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

Thesis

Submitted for Partial Fulfillment of MD Degree
In Internal Medicine

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2020

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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 Milletus

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 ..... Gammaglutamyl 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-IFNα . Pegylated interferon-α

P-gp ..... P-glycoprotein

PIs ..... Protease inhibitors

PLT ..... Platelet

PPARγ ..... 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 naive 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 Gastro-enterolgy 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-IDSA, 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)*:**

$$APRI = AST\ (/ULN)\ /\ Platelets\ (10^9/\mathrm{L})\ \mathrm{x}\ 100$$

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)***.