

Assessment of cardiac functions before and after treatment of Egyptian chronic hepatitis C patients using directly acting antivirals

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

Abbr.	Full-term
a.a	: Amino acid
AASLD	: American Association for the Study of Liver Diseases
AFP	: Alpha-Feto Protein
ALT	: Alanine Aminotransferase
AST	: Aspartate Aminotransferase
ART	: Anti-retroviral therapy
BCLC	: Barcelona-Clinic Liver Cancer
BMI	: Body Mass Index
CBP	: Childbearing period
CCM	: Cirrhotic cardiomyopathy
CD34	: Cluster of Differentiation 34
CDC	: Centers for Disease Control
CK7	: Cytokeratin 7
CKD	: Chronic Kidney Disease
CLIP	: Cancer of the Liver Italian Program
CMR	: Cardiovascular diseases
CVD	: Cardiovascular Magnetic Resonance
DAAs	: Direct Acting Antivirals
DAC	: Daclatasvir
DDIs	: Drug-drug interactions
DM	: Diabetes Mellitus
DSV	: Dasabuvir
DT	: Deceleration time
EASL	: European Association for the Study of the Liver
EBR	: Elbasvir
ECOG	: Eastern Cooperative Oncology Group
EF	: Ejection fraction
EDHS	: Egyptian Demographic Health Survey
eGFR	: Estimated glomerular filtration rate
EHIS	: Egyptian Health Issues Survey
EIA	: Enzyme immunoassay

ER	: Endoplasmic Reticulum
ESCRT	: Endosomal-Sorting Complex Required for Transport
FDA	: Food and Drug Administration
FE	: Fisher Exact
GLE	: Glecaprevir
GZR	: Grazoprevir
HCC	: Hepatocellular Carcinoma
HBV	: Hepatitis B virus
HCV	: Hepatitis C virus
HF	: Heart failure
HIV	: human immunodeficiency virus
HSP-70	: Heat shock protein 70
HTN	: Hypertension
IDSA	: Infectious Diseases Society of America
IFN	: Interferon
IL28B	: Interleukin 28B
INR	: International normalized ratio
IRES	: Internal ribosome entry site
ISDR	: Interferon Sensitivity Determining Region
KDa	: Kilodalton
LDLT	: Living Donor Liver Transplant
LDs	: Lipid Droplets
LDV	: Ledipasvir
LRT	: Locoregional therapy
LVEDD	: Left ventricular end diastolic diameter
LVESD	: Left ventricular end systolic diameter
LVEDV	: Left ventricular end diastolic Volume
LVESV	: Left ventricular end systolic Volume
MC	: Monte Carlo
MELD	: Model for End-stage liver Disease
MPAP	: Mean pulmonary arterial pressure
MSM	: men who have sex with men
NAT	: nucleic acid testing
NNPIs	: Non-nucleoside polymerase inhibitors
NPI	: Nucleotide polymerase inhibitors

NT-Pro BNP	: N terminal pro hormone brain natriuretic peptide
NTRs	: Non-Translated Regions
NS	: Non-strtuctural
OCLN	: Occludin
OBV	: Ombitasvir
OPTN	: Organ Procurement and Transplantation Network
ORF	: Open Reading Frame
OST	: opioid substitution therapy
PAH	: Pulmonary arterial hypertension
PCR	: Polymerase chain reaction
PEI	: Percutaneous ethanol injection
PIB	: Pibrentasvir
PTV	: Paritaprevir
PWID	: People who inject drugs
RBV	: Ribavirin
RCT	: Randomized control trial
RDTs	: Rapid diagnostic tests
RFA	: Radiofrequency Ablation
ROS	: Reactive Oxygen Species
SD	: Standard deviation
SIM	: Simeprevir
SOF	: Sofosbuvir
SRB 1	: Scavenger Receptor B1
SVR	: Sustained Virological Response
TACE	: Transcatheter arterial chemoembolization
TAPSE	: Tricuspid Annular Plane Systolic Excursion
TDI	: Trans doppler imaging
TGF-beta.	: Transforming Growth Factor beta
TNM	: Tumor, node, and metastases
VEL	: Velpatasvir
VIP	: Vasoactive Intestinal peptide
VOX	: voxilaprevir.
WHO	: World Health Organization

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Abstract

Introduction: Hepatitis C virus (HCV) infection is one of the main causes of chronic liver diseases worldwide. HCV infection has been associated with numerous extra-hepatic manifestations. Also, up to 50 percent of patients with advanced cirrhosis have features of cardiac dysfunction. Treatment for chronic HCV infection is evolving from interferon-based therapy to directacting antiviral agents. **aims & Methods:** The aim of the study is to assess the effect of treatment of naïve Egyptians chronic hepatitis C patients on cardiac functions using direct acting antivirals. This study is a prospective cohort study that was conducted on 90 treatment-naïve adult patients with chronic hepatitis C infection. **results:** Assessment of LV systolic functions using EF % revealed no significant difference between the studied groups regarding EF before and after treatment (P value 0.266 ,0.169 respectively) Change in EF was significantly higher in non-cirrhotic group (P value 0.024) . EF significantly increased in non-cirrhotic group after treatment(P value 0.003). Assessment of diastolic function using E/A ratio revealed no significant difference between the studied groups regarding E/A ratio before and after treatment(P value 0.752, 0.881 respectively) . E/A ratio was non-significantly changed in both groups(P value 0.202, 0.108 respectively) . Assessment of mean pulmonary artery pressure (MPAP) revealed No significant difference between the studied groups regarding MPAP before and after treatment (P value 0.466, 0.923 respectively) **conclusion:** Treatment of chronic HCV infection using DAAs (Sofosbuvir, Daclatasvir, Ribavirin) has no clinically significant effect on cardiac functions.However, some sort of sub-clinical myocardial affection can occur for further analytical studies.

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver diseases worldwide. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules (*Messina et al., 2015*).

HCV infection has been associated with numerous extra-hepatic manifestations. They are lichen planus, oral cancer, porphyria cutanea tarda, membranous glomerulonephritis, etc. In addition, autoimmune diseases like autoimmune thyroiditis and mixed cryoglobulinemia are also found. Although HCV is primarily a hepatotropic virus, has tropism for other tissues besides the liver. It has been isolated from the myocardium of patients with myocarditis and cardiomyopathy hence, its inclusion among the cardiotropic viruses (*Sanchez and Bergasa, 2008*).

Also, up to 50 percent of patients with advanced cirrhosis have features of cardiac dysfunction. The term "cirrhotic cardiomyopathy" has been used to describe such patients, who are characterized as having normal to increased cardiac output and contractility at rest, but a blunted response to pharmacologic,

physiologic, or pathologic stress. Patients may also have electrophysiological abnormalities. It is thought to be related to both portal hypertension and cirrhosis. Cardiomyopathy can occur from any cause of cirrhosis, although patients with alcoholism or hemochromatosis may have additional contributing causes to cardiac dysfunction (*Zardi et al., 2010*).

Treatment for chronic HCV infection is evolving from interferon (IFN)-based therapy to direct-acting antiviral (DAA) agents. Previous interferon-based anti-HCV therapies were mostly not tolerated by patients with advanced heart failure (HF), and had limited elimination efficacy (*Petta et al., 2016*).

With the introduction of novel interferon-free highly efficient and well tolerated anti-HCV combination therapies, the issue of causal relationship between HCV infection and cardiac disease may finally be resolved since these new highly anti-HCV-specific drugs lack the complex unspecific side-effects upon cardiac functions which have always confounded interpretation of treatment results (*Kohli et al., 2014*).

However, new regimens comprised of DAAs that target different steps in the HCV life cycle are in development and some have received breakthrough therapy status by the U.S. Food and Drug Administration (FDA). Also, recent retrospective studies, case reports and post marketing reports