Evaluation of the Role of Different Apo lipoprotein-E Genotypes in the Outcome of Treatment by Interferon and Ribavirin in Egyptian Hepatitis C Patients

(Thesis)

Submitted for Partial Fulfillment of Master Degree in Internal Medicine

By

Mohamed Omar Khalifa

MB.B.Ch.

Alexandria University

Under Supervision of

Professor Dr./Sayed Mohamed Shalaby

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain Shams University

Dr./Moataz Mohammed Sayyed

Assistant Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain Shams University

Dr./Wesam Ahmed Ibrahim

Assistance Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain Shams University

Faculty of Medicine

Ain Shams University

2015

بسم الله الرحمن الرحيم

"قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ"

صدق الله العظيم

(سورة البقرة:32)

Acknowledgement

At first and foremost thanks to “Allah “the most merciful who gave me the power to finish this work. I wish to express my deepest appreciation and sincere gratitude to **prof. Dr.Sayed Mohamed Shalaby** , professor of internal medicine and Gastroenterology ,Ain Shams University, for his precious help throughout all stages of this work outstanding kind support and valuable instructions.

My greatest respect, appreciation and thanks to **Prof. Dr. Moataz Mohammed Sayyed,** Assistant Professor of Internal Medicine and Gastroenterology, Ain Shams University, for his valuables help, planning and supervision of this study.

It was a great honor to me to work under his guidance. It is a great honor to express my thanks to **Prof Dr. Wesam Ahmed Ibrahim** Assistance Professor of Internal Medicine and Gastroenterology, Ain Shams University, who was very kind, supportive and helpful throughout all the stages of this work. She had such a great influence on my character and behavior.

I’m deeply grateful to my mother and father for their great support and help throughout my life not only this great study.

List of Contents

LIST Of TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABB	Meaning
AD	Alzheimer's disease
AHC	Acute Hepatitis C
Apo E	Apo lipoprotein E
ARFP	Alternate Reading Frame Protein
CHC	Chronic hepatitis C
CHD	Coronary Heart Disease
CM	Chylomicrons
CNS	Central Nervous System
CVD	Cardiovascular Disease
DAA	Direct-Acting Antivirals
eIF2α	Eukaryotic Initiation Factor 2α
eRVR	Extended Rapid Viral Response
GAS	Gamma Activated Sequence
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High-Density Lipoproteins
HLP III	Type III Hyperlipoproteinemia
HRT	Hormone Replacement Treatment
HSPG	Heparin Sulphate Proteoglycan
IDLs	Intermediate-density lipoprotein
IFNAR	Interferon Alpha/Beta Receptor
IFNα	Interferon-Alpha
IL-2	Interleukin 2
IRFs	Interferon Regulatory Factors

ISGs	IFN Stimulated Genes
ISREs	Interferon Stimulated Response Elements
Jak	Janus kinase
LDL-C	Low-Density Lipoprotein Cholesterol
LRP	Receptor-Related Protein
OAS	Oligoadenylate Synthetase
PAMPs	Pathogen Associated Molecular Patterns
PCR	Polymerase Chain Reaction
PKR	Protein Kinase R
PP2A	Protein Phosphatase 2A
PRMT1	Protein Arginine Methyltransferase-1
PRRs	Pattern Recognition Receptors
rNTP	Ribonucleoside Triphosphates
SAMe	S-Adenosyl-Methionine
SNPs	Single Nucleotide Polymorphisms
SOCS	Suppressor Of Cytokine Signalling
STAT	Signal Transducer And Activator Of Transcription
SVR	Sustained Viral Response
TC	Total Plasma Cholesterol
TcPTP	T Cell Protein Tyrosine Phosphatase
TLR	Toll-Like Receptor
TYK2	Tyrosine Kinase 2
VLDL	Very-Low Density Lipoprotein

Abbreviations are alphabetically ordered

INTRODUCTION

and

aim of the work

INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem. More than 170 million people worldwide are infected with HCV (Poynard et al., 2003; Shepard et al., 2005). HCV is a causative agent of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (Hishiki et al., 2010). In Egypt, HCV prevalence is ~15%, which is considered the highest prevalence worldwide **(Egyptian Ministry of Health, 2007; El-Zanaty and Ann Way, 2009)**

There are several possible outcomes after infection with hepatitis C virus (HCV) (Alter et al., 1992). Approximately 15% to 20% of infected individuals clear the virus, as evidenced by the presence of anti-HCV antibodies, but absence of viral RNA in serum. The remaining individuals (~85%) become chronically infected, with HCV RNA readily detectable in serum **(Seeff and Hoofnagle, 2002).**

The consequences of chronic infection also vary: some individuals develop minor or no liver damage whereas others suffer from progressive chronic hepatitis leading to cirrhosis, and even hepatocellular carcinoma. The reasons for the diversity of outcomes of HCV infection are unclear at least 6

major HCV genotypes are identified **(Robertson et al., 1998, NIH Consens State Sci Statements, 2002).**

However, infection with a particular genotype is not thought to influence disease outcome **(Alric et al., 2000)**. Alternatively, host factors may be important. Some factors include male sex, an older age at infection, increased alcohol intake, co-infection with Human Immunodeficiency Virus 1(HIV-1) or Hepatitis B virus and insulin resistance **(Price et al., 2006).**

HCV particles circulating in the blood of HCV carriers associate with lipoproteins, such as low-density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons; thus, it is termed a lipo-viro particle (LVP) **(Hishiki et al., 2010).**

It has been suggested that the virus might gain entry into cells via a hitchhiker method with the lipoproteins **(Agnello et al., 1999).** Specifically, entry might involve LDL receptors (LDLRs) **(Price et al., 2006**). COS-7 cells transfected with the human gene for LDLR bind more HCV particles than untransfected cells, and antibodies that block binding of ligands to LDLRs also block binding of HCV to cells **(Monazahian M et al., 1999**).

The virus also has been shown to bind directly to certain apolipoproteins, which might facilitate entry Several lipoproteins groups contain Apolipoprotein-E (ApoE), a polymorphic and multifunctional protein with numerous roles in lipoproteins metabolism. The three common isoforms apoE2, apoE3 and apoE4 show isoform-specific functional properties including different susceptibilities to diseases **(Kuhlmann et al., 2010).**

AIM OF THE WORK

Evaluation of the effect of different genotypes of Apo lipoprotein-E on the outcome of treatment by Interferon and Ribavirin in Egyptian hepatitis C patients.

Chapter 1

Hepatitis C Virus

INTRODUCTION

Hepatitis C virus (HCV or sometimes HVC) is a small (55–65 nm in size), enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. Hepatitis C virus is the cause of hepatitis C in humans.

1. Taxonomy and structure

The hepatitis C virus belongs to the genus Hepacivirus a member of the family Flaviviridae. Until recently, it was considered to be the only member of this genus. However, a member of this genus has been discovered in dogs - canine hepacivirus. There is also at least one virus in this genus that infects horse s **(Burbelo et al., 2012).**

The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope **(Op De Beeck and Dubuisson, 2003).**