *Liver Int*. 2009;29:74–81.
2. Kamal SM, Nasser IA. Hepatitis C genotype 4: what we know and what we don't yet know. *Hepatology*. 2008;47:1371–1383.
3. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol*. 2011;9:509–516.
4. Kanwal F, Hoang T, Kramer JR, et al. Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. *Gastroenterology*. 2011;140:1182–1188.
5. Fried MW, Shiffman ML, Reddy RK, et al. Pegylated interferon alfa-2a in combination with ribavirin: efficacy and safety results from a phase III, randomized, actively controlled multi-center study. *N Engl J Med*. 2002;347:975–982.
6. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med*. 2011;364:2405–2416.
7. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335–1374.
8. Cholongitas E, Papatheodoridis GV. Review article: novel therapeutic options for chronic hepatitis C. *Aliment Pharmacol Ther*. 2008;27:866–884.
9. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of Boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicenter phase 2 trial. *Lancet*. 2010;376:705–716.
10. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype 1 infection in treatment-naïve patients: results from QUEST-1, a phase III trial. *J Hepatol*. 2013;58:S567–S577.
11. Manns M, Marcellin P, Poordad FPF, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naïve patients: results from QUEST-2, a phase III trial. *J Hepatol*. 2013;58:S567–S577.

12. Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology*. 2013;58:1918–1929.
13. Lawitz E, Lalezari JP, Hassanein T, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomized, double-blind, phase 2 trial. *Lancet Infect Dis*. 2103;13:401–408.
14. Younossi ZM, Stepanova M, Henry L, et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *J Hepatol*. 2014;60:741–747.
15. Lok AS, Gardiner DF, Lawitz E, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *N Engl J Med*. 2012;366:216–224.
16. Lalezari J, Lawitz E, Rodriguez-Torres M, et al. Once daily PSI-7977 plus PegIFN/RBV in a phase 2b trial: rapid virologic suppression in treatment-naive patients with HCV GT2/GT3. *J Hepatol*. 2011;54:S25–S44.
17. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med*. 2013;368:1867–1877.
18. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1-5, 2013; Washington, DC.
19. Sulkowski MS, Jacobson IM, Ghalib R, et al. Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0-2: COSMOS study subgroup analysis. *J Hepatol*. 2014;60:S4.
20. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med*. 2014;370:1879–1888.
21. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med*. 2014;370:211–221.
22. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. *Gastroenterology*. 2014;146:736–743.
23. Food and Drug Administration. FDA hepatitis update—important safety information: harvoni and Sovaldi. http://content.govdelivery.com/accounts/USFDA/bulletins/f97c71. Published March 21, 2015. Accessed March 21, 2015.
24. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantifications: a report from the American Society of Echocardiography Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
25. Munagala VK, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Association of newer diastolic function parameters with age in healthy subjects: a population-based study. *J Am Soc Echocardiogr*. 2003;16:1049–1056.
26. Strader D, Wright T, Thomas D, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology*. 2004;39:1147–1171.
27. El Zayadi AR, Badran HM, Barakat EM, et al. Hepatocellular carcinoma in Egypt: a single center study over a decade. *World J Gastroenterol*. 2005;11:5193–5198.
28. De Clercq E. The race for interferon-free HCV therapies: a snapshot by the spring of 2012. *Rev Med Virol*. 2012;22:392–411.
29. Sherman RE, Li J, Shapley S, Robb M, Woodcock J. Expediting drug development—the FDA's new "breakthrough therapy" designation. *N Engl J Med*. 2013;369:1877–1880.
30. Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology*. 2002;36:S21–S29.
31. Marinho RT, Barreira DP. Hepatitis C, stigma and cure. *World J Gastroenterol*. 2013;19:6703–6709.
32. Rechciński T, Matusik D, Rudziński T, et al. Cardiotoxic properties of interferon: aggravation of atrio-ventricular block during treatment of chronic hepatitis C with peginterferon—a case report. *Pol Arch Med Wewn*. 2007;117:49–52.
33. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest*. 1991;99:557–561.
34. Jones RL, Ewer MS. Cardiac and cardiovascular toxicity of nonanthracycline anticancer drugs. *Expert Rev Anticancer Ther*. 2006;6:1249–1269.
35. Erol MK, Erol S, Koruk M, Ertek M, Bozkurt E. Effects of interferon-alpha therapy on cardiac function in patients with chronic hepatitis B infection. *Heart Vessels*. 2004;19:263–266.
36. Friess CG, Brown TD, Wrenn RC. Cardiovascular rhythm effects of gamma recombinant DNA interferon. *Invest New Drugs*. 1989;7:275–280.
37. Fukuhara M, Matsumaura K, Ohmori S, et al. Effects of interferon on circadian changes in blood pressure and heart rate variability in patients with chronic hepatitis. *Am J Hypertens*. 1999;12:519–523.
38. Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*. 1998;27:28–34.
39. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L. The cardiac response to exercise in cirrhosis. *Gut*. 2001;49:268–275.
40. Kirkwood JM, Ernstoff MS. Interferons in the treatment of human cancer. *J Clin Oncol*. 1984;2:336–352.
41. Kadayifci A, Aytemir K, Arslan M, Aksoyek S, Sivri B, Kabakci G. Interferon-alpha does not cause significant cardiac dysfunction in patients with chronic active hepatitis. *Liver*. 1997;17:99–102.
42. Kühl U, Pauschinger M, Schwimmbeck PL, et al. Interferon-beta treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation*. 2003;107:2793–2798.
43. Sartori M, Andorno S, La Terra G, et al. Assessment of interferon cardiotoxicity with quantitative radionuclide angiocardiography. *Eur J Clin Invest*. 1995;25:68–70.
44. Food and Drug Administration. Potential signals of serious risks/new safety information identified from the FDA Adverse Event Reporting System (FAERS). http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm. Published 2014. Updated July 10, 2014. Accessed August 29, 2014.
45. Ahmad T, Yin P, Saffitz J, et al. Cardiac dysfunction associated with a nucleotide polymerase inhibitor for treatment of hepatitis C. *Hepatology*. 2015;62:409–416.