ORIGINAL ARTICLE

EFFECTS OF INTERFERON THERAPY ON HEART

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Background: Hepatitis C virus (HCV) infection is a major health problem worldwide. Around 185 million people are suffering from HCV infection all over the world, out of which 10 million people are residing in Pakistan. 4.7% (2–14% by different studies) of Pakistanis are suffering from this deadly disease. Interferon+Ribavarin IFN/RIB is the mainstay of treatment for this infection. Various cardiovascular adverse reactions have been reported of this therapy. We conducted this study at Punjab Institute of cardiology to look for the cardiac safety of interferon therapy in our population. **Methods:** We studied HCV infected patients planned for interferon therapy between 21st of November 2012 to 20th of August 2014. Echocardiography was performed before, during and after the completion of therapy. Pegylated interferon once a week plus ribavirin therapy was given to the patients. Patients received 16-40 injections of pegylated interferon depending upon the decision of hepatologist. Patients with prior structural heart disease, patients who did not start the treatment or patients who did not turn up on follow up were excluded from the study. **Results:** A total of 102 patients planned to have interferon therapy were screened echocardiographically. One patient died after 5 injections due to infection (a non-cardiac cause). 46 patients completed the treatment and the follow up. None of the patients had any acute cardiac event. All patients had normal biventricular systolic function at the end of study. None of the patients had significant valvular heart disease or pulmonary hypertension. Reversal of E/A ratio or E/A ratio>2, parameters of diastolic dysfunction and mild pericardial effusion were noted in a statistically significant number of patients. **Conclusion:** Interferon therapy for HCV infection is cardiac safe in patients who have structurally normal heart. Female patients have propensity of adverse events like severe diastolic dysfunction and mild pericardial effusion. The safety of drug in patients already having cardiac ailment needs to be studied. Moreover HCV infection itself is not injurious to the heart.

Keyword HCV infection, Interferon Therapy, Cardiac effects, Echocardiography

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INTRODUCTION

Hepatitis C virus (HCV) is major health problem all over the world. More than185 million (2–3% of the total population) is having HCV infection.[1] Each year around 500000 people die due to HCV related liver diseases.[2] The condition is even worse in our country. Around 10 million (4.7%) of Pakistanis are HCV positive.[3] Various studies conducted in Pakistan reported HCV infection from 2.2–14% (in Punjab 6.7%, in Sindh 5%, in Baluchistan 1.5%, and in Khyber Pukhtunkhwa 1.1%).[3] This figure is highest as compared to the neighbouring countries (India 0.66%, Afghanistan 0.31%, Iran 0.87% and Nepal 1%).[3] Interferon plus ribavirin therapy is the main stay of treatment for HCV infection. Many people in Pakistan are getting this treatment. Interferon therapy has many side effects including constitutional, gastrointestinal, psychiatric, dermatological, thyroid, visual, auditory, renal, respiratory, lab abnormalities and last but not the least cardiovascular impairment.[4] The reported side effects are arrhythmias, myocardial infarction, cardiomyopathy, myocarditis, pericarditis, pericardial effusion and diastolic dysfunction.[5–8] To know the cardiac safety of this drug in our population, we conducted this study at Punjab institute of cardiology, Lahore.

MATERIAL AND METHODS

This is a descriptive case series. 102 HCV infected patients planned for interferon therapy were referred for echocardiography by hepatologist between 21st of November 2012 to 20th of August 2014. Echocardiography was performed before, during and after the completion of therapy. Pegylated interferon once a week plus ribavirin therapy was given to the patients. Patients received 16–40 injections of pegylated interferon depending upon the decision of hepatologist. Patients with prior structural heart disease, patients who did not start the treatment or patients who did not turn up on follow up were excluded from the study. In echocardiography ejection fraction was taken to assess left ventricular systolic and E/A ratio for diastolic dysfunction. E/A ratio <1 and >2 taken as abnormal. Pericardium was seen to look for any effusion. Valves were assessed. For right ventricular systolic function S wave12 cm /sec on tissue Doppler imaging was taken as normal, less than that was taken as impaired RV systolic function. Baseline demographic variables, ECG, risk factors for ischemic heart disease and symptoms during the therapy were also noted.

Statistical analysis was performed with SPSS Version 20.0. Categorical variables were reported as frequencies and percentages, continuous variables were

expressed as mean±SD. For quantitative analysis independent sample *t*-test was applied, and for qualitative analysis Chi-Square was applied. The *p* value ≤0.05 considered significant. Test was applied as two tailed.

RESULTS

A total of 102 patients, 48 (47.1%) males and 54 (52.9%) females with a mean age of 39.36±1.09 planned to have interferon therapy were screened echocardiographically (Table-1). Out of 102 patients, one patient had ischemic cardiomyopathy so she was excluded from the study. One patient died after 5 injections due to infection without any echocardiographic follow up, she was also excluded. 49 patients either did not start the treatment or had no follow up, they were also excluded. Five patients started the treatment but lost follow up after their first visit. Fourty-six patients completed the treatment and the echocardiographic follow up, out of which 35 patients had echocardiography before and after the completion of therapy and 11 patients had all three visits, i.e., before during and after the treatment figure-1.

There were 5 patients who started the treatment and had their first follow up during the treatment but afterwards either stopped the treatment or lost follow up. The reason for stopping the treatment in one patient was weakness and in another patient insomnia and shortness breath, while in third patient there was no response to the therapy, so the treatment was stopped.

In two other patients no follow up afterwards so the reason was not known. Interestingly all these patients had unchanged cardiac status on their first follow up. Few patients developed symptoms and non-cardiac ailment as follows, chest pain atypical in 2 (3.92%) patients, shortness of breath in 6 (11.76%) patients, palpitation in 3 (5.88%) patients, weakness in 3 (5.88%) patients and thyrotoxicosis in 1 (1.96%) patient (propranolol used to control the symptoms) table-6.

As far as gender based differences are, all patients who had mild pericardial effusion and severe diastolic dysfunction (E/A>2) were females, moreover most of the symptoms during therapy also appeared in females. So there is a definite propensity of adverse events in females. (Table-7)

Another interesting finding in the data was all patients infected with HCV screened before the start of treatment had normal heart, except for the one patient who had ischemic cardiomyopathy. So HCV infection itself does not damage the heart.

When we looked at the diastolic dysfunction, at baseline 7(15.21%) patients had mild left ventricular diastolic dysfunction, i.e., E/A<1 (Table-2). During treatment 4 (36.36%) patients developed mild diastolic dysfunction. After the completion of therapy, 7 (15.21%) patients had mild diastolic dysfunction, while 2 (4.34%) patients developed severe diastolic dysfunction, i.e., >2, which had a statistically significant value. (*p*-0.032)

Biventricular systolic function remained normal throughout the study period. No adverse acute cardiac event was noted during the study (Table-3). Similarly all patients had normal or trivial to mild valvular disease throughout the study, no patient had moderate or severe valvular disease during or after the therapy. (Table-5)

Pericardium was normal in all patients at baseline. Two (18.18%) patients developed mild pericardial effusion during the therapy which settled after the completion of therapy. None of the patients had significant pericardial disease during or after the therapy. (Table-4).

Table-1: Basic Demographic Information

		Frequency	Percentage
Total Patient	102	Median Follow Up	16 (15.69%)
		Long term Follow Up	46 (45.1%)
Gender	Male	48	47.1 %
	Female	54	52.9 %
Age	Mean±SD	39.36±1.09	
Risk Factors for CAD	Diabetes	22	21.6%
	Smoking	14	13.7%
	Family History	14	13.7%
	Hypertension	34	33.3%
	Hyperlipidemia	7	6.9%
Baseline ECG	Normal	69	67.6%
	Abnormal	4	3.9%
Baseline EF	30–40	1	1%
	>50%	101	99%
Baseline Valve	Normal	96	94.1%
	Trivial to mild disease	6	5.9%
Baseline E / A Ratio	Normal >1	81	79.4%
	Abnormal <1	19	18.6
	Abnormal (>2)	0	0 %
Baseline Pericardium	Normal	102	100%
Therapy	Pegylated Interferon plus Ribavarin	51	50%

Table-2: Diastolic dysfunction of the patients

E/A ratio	Normal	Abnormal (<1)	Abnormal (>2)	*p* value
Baseline (n=46)	38 (82.6%)	07 (15.21%)	0	0.032
During treatment (n=11)	07 (63.63%)	04 (36.36%)	0	
After treatment (n=46)	37 (80.43%)	07 (15.21%)	02 (4.34%)	

Table-3: Biventricular Systolic function of the patients

Biventricular systolic function	Baseline before therapy (n=46)	During therapy (n=11)	After completion of therapy (n=46)	*p* value
LVEF	64.26%±6.14%	69.36%±8.27%	63.59%±5.89%	0.218
RVSTDI	13.9cm/sec±1.97cm/sec	13.9cm/sec±2.64cm/sec	13.81cm/sec±1.73cm/sec	0.976

Table-4: Pericardial disease of the patients

Pericardium	Normal	Mild Effusion	*p*-value
Baseline(n=46)	46 (100%)	0	0.002
During therapy(n=11)	09 (81.81%)	2 (18.18%)	
After completion of therapy (n=46)	46 (100%)	0	

Table-5: Valvular status of the patients

Severity of the valve	Normal	Trivial-Mild	*p*-value
Baseline (n=46)	42 (91.3%)	04 (8.69%)	0.043
During therapy (n=11)	11 (100%)	0	
After completion of Therapy (n=46)	44 (95.65%)	02 (4.34%)	

Table-6: Symptoms and non-cardiac illness amongst 51 patients who started the treatment

Chest pain atypical	2 (3.92%) patients
Shortness of breath	6 (11.76%) patients
Palpitation	3 (5.88%) patients
Weakness	3 (5.88%) patients
Thyrotoxicosis	1 (1.96%) patient (propranolol used to control the symptoms)

Table-7: Gender based differences in symptoms and echocardiographic abnormalities

Gender Total(n=46)	Male n=17(36.95%)	Female n=29 (63.04%)	*p*-value
Pericardial effusion	0	2(6.89%)	0.523
E/A>2(severe diastolic dysfunction)	0	2(6.89%)	0.523
Shortness of breath	2(11.76%)	3(10.34%)	1.00
Palpitation	0	3(10.34%)	0.285
Atypical chest pain	0	2(6.89%)	0.52

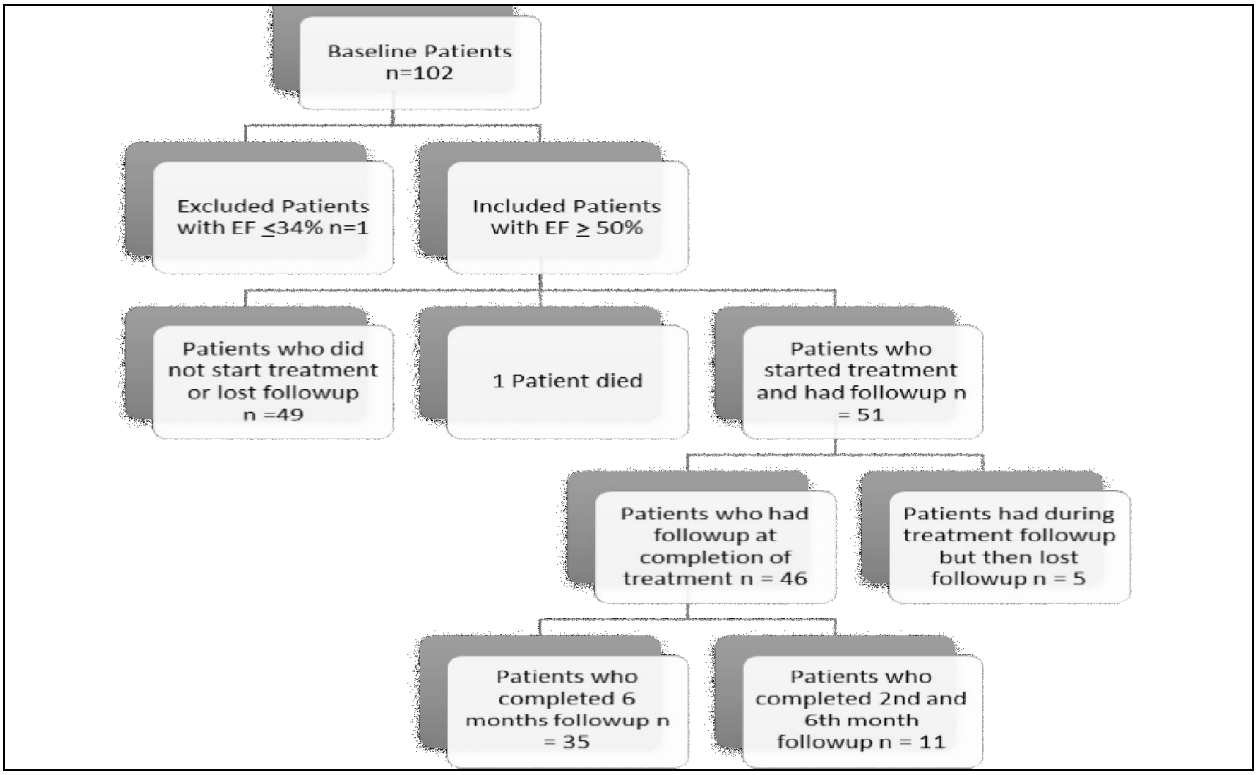

Figure-1: Follow up of the patients

DISCUSSION

Hepatitis C virus infection is a worldwide problem. Each year a major death toll is (>500000 people) due to HCV related complications.[2] HCV infection is endemic in Pakistan and around 10 million Pakistanis are infected with HCV.[3] Many people are getting treatment with interferon plus Ribavirin. Thus we must look into the cardiac safety of these drugs and this study gives a detailed insight into it.

Cardiomyopathy, myocardial infarction and myocarditis impairing the systolic function of both the ventricles are well known side effects of the interferon therapy.[5,6] However in our study biventricular systolic function remained normal throughout the study, no acute adverse cardiac event occurred same finding as reported by Erol *et al* in their study.[9] However 2 (4.34%) of our patients developed severe diastolic dysfunction.

Interferon therapy has been reported as causing pericarditis, pericardial effusion and tamponade and perimyocarditis by Popescue *et al*, Rauw *et al* and Myriam *et al.*[7,8,10] None of our cases developed acute pericarditis or myopericarditis but 2 of our patients developed mild pericardial effusion transiently during therapy which settled after the completion of therapy. Pegylated interferon was used in cases reported by Myriam and Popescue *et al*, and interferon –α 2b in case report of Rauw *et al*. In our study all patients received pegylated interferon, and probably pegylated interferon has more tendency to have adverse events like pericarditis or perimyocarditis.

All patients had normal valvular status or trivial to mild disease throughout the study. No patient developed significant valvular disease during the course of treatment. The same finding as reported by Almawardy *et al.*[11] But in their study only mitral regurgitation was studied and we studied all cardiac valves for the development of stenotic or regurgitant lesions both. One of our patient had mitral sclerosis to begin with and she had mild mitral stenosis (mitral valve area 2.32 cm^2) and slightly increased gradient across the aortic valve at the end of the study, but no significant deterioration in the valvular status of the patient.

None of our patients developed serious adverse cardiovascular events, for which interferon therapy had to be stopped. This is in accordance of results by Almawardy *et al*. Kouno *et al*[12] reported 0.62% of 643 patients in which interferon therapy had to be stopped due to adverse cardiovascular events, a small number but a significant one as compared to our study.

In our study female patients had more symptoms, pericardial disease and severe diastolic dysfunction as compared to the male patients. Myriam and Popescue *et al* both reported case of pericarditis and perimyocarditis in female patients. This is merely a chance finding or females are really prone to adverse events by interferon therapy, we exactly do not know and further study needs to be conducted.

We studied 102 patients at the baseline, all patients had normal echocardiogram or minor abnormalities. No patient had significant cardiac disease, apart from one patient who had ischemic cardiomyopathy. Maruyama *et al*[13] reported perfusion defects in 87% of 200 patients on thallium-201 scan which improved after interferon therapy suggesting definite myocardial injury by chronic HCV infection. We did not had thallium scan in our patients, so we might have missed micro injury of myocardium. HCV infection has also been associated with hypertension and congestive cardiac failure as reported by Younossi *et al*[14], but that was not the case in our study. We noted hypertension as a risk factor at the baseline of the study but did not study the development of hypertension during the course of treatment. The study has some limitations. This a small study, Study should be done on a larger scale to assess the exact magnitude of the problem. Follow up of all the patients could not be completed and we only studied the cardiac effects, the vascular effects like development of new onset hypertension was not monitored.

CONCLUSION

Interferon therapy for HCV infection is cardiac safe in patients who have structurally normal heart. Female patients have propensity of adverse events like severe diastolic dysfunction and mild pericardial effusion. The safety of drug in patients already having cardiac ailment needs to be studied. Moreover HCV infection itself is not injurious to the heart.

Disclosure: This article has no conflict of interest.

AUTHOR'S CONTRIBUTION

AWKF: echocardiography of all the patients and whole manuscript writing. SN: the treating physician and sending the patients for echocardiography. SAA: coordinated AWKF with SN. FA: maintaining the patients' record and sending the patients for follow up**.**

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