بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

MONA MAGHRABY

Clinical Effects of Simvastatin in Chronic Hepatitis C Patients Receiving Sofosbuvir/ Daclatasvir Combination

Thesis Submitted for the fulfillment of Master's degree in Pharmaceutical Sciences (Clinical Pharmacy)

Submitted By

Hossam Zakarya Mohamed

Lieutenant Colonel Pharmacist in the Egyptian Armed Forces

Under Supervision of

Prof. Dr. Nagwa Ali Sabri

Professor and Head of Clinical Pharmacy Department
Faculty of Pharmacy - Ain Shams University

General Dr. Hossam Zaki Hussein

Head of Hepatology Department
Kobri El koba Armed Forces Hospital

Dr. Sara Mahmoud Zaki

Associate professor of Clinical Pharmacy
Clinical Pharmacy Department
Faculty of Pharmacy - Ain Shams University

2021

List of Contents

List of abbreviations

AEs	**Adverse Events**
ALT	**Alanine Aminotransferase**
ApoB	**Apolipoprotein B**
ApoB100	**Apolipoprotein B100**
ApoE	**Apolipoprotein E**
AST	**Aspartate Aminotransferase**
AUC	**Area Under the Curve**
BMI	**Body Mass Index**
CAD	**Coronary Artery Disease**
CBC	**Complete blood Count**
CHC	**Chronic Hepatitis C**
Chol	**Cholesterol**
CK	**Creatinine Kinase**
CLDN1	**Claudin-1**
CRP	**C-reactive protein**
CV	**Cardiovascular**
DAAs	**Direct-acting Antiviral Agents**
DCV	**Daclatasvir**
DGAT	**Diacylglycerol Transferase-1**
DM	**Diabetes Mellitus**
EOT	**End of Treatment**
FBG	**Fasting Blood Glucose**
FDA	**Food and Drugs Administration**
FIB-4	**Fibrosis score-4**
GAGs	**Glycosaminoglycans**
Hb	**Hemoglobin**
HBV	**Hepatitis B Virus**
HCC	**Hepatocellular Carcinoma**
HCV	**Hepatitis C virus**
HDL	**High-density Lipoprotein**
HgbA1C	**Hemoglobin A1C**
HIV	**Human Immunodeficiency Virus**
HMG CoA	**3-hydroxy-3-methylglutaryl coenzyme A**
HSCs	**Hepatic Stellate Cells**
HTN	**Hypertension**
IL28B	**Interleukin 28B**
IQR	**Inter-Quartile Range**
IR	**Insulin Resistance**
LD	**Lipid Droplets**
LDL	**Low-density Lipoprotein Cholesterol**
LDLR	**Low-density Lipoprotein Receptor**
MTP	**Microsomal Triacylglycerol Transfer Protein**
MW	**Membranous Web**
NASH	**Nonalcoholic Steatohepatitis**
NPC1L1	**Neimann-Pick C1 Like 1**
OCLN	**Occludin**
ORR	**Objective Response Rate**
Peg-IFN	**PEGylated interferon**

PNPLA3	**Patatin-like Phospholipase Domain Containing 3**
RBV	**Ribavirin**
ROS	**Reactive Oxygen Species**
RTKs	**Receptor Tyrosine kinases**
SD	**Standard Deviation**
SNP	**Single Nucleotide Polymorphism**
SOF	**Sofosbuvir**
Sof/Dac	**Sofosbuvir / Daclatasvir**
SRB1	**Scavenger Receptor Class B Member 1**
SREBPs	**Sterol-regulatory Element Binding Proteins**
SVR-12	**Sustained Virological Response at 12 weeks after the end of treatment**
T3 and T4	**Tri iodothyronine and Tetra iodothyronine**
TChol	**Total Cholesterol**
TE	**Transient Elastography**
TG	**Triglyceride**
TLC	**Total Leucocytes Count**
US	**United States**
VEL	**Velpatasvir**
VLDL	**Very Low-density Lipoprotein**

List of Tables

List of Figures

Introduction

Hepatitis C virus (HCV) is one of the most common causes of chronic liver disease and the leading indication for liver transplantation worldwide **(Simon and Butt, 2015).**

In Egypt, hepatitis C virus (HCV) infection is a major public health burden, where it bears the highest prevalence rate in the world **(Gomaa et al., 2017).** Moreover, patients with chronic hepatitis C (CHC) are at increased risk of hepatic steatosis, fibrosis and cardiovascular diseases including accelerated atherosclerosis **(Simon and Butt, 2015).**

HCV utilizes peripheral lipid metabolism pathways including hepatocyte very-low-density lipoprotein for viral assembly and requires several apolipoproteins for production of infective particles **(Pedersen et al., 2016).**

As a result, chronic hepatitis C (CHC) is associated with reduced total cholesterol, LDL and apolipoprotein B (ApoB) levels as well as an increased rate of insulin resistance (IR) and type 2 diabetes mellitus **(Gitto et al., 2018).**

On the other hand, total cholesterol, low density lipoprotein cholesterol, and high-density lipoprotein

List of Figures *(Cont ...)*

Fig. No.	Title	Page No.

cholesterol levels increased post therapy regardless of the regimen **(Endo et al., 2017).**

The data available on the effect of IFN on lipids are conflicting (**Lange et al., 2010).** However, **Hsu*, et al. (2015)*** reported that viral eradication due to IFN may significantly decrease cardiovascular (CV) morbidity. But data regarding effect of direct-acting antiviral (DAA) on glucose and lipid metabolism are incomplete, extrapolated from clinical trials and partially contradictory **(Gitto et al., 2018).**

Recently, the findings demonstrate that DAA treatment may increase levels of TG, Chol and TG/Chol ratio loaded on a single VLDL particle in patients with chronic hepatitis C **(Sun et al., 2018).**

It was reported that the viral clearance due to direct-acting antiviral led to an improvement of glucose metabolism associated with a global worsening of lipid profile and this may have a potential impact of those alteration of the CV risk so, the patients who have one or more classical CV risk factors and are treated with DAA might be monitored for an accurate stratification of CV risk **(Gitto et al., 2018).**

Statins are HMG CoA reductase inhibitors which inhibit the rate-limiting enzyme of the mevalonate pathway and

have been shown to play an important role in the modulation of hepatic steatosis, cholesterol metabolism and fibrosis, and recent attention has focused upon their potential therapeutic role in CHC **(Simon and Butt, 2015).**

Statins appear to block HCV replication by inhibiting *de novo* cholesterol and geranylgeranylated protein synthesis, thus reducing expression of key HCV viral proteins and inhibiting pro-inflammatory signaling pathways **(Dimitroulakos et al., 2006, Zhao et al., 2010).**

Also, statins may exert antifibrotic effects **(Trebicka et al., 2010, Shirin et al., 2013).**

The role of statins as adjunctive therapy in HCV treatment has so far been limited to the previous standard of care, PEGylated interferon and ribavirin. Furthermore, in vitro studies have showed that statins increase the antiviral activity of different DAAs in an additive manner and delay or even prevent the development of resistance against DAAs (**Delang et al., 2009).**

According to **Kishta et al. (2017)** their search of the PubMed database and UMIN Clinical Trials Registry System, no clinical trial has been conducted for the combination of statins and DAAs.

The current study was conducted to investigate the clinical benefits of using simvastatin in CHC patients receiving Sofosbuvir/ Daclatasvir combination in terms of amelioration of lipid profile and glycemic status.

Chronic Hepatitis C

Hepatitis C virus overview

The hepatitis C virus (HCV) is the most common blood-borne infection in the United States, affecting up to 3.5 to 4 million Americans. It is also the most common cause of end-stage liver disease requiring liver transplant. HCV poses an under recognized public health challenge and remains undiagnosed in most of those infected (up to 70%) (**Foster et al., 2016).**

Furthermore, since 2007, HCV has surpassed the human immunodeficiency virus (HIV) as a cause of death in the United States, and contributed to a growing health care access and outcome disparity because it disproportionately affects those who are homeless, living below the poverty level, incarcerated, or with a history of injection drug use or alcohol abuse. The irony is that over the last 10 years, a revolution in HCV treatment with directly acting antiviral (DAA) therapies has occurred, increasing the cure rates from less than 50% to more than 90% in those who are able to traverse gaps in current practice from infection to diagnosis to access to care (**Cheung et al., 2016).**