Rapid and Sustained Virologic Response of Triple Therapy in Egyptian Patients with Chronic Hepatitis C Virus Infection

Thesis

Submitted for partial fulfillment of Master Degree
In Tropical Medicine

BY: **Amir SamyFily**

M.B.B.CH
Faculty of Medicine-Ain shams University

Supervised by

Professor / Mohammed Kamal Shaker

Professor and head of Tropical MedicineDepartement

Faculty of Medicine-Ain Shams University

Assistant professor /Fatma Ahmed Ali El-Din

Assistant professor of Tropical Medicine

Faculty of Medicine-Ain Shams University

Dr / Mai EsmailMehrez , MD

Fellow of Hepatology medicine

National Hepatology and Tropical Medicine Research Institute

Faculty of Medicine-Ain Shams University
2016

I wish to express my deepest appreciation and sincere gratitude to ***Prof. Dr. Mohammed kamal shaker*** Professor and head of Tropical Medicine Department, Faculty of Medicine, Ain Shams University, for his kind supervision and valuable instructions.

Words can never express my deepest gratitude, appreciation and greatest respect to **Ass. Prof.*DrFatma Ahmed Ali El-Din* Ass. Prof** of Tropical medicine , Faculty of Medicine, Ain Shams University, for her close supervision, continuous guidance, great help and indispensable advice in every step of this work.

I am also delighted to express my supreme gratitude and everlasting appreciation to **Dr. Mai EsmailMehrez** Fellow of Hepatology medicine National Hepatology and Tropical Medicine Research Institute, for her keen supervision, great support, endless help and continuous guidance during all stages of this work.

I am also delighted to express my deep gratitude and thanks to **DR. Rehab Auf** for her great effort in helping us in the statistical analysis. And her valuable time that she gave it.

A special dedication to my family for their never ending care. They were always supporting me and encouraging me to continue and finish this work.

List of Contents

Arabic summary	**--**

List of Abbreviations

AAR	ALT/AST ratio
AASLD	American Association for the Study of Liver Diseases
AFP	α-Foetoprotein
AIH	Autoimmune hepatitis
ALT	Alanine Aminotransferese
ANA	Antinuclear antibody
API	age/platelet index
APRI	AST to Platelet Ratio Index
AST	Aspartate Aminotransferese
BMI	Body Mass Index
CBC	Complete Blood Count
CHB	chronic hepatitis B
CHC	Chronic Hepatitis C
CLD	chronic liver disease
DAA	Direct acting antiviral
EASL	European Association of Study of Liver
ECM	Extracellular Matrix

ELF group	European Liver Fibrosis Group
FRT	Fibrosis routine test
GUCI	Göteborg University Cirrhosis Index
HA	Hyaluronic acid
HbcAg	Hepatitis B core Antigen
HbeAg	Hepatitis B e Antigen
HBIG	hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepato cellular carcinoma
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IFN	Interferon
IgG	Immunoglobulin G
IgM	immunoglobulin M
ISGs	IFN-stimulated genes
INR	International normalized ratio
IRES	Internal ribosome entry site
Kpa	Kilopascals

MAVS	mitochondrial antiviral signalling protein
MMP	matrix metalloproteinases
NHTMRI	National hepatology and tropical medicine research institute
NK cells	natural killer cells
LDL	low-density lipoproteins
LDLR	low-density lipoproteins receptor
MR elastography	Magnetic resonance elastography
NAFLD	Nonalcoholic fatty liver disease
NASH	Non alcoholicsteatohepatitis
NCCVH	National Committee for the Control of Viral Hepatitis
NHANES	National Health and Nutrition Examination Survey
NS	nonstructural proteins
NTR	nontranslated regions
ORFs	open reading frames
PBC	primary biliary cirrhosis
PCR	Polymerase Chain Reaction
PDGF	Platelet deriving growth factor
PICP	Procollagen type I carboxy-terminal peptide

PIIINP	Procollagen type III amino-terminal peptide
PIIINP or P3NP	Procollagen type III amino-terminal peptide
PDCs	plasmacytoid dendritic cells
PT	Prothrombin Time
RBV	Ribavirin
rER	rough endoplasmic reticulum
RIG-I	retinoic acid–inducible gene I
RNA	Ribonucleic acid
RVR	Rapid viral response
SNP	single nucleotide polymorphisms
SVR	Sustained viral response
TGF 1	transforming growth factor 1
TGFα	Transforming growth factor alpha
TGFβ	Transforming growth factor beta
TIMP-1	Metalloproteinase 1
TIMPs	tissue inhibitors of metalloproteinases
TLR3	Toll-like receptor 3
TLR9	Toll-like receptor 9
UTR	*untranslated region*
VCTE	Vibration-Controlled Transient Elastography

VEGF	Vascular Endothelial Growth Factor
VLDL	very low-density lipoproteins

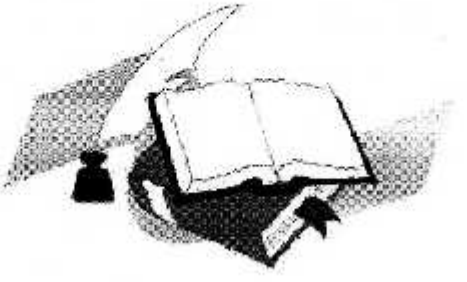
List of tables

(1) Tables in the results and discussion:

List of figures

(1) Figures in the review and results:

Introduction



Introduction

HCV is a global disease whose morbidity and mortality are increasing. The World Health Organization estimated that 3% of the world's population or approximately 130– 170 million people were chronically infected with HCV at the end of the 20th century, and 2.3– 4.7 million new infections per year. Hepatitis C virus is also responsible for 300 000 deaths annually ***(WHO, 1999).***

In Egypt, hepatitis C is highly endemic (up to 15 % of the population) , in 2008, a demographic health survey (DHS) was carried out in Egypt revealing HCV anti-body prevalence nationwide of 14.7 % and HCV RNA of 10% in age group (15–59) ***(El-Zanaty and Way, 2009)***

More than 90 % of Egyptian patients are infected with genotype IV ***(Ray et al., 2000).***

According to this significant burden of HCV, there is anticipated increase of HCV-related cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) over the course of the next decade ***(Maasoumy&Wedemeyer, 2012).***

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. Importantly, long-term benefits of sustained virological response (SVR) are the reduction of HCV-related hepatocellular carcinoma and overall mortality ***(van der Meer et al., 2012).***

Before the identification of HCV as the infectious agent for non-A, non-B hepatitis interferon α (IFN) led to a normalization of transaminases and an improvement of liver histology in some patients (***Choo et al., 1989***).

After the identification of HCV it became possible to measure success of therapy as the long-lasting disappearance of HCV-RNA from serum (SVR). Since then, SVR rates have increased from 5-20% with IFN monotherapy up to 40-50% with the combination of IFN+ ribavirin (RBV) (***McHutchison et al., 2002***)

The development of pegylated interferon α (PEG-IFN) improved the pharmacokinetics of IFN, allowing more convenient dosing intervals and resulting in higher SVR (***McHutchison et al., 2009***).

In HCV genotype VI , the most prevalent in Egypt, According to ***El Makhzangy et al,(2009),*** sustained virologic response in Egyptian patients