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Original Article

Types and predictors of interferon/ribavirin induced cardiac complications in the Egyptian patients with chronic hepatitis C virus

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ABSTRACT

Background and aim: Interferon-based therapy is known to be associated with significant side effects, including the cardiac complications; these may affect the patients' adherence to therapy and consequently the response rate. The aim of this study was to detect types and predictors of interferon-induced cardiac complications in Egyptian hepatitis-C-virus-infected patients treated with pegylated interferon/ribavirin combination therapy.

Methods: A total of 194, chronic hepatitis C virus (HCV) patients were followed up from the time of receiving treatment till one year after end of treatment, to detect cardiac disorders and to determine the response status. Patients were assessed by through history taking, full clinical examination, full evaluation of laboratory parameters, and cardiac assessment using the standard 12-lead electrocardiography and Transthoracic Doppler Echocardiography. Patients in the final analysis were divided into: group A (patients who developed cardiac disorders) and group B (patients who did not develop cardiac disorders).

Results: The baseline clinical features (cardiovascular risk factors and hemodynamics) were comparable in both groups. Patients who developed cardiac disorders had higher baseline ALT level, hepatic fibrosis, and activity than patients without cardiac disorders ($p < 0.05$). The confirmed cardiac complications represented 18.6% ($n = 36$) and included left ventricular systolic and diastolic dysfunctions, pericardial effusion, arrhythmia, myocardial ischemia, and heart failure. Hepatic activity in the liver biopsy, ejection fraction, and left ventricular end-diastolic dimension were independent predictors for cardiovascular complications.

Conclusion: Pegylated interferon therapy of chronic HCV is associated with many types of cardiac complications, predictors of which are higher baseline ALT, viral load, hepatic fibrosis, and hepatic histological activity index.

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1. Introduction

Hepatitis C virus (HCV) infection is the most common cause of newly diagnosed chronic liver disease world wide[1] and is the single most important cause of liver disease in Egypt,[2,3] with the latest anti-HCV antibody prevalence of 14.7%.[4] Hence, it is very important that the disease be treated in its early stages, which will effectively reduce the morbidity and mortality associated with this disease.[5] The currently recommended therapy for chronic HCV is the combination of pegylated interferon alpha (Peg-IFN-α) and ribavirin (RBV) that was proved to be superior to the standard interferon alpha and RBV.[6,7] Peg-IFN-α based therapy is known to be associated with significant side effects that may have an impact on tolerability, compliance, ability to maintain optimal dosing regimens, and ultimately response to therapy if dose reductions or discontinuations are required.[8]

Cardiac complications of treatment with Peg-IFN-α are detected in <5% of the patients in nonrandomized studies.[9] A wide range of cardiac complications have been reported, including dilated cardiomyopathy (which mostly occurs after prolonged time of treatment), arrhythmias, and ischemic heart disease. Most cardiotoxic effects, including cardiomyopathy, are reversible following cessation of IFN-α.[10] Other less common and less dangerous side effects are low-level conduction impairment or reversible hypertension. The exact physiopathology of this cardiotoxicity remains unknown.[11]

In Egypt, only few registries are available till now despite the overwhelming increase in the number of people infected with HCV and on treatment with interferon. *The aim of this study* was to detect types and predictors of interferon-induced cardiac complications in Egyptian HCV-infected patients treated with pegylated interferon/RBV combination therapy.

2. Subjects and methods

2.1. Study

It was a prospective, observational study.

2.2. Subjects

This study has been carried out on Egyptian HCV cases attending HCV treatment clinics in Damietta and Zagazig University Hospitals, Egypt. Cases included were referred to the cardiology outpatient clinics for further assessment. All patients were candidate for treatment by Peg-IFN-α and RBV according to the modified guidelines of the National Committee for Control and Prevention of viral hepatitis "C" in Egypt.[12] Patients with chronic hepatitis B (HBV), HBV/HCV coinfection, decompensated liver cirrhosis, autoimmune hepatitis, cardiac disease (cardiomyopathy, arrhythmias, ischemia, myocarditis, and more than mild valvular disorders), advanced renal impairment, thyroid dysfunction, and psychiatric disorders were excluded from the study.

Patients were classified in the final analysis into two groups: group A – patients who developed cardiac disorders, and group B – patients who did not develop cardiac disorders.

Approval was obtained for performing the study from the Institutional Review Board of the Faculty of Medicine, Zagazig University, Egypt. After giving an informed consent, all participants were subjected to the following:

1- Baseline demographic data collection regarding age, sex, and associated chronic diseases. Cardiac evaluation included general examination, electrocardiography (ECG), and echocardiographic (Echo) studies.
2- Baseline laboratory data included HCV-RNA (by PCR) level (copies/ml), bilirubin, ALT (IU/L), AST (IU/L), serum creatinine level, complete blood count (CBC), and liver biopsy (grading of activity and staging of fibrosis were evaluated by Ishak's[13] classification, which classifies hepatic activity by a score from 1 to 18 and hepatic fibrosis from 1 to 6).
3- Treatment regimens: The dose of Peg-IFN-alpha-2a was 180 μg subcutaneously around the umbilicus once per week together with RBV, using 1000 mg/day for those ≤75 kg in weight and 1200 mg/day for those >75 kg in weight.
4- Patient monitoring: Patients were assessed at weeks 0, 1, 2, and 4 of treatment and thereafter monthly and on development of symptoms. At each visit, the following were done:
   - Laboratory tests, including: serum ALT, AST, bilirubin, creatinine, and CBC. Body weight and symptom checklist were recorded at each visit and dose modifications to the Peg-IFN or RBV were made when recommended.
   - Assessment of the response status for the combination therapy, by quantitative and qualitative PCR, at baseline, week 12, week 24, week 48, and 6 months after discontinuation of antiviral therapy to evaluate sustained virological response (SVR).
   - Cardiological assessment included:
     a Symptoms analysis, including shortness of breathing (SOB), paroxysmal nocturnal dyspnia (PND), palpitation, and chest pain.
     b Clinical examination, including blood pressure, pulse (for rate and rhythm), signs of heart failure (HF), neck veins for congestion, lower limbs for edema, fine bilateral basal crepitations, or additional heart sounds (S3 or S4).
     c Standard 12-lead ECG to document the presence of significant ST-T wave changes suggestive of ischemia (when the resting ECG reveals ST-segment depression greater than 0.1 mV (1 mm), deep T-wave inversion, and/or ST-segment elevation of 0.2 mV (2 mm) in chest leads and 0.1 mV (1 mm) in limb leads),[14] and rhythm or conduction disturbance.
     d Transthoracic Doppler Echocardiography (Echo): Conventional echo and Doppler studies were performed for all patients using a Hewlett Packard (SONOS 5500) echo-set using a 2.5 MHz transducer. Echo study was obtained at rest with the subjects in the left lateral decubitus position. Two-dimensional-guided M-mode (2D Echo) measurements were carried out for the following: left ventricular end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), and ejection fraction (EF) %. Doppler study of the mitral valve flow measured the E-wave, A-wave, and E/A ratio from the apical 4-chamber view. Evaluation of the pericardium was done.