ASSOCIATION OF HUMAN CYTOMEGALOVIRUS WITH HEPATITIS C VIRUS INFECTIONS AND ITS IMPACT ON ANTIVIRAL THERAPY

Thesis

Submitted for partial fulfillment of MD degree in Medical Microbiology and Immunology

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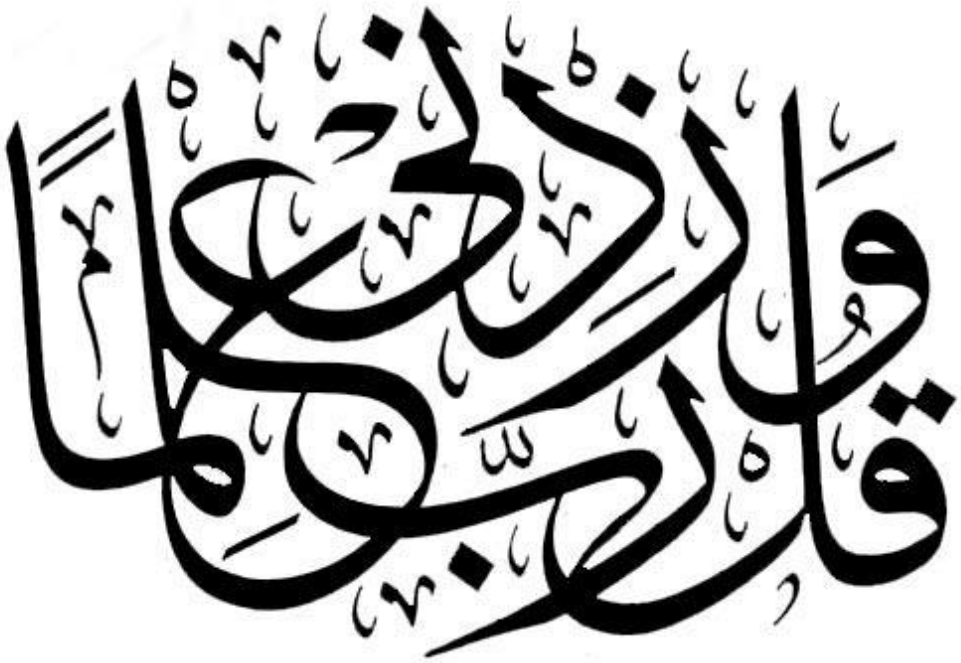

صدق الله العظيم

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Abstract

More than 170 million patients worldwide are chronically infected with HCV. CMV infection enhances HCV pathogenesis. The study was conducted to determine the response rate to treatment with pegylated interferon alpha and ribavirin in chronic HCV patients co-infected with CMV. Fifty cases were included (19 females &13 males) referred to outpatient clinic of the national hepatology and tropical medicine research institute (NHTMRI). The study found that CMV- HCV co-infection is predominant in Egypt, and that CMV co-infection may influence HCV treatment outcome.

Key words: HCV-CMV-Interferon alpha -ribavirin .

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Finally, to the soul of my father, the first to teach me.

SUMMARY

More than 170 million patients worldwide are chronically infected with HCV. Prevalence rates range from 0.5% in Northern European countries to 28% in some areas of Egypt**.** CMV infection enhances HCV pathogenesis by preventing the normal mechanisms responsible for HCV clearance, thus playing vital role in HCV persistence and pathogenicity.

This study was conducted to determine the response rate to treatment regimen of pegylated interferon alpha and Ribavirin in chronic HCV patients coinfected with CMV, and to examine the effect of CMV coinfection on outcome of treatment with pegylated interferon alpha and Ribavirin in chronic HCV patients. The study included a total of 50 cases (19 females and 31 males) with the mean age of 41 ± 10.8 years. They were referred to the Outpatient Clinic of The National Hepatology and Tropical Medicine Research Institute (NHTMRI) to be assessed to start antiviral treatment (pegylated interferon plus ribavirin) based on laboratory and clinical decision.

To examine the role of HCMV infection in HCV response to antiviral therapy, two groups of HCV patients were classified group 1 (positive HCV PCR and negative CMV Ig G) and included 15 patients versus group 2 (positive HCV PCR and positive CMV Ig G) and included 35 patients. On comparing the effect of presence of CMV- on response to combined anti HCV treatment regimen in the 2 studied groups, the non responders were higher in group 2 (65.7 %) than in group 1 (53.3 %) but with no statistical significance.

In conclusion our study found that CMV – HCV coinfection is predominant in Egypt, and CMV co-infection may influence the HCV treatment outcome, despite it failed to have statistical significance.

LIST OF CONTENTS

LIST OF ABBREVIATINS

$	American Dollar
AASLD	The American association for the study of liver diseases
AEs	Adverse effects
AIDS	Acquired immune deficiency syndrome
AFP	Alpha fetoprotein
ALT	Alanine transaminase
APCs	Professional antigen presenting cells
ARFP	Alternate reading frame protein
AST	Aspartate transaminase
C protein	HCV core protein
Cal	Calibrator
CD	Cluster of differentiation
CDC	The centre for disease control and prevention
cDNA	Complementary DNA
CHC	Chronic hepatitis C
CLDN - 1	Claudin – 1
CMV	Cytomegalovirus
CMV - DNA	Cytomegalovirus – Deoxyribonucleia acid
CTL	Cytotoxic CD 8+ T lymphocytes
DAAs	Direct acting antivirals
DCs	Dendretic cells
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
dNTPs	Deoxy nucleotide triphosphates
E1	Membrane associated envelop glycoprotein – 1
E2	Membrane associated envelop glycoprotein – 2
EDHS	The Egyptian Demographic and Health Survey study
EASL	European Association for the Study of the Liver
EGFR	Epidermal growth factor receptor
ELISA	Enzyme Linked Immuno Sorbant Assay
EMA	European medicine association
ER	Endoplasmic reticulum
FDA	Food and drug administration
GAG	Glucoseaminoglycan
GBS	Guillian Barrè syndrome
gH	Glycoprotein H
gL	Glycoprotein L
gB	Glycoprotein B
HAV	Hepatitis A Virus
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCC	hepatocellular carcinoma
HCMV	Human cytomegalovirus
HCMV IE genes	Human cytomegalovirus immediate early genes
HCV	hepatitis C virus
HCV - RNA	Hepatitis C virus – ribonucleic acid
HCV Ab	Hepatitis C Antibody
HIV	Human immunodeficiency virus
HLA	Human leucocytic antigen
HRP-Conjugate	Horse radish peroxidase – conjugate
IAS – USA	International antiviral society – USA
ICU	Intensive care unit
IDSA	Infectious disease society of America
IE1	Immediate early protein 1
IE2	Immediate early protein 2
IFN γ	Interferon gama
IFNs	Interferons
Ig G	Immunoglobulin G
IgM	Immunoglobulin M
IL - 2	Interleukin 2
IL - 6	Interleukin 6
IL - 8	Interleukin 8
IL - 10	Interleukin 10
IL - 12	Interleukin 12
IL - 15	Interleukin 15
IL - 21	Interleukin 21
IL28B gene	Interleukin 28 B gene
IR	Insulin resistance
IRES	Internal ribosome entry site
ISGF3	Interferon stimulated gene factor 3
ISGs	Interferon stimulated genes
ISRE	Interferon stimulated response element
IU/ml	International unit per milliliter
IV	Intravenous
JAK - STAT	Janus kinase – signal transducer and activator of transcription
kPa	Kilopascal
LDL	Low density lipoprotein
LDL – R	Low density lipoprotein receptor
LDs	Lipid droplets
mDCs	Myeloid dendretic cells
MHC	Major histocompatibality complex
miR-122	Micro RNA - 122
ml	Milli liter

Mn_2	Manganese
NAFLD	No n alcoholic fatty liver disease
NF-κB	Nuclear factor κ B
NHTMRI	National hepatology and tropical medicine research institude
NK	Natural killer cell
Nm	Nanometer
NR	Non responders
NS	Non structural protein
NS2	Non structural protein 2
NS3	Non structural protein 3
NS3/4A PIs	Non structural protein 3/4 A protease inhibitors
NS4A	Non structural proteins 4 A
NS4B	Non structural proteins 4 **B**
NS5A	Non structural proteins 5 A
NS5B	Non structural proteins 5 B
NTR	Non translated region
Nt	Nucleotide
OAS1	oligoadenylate synthetase 1
OCLN	Occludin
OD	Optical density
OLT	Orthotropic liver transplantation
ORF	Open reading frame
P48	Protein 48
PAMPs	Pathogen associated molecular patterns
PAT	Parentral anti shistosomal therapy
PCR	Polymerase chain reaction
pDCs	Plasmacytoid dendretic cells
PDGFR α	Platelet derived growth factor receptor alpha
PegIFN	Pegylated interferon
PIs	Protease inhibitors
PKR	Protein kinase R
QS	Quantitation standard
RBCs	Red blood cells
RBV	Ribavirin
RdRNAp	RNA dependant-RNA polymerase
RIBA	Recombinant immunoblot assay
RIG –I	Retinoic acid – inducible gene I
RNA	Ribonucleic acid
RR	Relapsed responders
S/CO	Sample – cut off
SNPs	Single nucleotide polymorphism
SOT	Solid organ transplantation

SR – B1	Scavenger receptor B type 1
SVR	Sustained virological response
TGF -β	Transformation growth factor beta
Th	T helper cells
Th 1	T helper cell type 1
Th 17	T helper cell 17
Th 2	T helper cell type 2
TIMP- 1	Tissue inhibitors of metalloproteinases - 1
TIMPs	Tissue inhibitors of metalloproteinases
TLR -3	Toll like receptor 3
TMA	Transcription mediated amplification
TNF α	Tumor necrosis factor alpha
Treg	T regulatory cells
Tδ	T helper delta subtype
UL	Unique long segment
UL54	Unique long segment 54 gene region
US	Unique short segment
USA	United states of America
UTR	Untranslated reigon
VLDL	Very low density lipoprotein
WHO	World health organization
µl	Micro liter
bDNA	Branched DNA
EIA	Enzyme immunoassay

LIST OF FIGURES

LIST OF TABLES