



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



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التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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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)*

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2021

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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
DAA s	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

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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

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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**).