Sofosbuvirin combination with ribavirin with or without pegylated interferon for treatment of Egyptian patients with hepatitis C infection

Thesis

Submitted for Partial Fulfillmentof Master Degree

in Internal Medicine

By

Ahmed Hassan Ahmed

M.B.B.Ch

Faculty of Medicine

Sohag University

Supervised by

Prof. Dr. Yehia Mohammed Al Shazly

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain-Shams University

Prof. Dr. Sherif Monier Mohamed

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain-Shams University

Dr. Ossama Ashraf Ahmed

Assintat Professor of Internal Medicine and Gastroenterology

Faculty of Medicine

Ain-Shams University

Faculty of Medicine

Ain-Shams University

2016

Acknowledgement

First, I would like to thank ***Allah*** *a lot for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

My profound thanks and deep appreciation to ***Prof. Dr.Yehia Mohammed Al Shazly****, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.*

I am also thankful to ***Prof. Dr. Sherif Monier Mohamed****, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his valuable supervision, co-operation and direction that extended throughout this work.*

I would like to direct my special thanks to ***Dr.Ossama Ashraf Ahmed****, Assintat Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for his valuable help, fruitful advice, continuous support offered to me and guidance step by step till this thesis finished.*

Finally my deep thanks to ***my family*** *for supporting me throughout my life.*

Ahmed Hassan Ahmed Hassan

List of contents

Content Page

List of Abbreviations

ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibodies
AST	Aspartat Aminotransferase
CBC	Compleat blood count
DAAs	Direct Acting Antiviral Agents
ELISA	Enzyme-Linked Immunosorbent Assay
ER	Endoplasmic reticulum
GT	Genotype
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTAs	Host Target Agents
HVRs	Hypervariable regions
IDUs	Injecting Drug Users
IFN	Interferon
INR	International normalisation ratio
LDL	Low-density lipoprotein
LSM	Liver stiffness measurement
PCR	Polymerase chain reaction
PEG-IFN	Pegylated interferon
P-gp	P-glycoprotein
PLTs	Platelets
RBV	Ribavirin
RdRp	RNA dependant RNA polymerase
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SD	Standard deviation
SOF	Sofosbuvir
SVR	Sustained virological response
WBCs	White blood cells

List of Tables

List of Figures

Introduction

Hepatitis C virus (HCV) is a significant public health problem and the leading cause of liver transplantation and hepatocellular carcinoma **(Moyer**, **2013).** Globally, approximately 180 million people are infected with HCV; the U.S. prevalence of HCV infection is 1.6%, which equates to an estimated 4.1 million infected people **(Armstrong, et al., 2006).** However, more recent surveillance data suggest that HCV infection has increased to 5.2 million people in the U.S. **(Chak, et al., 2011).**

The highest HCV prevalence in the world occurs in Egypt, where the prevalence of infection increases steadily with age, and high rates of infection are observed among persons in all age groups **(Perz, et al., 2006 and Abdel-Aziz, et al., 2000).** This pattern indicates an increased risk in the distant past followed by an ongoing high risk for acquiring HCV infection, although there are regional differences in average overall prevalence **(Perz, et al., 2006 and Medhat, et al., 2002).**

Hepatitis C virus (HCV) genotype 4 is the most frequent cause of chronic hepatitis C in the Middle East, North Africa, and sub-Saharan Africa **(Hoofnagle, 2002).** In countries such as Egypt, more than 90% of cases of chronic hepatitis C are caused by HCV genotype 4 **(Ray, et al., 2000).**

Transmission of HCV occurs via exposure to infectious blood. The population at highest risk for HCV transmission is intravenous drug users. Other risk factors are receipt of blood products and/or organ transplants prior to the blood screening initiative in 1992, needle stick injuries, multiple sex partners, being born to an HCV-positive mother, body piercing or tattoos, and hemodialysis. Higher rates of HCV infection are noted in incarcerated and homeless persons **(Hoofnagle and Di Bisceglie, 1997).**

Thirty percent of chronic HCV infections will result in cirrhosis of the liver, and 25% of cirrhotic persons will ultimately die from liver failure or liver cancer unless they receive a liver transplant. Since approval in 1991, interferon has become a backbone in the treatment of patients infected with HCV, providing a sustained virological response (SVR) in 15% to 25% of patients with genotype 1 infection when given as monotherapy **(Hoofnagle and Di Bisceglie, 1997).** The use of interferon alfa in combination with ribavirin almost doubled the response rates in genotype 1 infection, whereas genotype 2 or 3 patients had SVR rates of 70% to 85% **(McHutchison, et al., 1998).**

For more than a decade, there were no other classes of medications to augment treatment of genotype 1, but in 2011, the NS3/4A protease inhibitors boceprevir and telaprevir became available for the treatment of patients with HCV genotype 1 infection. A combination of a protease inhibitor with pegylated interferon alfa-2a and ribavirin provided SVR

rates of 68% to 75% in treatment-naïve patients with genotype 1 **(Poordad, et al., 2011 and Jacobson, et al., 2011).** However, the regimen had significant limitations due to contraindications and intolerance to interferon therapy, additive adverse effects of anemia from ribavirin, a low genetic barrier to the development of resistance inherent to protease inhibitors, and frequent dosing intervals **(Susser, et al., 2009 and Sarrazin, et al., 2007).**

Genotype 4 is the least studied of the HCV variants and until recently has been considered difficult to treat because conventional interferon monotherapy has resulted in disappointing virologic responses **(Koshy, et al., 2000, Zylberberg, et al., 2000 and Kamal, et al., 2000).** However, recent reports show that a combination therapy with pegylated interferon (PEG-IFN) alpha and ribavirin markedly improves treatment outcomes, resulting in a sustained virologic response (SVR) in 44%-69% of cases **(Hasan, et al., 2004, Alfaleh, et al., 2004 and El-Zayadi, et al., 2005)**.

Sofosbuvir (SOF) is a pyrimidine nucleotide analogue that inhibits HCV NS5B RNA dependent RNA polymerase that is essential for viral replication and is relatively conserved across HCV genotypes and HCV quasispecies **(Pawlotsky, 2014 and Keating, 2014).** Thus sofosbuvir has pangenotypic activity and a high barrier to resistance**.** Sofosbuvir in combination with ribavirin with or without pegylated interferon, and in combination with other anti HCV DAAs achieves high response rates in the treatment of hepatitis C **(Keating, 2014).**

Aim of the work

To evaluate Sofosbuvir in combination with ribavirin with or without pegylated interferon for treatment of Egyptian patients with hepatitis C infection .

Hepatitis C Infection

Epidemiology of HCV

Worldwide epidemiology

Hepatitis C Virus is one of the most important viral Hepatitis that appears to be endemic in many parts of the world. There are, however, substantial geographic and temporal variations in the incidence and prevalence of HCV infection, largely due to differences in regional risk factors for the transmission of HCV. The overall world prevalence of HCV was estimated to be 3% as an over 170 million person were infected. Such prevalence varies greatly from one country to another and even among the province within the same country. Most of the studies however were based on testing of selected populations such as blood donors **(Gough, et al., 2013).**

However, population-based surveys are rarely available for most parts of the world. Low rate area (0.1-0.9%) such as Northern Europe to 0.1–0.5% in Western Europe, North America, parts of Central and South America, intermediate area (1-5%), have been reported from Brazil, Eastern Europe, the Mediterranean area, the Indian subcontinent, and parts of Africa and Asia., High rate area >5% such Arabian peninsula, Africa and the highest prevalence of HCV has been found in Egypt (17–26%) **(Strasser, et al., 2013 and Grebely, et al., 2013).**

Epidemiology of HCV in Egypt:

Egypt has the highest prevalence of antibodies to HCV in the world, estimated nationally at 14.7%. An estimated 9.8% are chronically infected. Numerous HCV prevalence studies in Egypt have published various estimates from different Egyptian communities, suggesting that Egypt, relative to the other nations of the world, might be experiencing intense ongoing HCV transmission **(Miller and Abu-Raddad, 2010).**

For more than a decade, Egypt has been widely regarded as having an epidemic, with the highest recorded prevalence of HCV in the world **(Alter, 2007).** HCV is currently the most significant public health problem in Egypt **(Miller and Abu-Raddad, 2010).** Explanations for this unique epidemic in Egypt have been an ongoing subject of controversy. The iatrogenic role of parenteral antischistosomal therapy campaigns to control endemic schistosomiasis, which ceased some decades ago, is a widely held hypothesis **(Frank, et al., 2000).**

Viral structure

HCV is a small-enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb. It is a member of the genus hepacivirus within the Flaviviridae family. This viral family contains four genera, flavivirus, pestivirus, hepacivirus, and the newly defined genus pegivirus**(Stapleton, et al., 2011).** Novel hepaciviruses have been described from bats, primates, rodents, horses, bank voles and dogs