

Assessment of Hepatic Steatosis Before and After Treatment In Egyptian HCV Patients Treated With DAAs Using Non Invasive Parameters

Thesis

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List of Abbreviations

AAR	AST/ALT ratio
AFP	Alpha Fetoprotein
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
APRI	AST/platelet ratio
ARFI	Acoustic radiation force impulse imaging
AST	Aspartate aminotransferase
AUC	Area under the ROC curve
AUROC ...	Area Under the Receiver Operating Characteristics
BMI	Body mass index
CAP	Controlled attenuation parameter
CBC	Complete blood count
CCR5	C-C chemokine receptor 5
CHC	Chronic hepatitis C
CPK	Creatinine phosphokinase
CT	Computed Tomography
CTP	Child-Turcotte-Pugh
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
CypA	Cyclophilin A

DAA Direct acting antivirals
DCV Daclatasvir
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DM Diabetes Mellitus
EASL..... The European Association for the Study of the Liver
ECM Extracellular matrix
EGF Epidermal growth factor
eGFR Estimated glomerular filtration rate
EGFR Epidermal growth factor receptor
ELISA The enzyme-linked immunosorbent assay
EphA2 Ephrin receptor A2
FDA Food and Drug Administration
FIB-4 Fibrosis 4 score
G Genotype
GGT Gamma-glutamyl transferase
GT Genotype
Hb..... Hemoglobin
HbA1C Hemoglobin A1C
HBV Hepatitis B virus
HCC Hepatocellular carcinoma
HCV Hepatitis C virus
HDL High density Lipoproteins
HF Heart failure
HIV Human immunodeficiency virus

HOMA-IR Homoeostatic model assessments

HSC Hepatic stellate cells

IFG Impaired fasting glycemia

IFN Interferon

IL28B Interleukin 28B

INR International Normalized Ratio

IQR Interquartile range

IQR/M..... Interquartile range/Median

IU/ml International Units Per Millilitre

kPa Kilo-Pascal

LDL Low density Lipoproteins

LDV Ledipasvir

LLOQ Lower Limit Of Quantitation

LS Liver stiffness

MELD Model for End-Stage Liver Disease

METAVIR Meta-analysis of Histological Data in Viral Hepatitis

miR-122.... microRNA-122

MMP Matrix metalloproteinases

MMP-2 Matrix metalloproteinase 2.

MRE Magnetic Resonance Elastography

NAFL Nonalcoholic fatty liver

NAFLD Non Alcoholic Fatty Liver Disease

NASH Nonalcoholic steatohepatitis

NEFA Non-esterified fatty acids
NFS NAFLD fibrosis score
NIBMs..... Noninvasive Biomarkers
NIMs Non invasive markers
NNPI Non-nucleoside polymerase inhibitor.
NPIs..... Nucleoside polymerase inhibitors
NPV Negative predictive value
NS5A Nonstructural protein 5A
NS5B Nonstructural protein 5B
OATP Organic Anion Transporting Polypeptides
PCR..... Polymerase chain reaction
PDGF Platelet-derived growth factor
PEG Pegylated
peg-IFN α . Pegylated interferon- α
P-gp P-glycoprotein
PIs Protease inhibitors
PLT Platelet
PPAR γ Peroxisome proliferators-activated receptor γ
PPV Positive predictive value
RBV Ribavirin
RNA..... Ribonucleic acid
ROI Region of Interest
ROS Reactive oxygen species
S.Chol Serum Cholesterol

S.cr Serum creatinine
SD Standard deviation
SMAs Smooth- muscle antibodies
SOC Standard-of-care
Sof Sofosbuvir
SREBP1 .. Sterol regulatory element binding protein 1
SVR Sustained Virological Response
SWE Shear wave elastography
T3 Triiodothyronine
T4..... Thyroxine
TE Transient Elastography
TG Triglycerides
TGF Transforming growth factor
TIMPs Tissue inhibitor of metalloproteinases
TSH..... thyroid-stimulating hormone
T. Bil. Total bilirubin
ULN Upper limit of normal
US Ultrasound
VCTE Vibration-controlled transient elastography
VEGF Vascular endothelial growth factor
WBC..... White blood cells

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Abstract

Background: Hepatitis C virus (HCV) is a major health problem worldwide. More than one million people die each year from hepatitis C virus (HCV) related diseases.

Aim of the Work: to evaluate the effect of direct acting antiviral drugs on hepatic steatosis in naïve HCV chronically infected Egyptian patients after reaching SVR12.

Patients and Methods: study was carried out on 100 treatment naïve patients with chronic infection of HCV attending the out-patient clinic. The patients were diagnosed having HCV by detecting HCV antibodies by ELISA & PCR for HCV RNA at The Gastroenterology and Hepatology Department, Ain Shams University and Kobry El Koba Military Hospital between August 2017 till February 2019.

Results: The mean TG, mean s. cholesterol and APRI Score decreased significantly showing a high statistical significant difference between baseline and SVR12. The mean HDL and LDL significantly increased showing a high statistical significant difference between baseline and SVR12. NAFLD Score increased from baseline to SVR12 showing a statistical significant difference in NAFLD Score between baseline and SVR12. Fibroscan median mean decreased showing a highly statistical difference in Fibroscan Median between baseline and SVR12. Out of 100 patients, cirrhosis regressed to F3 in 33 patients, F2 in 3 patients and didn't regress to F1 in any patient, while the majority (43 patients) remained as F4 at SVR12.

Conclusion: APRI Score mean and Fibroscan median mean were significantly decreased, while NAFLD Score was increased among the studied groups from baseline and SVR12.

Key words: Hepatic Steatosis, HCV, DAAs, Invasive Parameters

INTRODUCTION

Hepatitis C virus (HCV) infection is a common liver disease worldwide with a high rate of chronicity (75–80%) in infected individuals (*Jamak and Kianoush, 2016*).

Nowadays, interferon (IFN)-free direct-acting antiviral regimens have been developed for HCV treatment. Despite their cost, these direct-acting antiviral regimens are now the treatment of choice for all HCV genotypes. Sustained virologic response (SVR) at 12 weeks (SVR12), i.e., undetectable HCV RNA levels 12 weeks after completing treatment, is achieved in 90–95 % of non-cirrhotics, depending on genotype, treatment experience, and regimen used (*Hartman et al., 2015 and Bailly et al., 2015*). Comparable responses can be achieved in cirrhotics, but an extended treatment duration and/or ribavirin may be required based on the regimen (*AASLD-IDS, 2016*). However, SVR12 may be achieved in only 80–85 % of decompensated cirrhotics with most regimens, although newer options approach SVR rates of 95 % (*Foster et al., 2016 and Curry et al., 2015*).

HCV uses host lipid metabolism for its lifecycle and can cause hepatic steatosis and insulin resistance (*Del Campo and Romero-Gomez, 2009*). Approximately 40–80 % of HCV-positive patients that are biopsied have steatosis,

defined as excessive triglyceride deposition in hepatocytes (*Asselah et al., 2006*).

There are several factors which can affect the development of steatosis in chronic hepatitis C: (i) viral factor (HCV genotype3), (ii) host factors (alcohol consumption, overweight, hyperlipidemia, diabetes mellitus, insulin resistance) and (iii) drug therapy (corticosteroids, amiodarone, methotrexate etc.) (*Asselah et al., 2006*). Recent studies suggest that liver steatosis in chronic hepatitis C may be the expression of a direct cytopathic effect of hepatitis C virus (*Castéra et al., 2004*).

Currently, liver biopsy is the ‘gold standard’ for assessing the severity of hepatic fat deposition but biopsy is an invasive procedure and, in some patients, will result in complications such as internal bleeding, biliary leakage, hematoma formation, and infection. Up to 3% of patients require hospitalization after elective biopsy. The cost of biopsy is another important issue, this is why attention has shifted to non-invasive measures of hepatic fat detection (*Mazahar et al., 2009*).

The APRI was developed by *Wai et al.* and is calculated based on AST levels and platelet counts. According to the results obtained in that study, the lower and upper cut-off values for the definition of significant fibrosis and cirrhosis are determined (*Wai et al., 2004*). To evaluate

significant fibrosis, the following cut-off values are used: lower than 0.5 (absence of significant fibrosis, Ishak stage 0-2); and higher than 1.5 (presence of significant fibrosis, Ishak stage 3-6). To evaluate cirrhosis, different cut-off values are used. The absence of cirrhosis (Ishak stage 0-4) is defined as values lower than 1, and cirrhosis (Ishak stage 5-6) is defined as values higher than 2 [6]. The formula for calculating the APRI test is as follows (*Wai et al., 2003*):

$$APRI = AST (/ULN) / Platelets (10^9/L) \times 100$$

NAFLD fibrosis score (NFS), developed in 2007 by Angulo et al., the authors determined that hyperglycemia, albumin, age, body mass index (BMI), platelet count, and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio were solitary predictors of advanced fibrosis. They summarized that the NAFLD fibrosis score can accurately identify whether advanced fibrosis is present in NAFLD (*Angulo et al., 2007*).

Fibroscan is a new method, which presents better results in various studies with respect to differentiating between cirrhotic and noncirrhotic patients. It is considered a quick and easy noninvasive procedure for diagnosing cirrhosis and has been presented as an alternative to liver biopsy in patients with a formal contraindication (*Sebastiani et al., 2006*).