Study on Outcome of Nucleotide Polymerase Inhibitor (Sofosbuvir) in Treatment of Chronic Hepatitis C Among Egyptian Cirrhotic and Non-cirrhotic Patients

Thesis

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ALT..... Alanine amino transferase.

ANA ..... Anti-Nuclear Antibody.

ASMA ..... Anti-Smooth Muscle Antibody.

AST ..... Aspartate amino transferase.

CHC ..... Chronic Hepatitis C.

CHB……. Chronic Hepatitis B.

CLD..... Chronic Liver Disease.

ECM..... Extra-Cellular Matrix.

EIA……. Enzyme Immuno-assays.

FDA..... Food and Drug Adminestraion.

EASL…… European Association for the Study of the Liver.

AASLD.... American Association for the Study of the Liver Disease.

WHO…… World Health Organisation.

RIBA…… Recombinant Immunoblot Assays.

HBV ..... Hepatitis B Virus.

HAV……. Hepatitis A Virus.

HCC ..... Hepatocellular Carcinoma.

HCV ..... Hepatitis C Virus.

HEV ..... Hepatitis E Virus.

HVR……. Hyper Variable Regions.

HIV..... Human Immunediffiency Virus.

IL28B ..... Interleukin 28B.

INR..... International Normalized Rtio.

KPa..... KiloPascal.

LF ..... Liver Fibrosis.

LS ..... Liver Stiffness.

CTP…….. Child-Turcotte-Pugh.

NASH ..... Non Alcoholic Steatohepatitis.

HVPG….. Hepatic Vein Pressure Gradient.

EDHS…... Egypt Demographic and Health Study.

LSPS…… Liver stiffness Spleen diameter to Platelet ratio Score.

LLOQ….. Lower Limit Of Quantitation.

NNIs……. Non Nucleoside Polymerase Inhibitors.

NI……. Nucleoside Polymerase Inhibitors.

NPV ..... Negative Predictive Value.

PCR ..... Polymerized Chain Reaction.

DAA……. Direct Antiviral Agents.

PEG-INF. Pegylated Interferon

PT ..... Prothrombin Time.

PTT ..... Partial Thromboplastin Time.

AFP…….. Alpha Fetoprotein.

PLT…….. Platelets.

TG ……Triglycerides.

RBV..... Ribavirin.

RNA ..... Ribonucleic Acid.

IFN…….. Interferon.

SOF ..... Sofosbuvir.

LDV……. Ledipasvir.

BOC……. Boceprevir.

TLV……... Telaprevir.

SVR12..... Sustained Virological Response at week 12 after treatment.

SVR24..... Sustained Virological Response at week 24 after treatment.

HCV GT….. Hepatitis C Virus Genotype.

SVR..... Sustained Virological Response.

EVR..... Early Virological Response.

RVR ..... Rapid Virological Response.

SWE ..... Shear Wave Elasticity.

TE..... Transient Elastography.

US…… Ultrasonography.

CT…… Computed Tomography.

MRI…….. Magnetic Resonance Imaging.

MRE ……. Magnetic Resonance Elastography.

IQR…… Interquartile Range.

LRE……... Liver Related Events.

eGFR….... Estimated Glomerular Filtration Rate.

OBV/PTV/r+DSV… ombitasvir /paritaprevir/ribavirin and dasabuvir

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INTRODUCTION

HCV infection is a serious health issue. Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease and cirrhosis. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures **(Lavanchy and McMahon, 2000).** The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis **(Lavanchy and McMahon, 2000).**

Liver cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease **(Schuppan and Afhdal, 2008).**

With great advancements in the therapeutic modalities used for the treatment of chronic liver diseases, the accurate assessment of liver fibrosis is a vital need for successful individualized management of disease activity in patients. Transient ultrasound Elastography (Fibroscan) is an ultrasound-based technology for quantitatively assessing hepatic stiffness that has been introduced

in the last several years **(Ziol et al., 2005).** Stiffness was significantly correlated with fibrosis stage **(Foucher et al., 2006)**. Fibroscan is considered to be a reliable method for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis **(Friedrich-Rust et al., 2008).**

Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, have resulted in improved management, quality of life, and life expectancy of patients **(Schuppan and Afhdal, 2008).** The standard care for patients with HCV infection continues to include 24 to 48 weeks of treatment with peginterferon-alfa 2a and ribavirin. Treatment with interferon is associated with troublesome side effects, including influenza-like symptoms, depression, fatigue and cytopenias. A substantial proportion of patients with HCV infection are unable or unwilling to receive interferon-based regimen **(Gane et al., 2013)**.

The addition of the recently approved directly acting antiviral agents telaprevir or boceprevir to pegylated interferon-alfa and ribavirin has resulted in improved sustained virologic response (SVR) rates; however, adverse reactions, high pill burdens, and drug interactions continue to make treatment challenging **(Bacon et al., 2011).** Furthermore, certain host and viral factors including black race, advanced liver fibrosis, *IL28B* CT or TT genotypes, high baseline HCV viral loads, and prior treatment experience appear to remain associated with poorer

treatment outcomes **(Poordad et al., 2013; Jacobson et al., 2011).**

Recent studies show that interferon-free, directly acting antiviral agent–only regimens can successfully achieve sustained virological response "SVR" **(Poordad et al., 2013).**

Sofosbuvir is an oral nucleotide analogue inhibitor of the HCV-specific NS5B polymerase with in vitro activity against all HCV genotypes **(Jacobson et al., 2013).** The viral kinetics during treatment were nearly identical in all treatment groups. Viral suppression was rapid in all patients, regardless genotype, status with respect of previous treatment, baseline viral load, race or ethnic group, IL28B status and presence or absence of interferon during the regimen **(Gane et al., 2013)**.

The most common recorded adverse effects with Sofosbuvir plus Ribavirin regimen were headache, fatigue, insomnia, nausea, rash and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not receive **(Gane et al., 2013)**.

The pangenotypic antiviral efficacy of sofosbuvir supports the continued investigation of sofosbuvir with ribavirin in patients with HCV infection **(Gane et al., 2013)**.