Non Invasive Assessment of Hepatic Fibrosis Regression in Hepatitis C Virus Infected Patients Treated with Sofosbuvir Based Therapy

Thesis

Submitted for Partial Fulfillment of Master Degree in Tropical Medicine

By

Kerolous Boles Anwar Dous
M.B.B.ch
Faculty of Medicine-Sohag University

Under Supervision of

Prof. Ahmed Abbas Abdo EL-khattib
Professor of Tropical Medicine
Faculty of Medicine-Ain Shams University

Dr. Adham Mohamed Hamdan EL-Nakeeb
Head of Hepatology & Gastroenterology Department
Sohag Cardiology and Hepato-Gastroentrology Center

Dr. Heba Ismail Saad
Lecturer of Tropical Medicine
Faculty of Medicine-Ain Shams University

Faculty of Medicine
Ain Shams University
2019

Acknowledgment

First and foremost, I feel always indebted to ***God,*** *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to ***Prof. Ahmed Abbas Abdo El-khattib,*** *Professor of Tropical Medicine, Faculty of Medicine-Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Dr. Adham Mohamed Hamdan El-Nakeeb,*** *Head of Hepatology & Gastroenterology Department Sohag Cardiology and Hepato-Gastroentrology Center, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Dr. Heba Ismail Saad,*** *Lecturer of Tropical Medicine, Faculty of Medicine-Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all ***my family*** *for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Kerolous Boles

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
AASLD	*American Association for the Study of Liver Diseases*
Ab	*Antibody*
AFP	*Alpha feto protein*
AIH	*Autoimmune Hepatitis*
ALB	*Serum albumin*
ALD	*Alcoholic liver disease*
ALP	*Alkaline phosphatase*
ALT	*Alanine Aminotransferase*
Apo A1	*Apolipoprotein A1*
APRI	*Aspartate Aminotransferase-Platelet Ratio Index*
APRI	*AST to Platelet Ratio Index*
ARFI	*Acoustic Radiation Force Impulse Imaging*
AST	*Aspartate Aminotransferase*
BCRP	*Breast cancer resistance protein*
BMI	*Body Mass Index*
BOC	*Boceprevir*
CBC	*Complete blood count*
CHB	*Chronic Hepatitis B*
CHC	*Chronic Hepatitis C*
CrkII	*C10 regulator of kinase II*
CT	*Computed Tomography*
CTLs	*Cytotoxic T Lymphocytes*
CTP	*Child-Turcotte Pugh*
DAAs	*Direct-acting antiviral agents*
DCs	*Dendritic Cells*
DCV	*Daclatasvir*
DSV	*Dasabuvir*

List of Abbreviations (Cont...)

Abb.	Full term

EASL .....*European Association for Study of Liver*
ECM .....*Extracellular Matrix*
FDA .....*Food and Drug Administration*
FFAs .....*Free Fatty Acids*
FIB-4.....*Fibrosis-4 Score*
FIB-4.....*The Fibrosis 4 index*
GMBF .....*Gastric Mucosal Blood Flow*
GT1 .....*Genotype 1*
GUCI .....*Göteborg University Cirrhosis Index*
HA .....*Hyaluronic Acid*
Hap .....*Haptoglobin*
HB .....*Haemoglobin*
HBsAg .....*Hepatitis B surface antigen*
HCC .....*Hepatocellular Carcinoma*
HCV .....*Hepatitis C virus*
HSCs .....*Hepatic Stellate Cells*
HVTT .....*Hepatic Vein Transit Times*
ICC .....*Intraclass Correlation Coefficient*
IDSA .....*Infectious Diseases Society of America*
IFN .....*Interferon*
IFNα .....*Interferon Alpha*
IMPDH .....*Inhibition inosine 5'-monophosphate dehydrogenase*
INR .....*International normalized ratio of prothrombin*
IQR .....*Interquartile Range Interval*
IR .....*Insulin Resistance*
IUs .....*International Units*
LDV .....*Ledipasvir*
LS .....*Liver Stiffness*

List of Abbreviations (Cont...)

Abb.	Full term

LSM .....Liver stiffness measurements
LT .....Liver Transplantation
MFs .....Myofibroblasts
MMP .....Matrix Metalloproteinase
MRE .....Magnetic Resonance Elastography
MRI .....Magnetic Resonance Imaging
MRP2.....Multidrug resistance-associated protein 2
MTl - MMP .....Membrane Type Matrix Metalloproteinase-L
mTOR .....Mechanistic target of rapamycin
MTP .....Microsomal Triglyceride Transfer Protein
NAAT .....Nucleic Acid Amplification Test
NAFLD .....Non-alcoholic fatty liver disease
NASH .....Non-Alcoholic Steatohepatitis
NAT .....Nucleic Acid Test
NCCVH .....National Committee for the Control of Viral Hepatitis
NNPIs .....Non-Nucleotide Polymerase Inhibitors
NPIs .....Nucleotide / Nucleoside Polymerase Inhibitors
NPV .....Negative Predictive Value
NS3/4A .....Nonstructural proteins 3/4A
NS5B .....Nonstructural protein 5B
OATP .....Organic anion transporting polypeptide
OBV .....Ombitasvir
PBC .....Primary Biliary Cholangitis
PCR .....Polymerase chain reaction
PFV .....Portal Flow Velocity
P-gp .....P-glycoprotein
PI .....Protease Inhibitors
PICP .....Procollagen Type I Carboxy Terminal Peptide

List of Abbreviations (Cont...)

Abb.	Full term
PIIINP	*Procollagen Type III Amino-Terminal Peptide*
PLT	*Platelet*
PPAR-α	*Peroxisome Proliferator-Activated Receptor Alpha*
PSC	*Primary Sclerosing Cholangitis*
pSWE	*Point Shear-Wave Elastography*
PTV/r	*Paritaprevir/Ritonavir*
PVBF	*Portal Venous Blood Flow*
PVC	*Polyvinylchloride*
RASs	*Resistance-Associated Substitutions*
RBV	*Ribavirin*
RNA	*Ribonucleic Acid*
ROC	*Receiver Operating Characteristic Curve*
ROI	*Region of Interest*
ROS	*Reactive Oxygen Species*
SIM	*Simeprevir*
SOC	*Standard of Care*
SOCs	*Suppressor of Cytokine Signaling*
SOF	*Sofosbuvir*
SR	*Success Rate*
SS	*Spleen Stiffness*
SVR	*Sustained Virological Response*
SWV	*Shear Wave Velocity*
T.Bil	*Total bilirubin*
TCR	*T-cell receptor*
TE	*Transient Elastography*
TGF-β1	*Transforming Growth Factor-β1*
TIMPs	*Tissue Inhibitors of Metallo-Proteinases*
TLV	*Telaprevir*

List of Abbreviations (Cont...)

Abb.	Full term
TNF-α	*Tumor Necrosis Factor Alpha*
USA	*United State of America*
VAP	*Velpatasvir*
VLDL	*Very Low Density Lipoprotein*
VTQ	*Virtual Touch™ Quantification*
WBCs	*White blood cells*
WHO	*World Health Organization*
γGT	*Gamma Glutamyl Transferase*

ABSTRACT

Background: Hepatitis C virus (HCV) is a major health problem worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes, accompanied by hepatocellular carcinoma (HCC).

Aim of the Work: To evaluate early changes of hepatic fibrosis-related parameters in patients with chronic HCV patients using liver stiffness measurement using Shear wave elastography (Siemens-Acuson S2000) and serum parameters as APRI, FIB4 before and after sofosbuvir-based antiviral therapy.

Patients and Methods: This study were conducted on 109 Egyptian patients with chronic hepatitis C who were collected from viral hepatitis treatment unit in Sohag Cardiology and Hepato-Gastroentrology Center and followed up in the period between July 2017 and September 2018.

Results: The mean age of the studied patients was 45.76 ±13.91 years, 67 (61.50%) of them were males while 42 (38.50%) were females. A history of diabetes was reported in 8 (7.30%) patients, 11 (10.10%) of our patients were hypertensive while 3 (2.80%) patients were ischemic heart disease. A total of 109 HCV-infected patients treated with sofosbuvir based therapy for 12 weeks were identified, 84 (77.10%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day and 25 (22.90%) were treated with sofosbuvir 400 mg/day and daclatasvir 60 mg/day with weight-based ribavirin (1000 mg { below 75 kg} to 1200 mg {above 75mg}).

Conclusion: Sofosbuvir-based treatment regimens for CHC result in significant reduction in Liver stiffness measurements (LSM) by pSWE with significant changes in the distribution of patients among the fibrosis stages except liver fibrosis stage 4 (F4) and significant improvement in fibrosis scores (FIB4 and APRI) 24 weeks post treatment.

Keywords: *Sofosbuvir - Hepatitis C Virus - Hepatic Fibrosis Regression*

INTRODUCTION

Hepatitis C virus (HCV) is a major health problem worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes, accompanied by hepatocellular carcinoma (HCC) ***(EASL, 2014).***

In 2015, the global prevalence of HCV infection was 1.0%, with the highest prevalence in the Eastern Mediterranean Region (2.3%) followed by the European one (1.5%). The annual mortality due to HCV related complications is estimated to be approximately 700000 deaths ***(WHO, 2016).***

The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time, reduces morbidity and mortality, and is considered in most cases to be equivalent to cured HCV infection ***(van der Meer, 2012).***

Liver fibrosis is the main determinant of hepatitis C virus–related morbidity and mortality ***(Poynard et al., 1997).*** In addition, the stage of fibrosis is prognostic and provides information on the likelihood of disease progression and response to treatment ***(Marcellin et al., 2002).***

Liver biopsy is currently the gold standard for staging fibrosis, but it has well-documented complications of pain, bleeding, and rarely, death ***(Bravo et al., 2001).*** Liver biopsy is

also expensive, as are the costs associated with treating its complications. In addition, inter- and intra-observer error may lead to incorrect staging ***(Marcellin et al., 2002),*** as may sampling error in up to 33% of biopsies ***(Regev et al., 2002).***

More recently, clinical investigators have been searching for noninvasive serum markers of fibrosis ***(Afdhal, 2003).*** These can be individual markers or a series of markers from which a fibrosis index can be derived. In either case, these marker tests must have the following characteristics: they must be reliable, accurate, reproducible, and easy to perform. In addition, they must reflect total mass of liver collagen and extracellular matrix (ECM) and be able to reflect both fibrogenesis and fibrosis regression. The ideal marker test would be able to accurately stage disease and also be sensitive to changes in fibrosis induced by therapy or the natural history of disease progression ***(Afdhal, 2004).***

No single marker fulfill all of the proposed criteria to merit routine clinical use, A combination of markers including those that reflect alterations in hepatic synthetic function and markers of extracellular matrix turnover are emerging as useful diagnostic tests for differentiating early from advanced cirrhosis ***(Thabut et al., 2003).***

Noninvasive approach to assessment of severity of hepatitis C include clinical symptoms and signs, routine biochemical and hematologic blood tests, serum markers of fibrosis and inflammation, combinations of clinical and blood