Correlation Between Serum Neopterin And Response To Treatment of chronic Hepatitis C Virus Infection

Chesis

Submitted for Partial Fulfillment of Master Degree in Internal Medicine

By

Essam Lotfy Abd-Elhamed Eid

M.B, B.Ch Alexandria University

Under Supervision of

Prof. Dr / Rawia Abd El-Salam Ibrahim Elfiky

Professor of Internal Medicine Faculty of Medicine – Ain Shams University

Prof. Dr/ Noha Abd El Razek El Nakeeb

Professor of Internal Medicine Faculty of Medicine – Ain Shams University

Dr/ Mohamed Lotfy Soliman

Lecturer of Internal Medicine Faculty of Medicine – Ain Shams University

Faculty of Medicine

Ain Shams University

2016





First and foremost, I feel always indebted to **Allah** the Most Beneficent and Merciful.

I wish to express my deepest gratitude and thanks to **Prof. Dr / Rawia Abd El-Salam Ibrahim Elfiky,** Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for her constructive criticism, unlimited help and giving me the privilege to work under her supervision.

My most sincere gratitude is also extended to **Prof. Dr/ Noha Abd El Razek El Nakeeb,** Professor of Internal Medicine, Faculty of Medicine – Ain Shams University, for her enthusiastic help, continuous supervision, guidance and support throughout this work.

Words fail to express my appreciation to **Dr/ Mohamed Lotfy Soliman,** Lecturer of Internal Medicine, Faculty of
Medicine – Ain Shams University, for the efforts and time he
has devoted to accomoplish this work.

Last but not least, I can't forget to thank all members of my Family, especially my **Parents** and my **Wife**, for pushing me forward in every step in the journey of my life.

List of Contents

| Subject | Page No. |
|-----------------------|----------|
| List of Abbreviations | i |
| List of Tables | vi |
| List of Figures | ix |
| Introduction | 1 |
| Aim of the Work | 3 |
| Review of Literature | |
| Hepatitis C Virus | 4 |
| Neopterin | 91 |
| Patients and Methods | 109 |
| Results | 115 |
| Discussion | 130 |
| Summary | 144 |
| Recommendations | 147 |
| References | 148 |
| Arabic Summary | — |

List of Abbreviations

List of Abbi eviations

Full-term

AASLD : American Association for the Study of Liver Disease

ADV : Adefovir dipivoxilAFP : Alpha Fetoprotein

Abbr.

AHA : Autoimmune-hemolytic anemia

AHC : Acute Hepatitis C

Alb-IFN : Albumin interferon

ALT : Alanine aminotransferase

ANA : Antinuclear antibodies

ARF : Alternate Reading FrameASH : Alcoholic steatohepatitis

AST : Aspartate aminotransferase

b-DNA : Branched DNA

BID : Twice-a-day

BMI : BodyMass Index

BOC : Boceprevir

BUN : Blood Urea Nitrogen

CBC : Complete Blood Count

cccDNA : Covalently closed circular DNA

CCG : Cysteine- Cysteine-Glycine

CD4 : CD81 Cluster of differentiation 4 and 81

CDC : Center for Disease Control and Prevention, USA

cEVR : Complete early virological response

CHC : Chronic hepatitis C

Abbr. Full-term **CIFN** : Consensus interferon **CNI** : Calcineurin inhibitors **CP** : Child-Pugh : Child-Pugh-Turcotte **CPT DAAs** : Directly acting antivirals \mathbf{DM} : Diabetes Mellitus **DNA** : Deoxy ribonucleic acid E1&E2 : Envelope protein 1 and 2 **EASL** : European Association for the Study of the Liver **EBV** : Epstein-Barr virus **ECG** : Electrocardiogram **EHM** : Extrahepatic manifestation **EIA** : Enzyme Immunoassay **ELISA** : Enzyme linked immunosorbent assay **EMA** : European Medecines Agency : Endoplasmic reticulum ER : Endoscopic retrograde cholangiography **ERC** : Extended rapid virological response eRVR **ETR** : End of Treatment Response

: Early virologic response

: Early Virological Response

: Entecavir

: Everolimus

: Frame shift

ETV

EVL

EVR

EVR

 \mathbf{F}

Full-term

GFR : Glomerular filtration rate

GGT : Gamma Glutamyl Transpeptidase

GH : Growth hormone

Abbr.

GM-CSF : Granulocyte macrophage colony stimulating factor

GN : Glomerulonephritis

GTP : Guanosine Triphosphate

HAART : Highly Active Antiretroviral Therapy

HALT-C: Hepatic C Antiviral Long term Treatment Against Cirrohsis

HBcAgHepatitis B core antigenHBeAgHepatitis B early antigen

HBsAg : Hepatitis B surface antigen

HBV: Hepatitis B virus

HCC: Hepatocellular carcinoma

HCV Abs : Hepatitis C virus antibodies

HCV RNA: Riboneucleic acid of hepatitis C virus

HCV : Hepatitis C virus

Hgb : Hemoglobin

HIV : Human immunodeficiency virus

HRS : Hepatorenal syndrome

I.M : Intramuscular

IASL : International Association for the Study of the Liver

IFN a : Interferon a

IFNα : Interferon Alfa

IGF-1 : Insulin growth factor-1

| Abbr. | Full-term |
|-------|---|
| IgM | : Immunoglobulin M |
| INR | : International normalised ratio |
| IPF | : Idiopathic pulmonary fibrosis |
| ISDR | : Interferon-a Sensitivity Determining Region |
| ITP | : Immune thrombocytopenic purpura |
| IU | : International Unit |
| LAM | : Lamivudine |
| LDL | : Low density lipoproteins |
| LDLT | : Living donor liver transplantation |
| LdT | : Telbivudine |
| LEL | : Large Extracellular Loop |
| LPS | : Lipopolysaccharide |
| LTx | : Liver transplantation |
| MELD | : Model for End-Stage Liver Disease |
| MMWR | : Morbidity and MortalityWeekly Report |
| MPGN | : Membranoproliferative glomerulonephritis |
| NASBA | : Nucleic acid sequence based amplification |
| NASH | : Non-alcoholic steatohepatitis |
| NHL | : Non-Hodgkin lymphoma |
| NIH | : National Institute of Health |
| NNI | : Non-nucleoside inhibitors |
| NPV | : Negative Predictive Value |
| NS | : Non-Structural protein |
| | |

Abbr. Full-term

NS2,NS3, NS4,NS5 Non Structural proteins 2, 3, 4, 5

NTR : Non-translated regions

P7 : Protein 7

PCR : Polymerase chain reaction

PCT: Porphyria cutanea tarda

PDGF: Platelet-derived growth factor

PEG-IFN: Pegylated interferon

PPV : Positive Predictive Value

PT : Prothrombin time

QD : Once-a-day

QW : Once-a-week

RBCs: Red Blood Cells

RBV: Ribavirin

RF : Rheumatoid factor

RIBA : Recombinant ImmunoBlot Assay

RNA : Ribonucleic acid

RT-PCR : Real time polymerase chain reaction

RVR : Rapid virologic response

RVR : Rapid Virological Response

S.C : Subcutaneous

SD : Standard Deviation

SEL : Small Extracellular Loop

SOF : Sofosbuvir

SRL : Sirolimus

| Abbr. | Full-term |
|-------|--|
| SSRI | : Serotonin reuptake inhibitor |
| SVR | : Sustained virologic response |
| TDF | : Tenofovir disoproxil fumarate |
| TGF-β | : Transforming growth factor β |
| TID | : Three times a day |
| TLV | : Telaprevir |
| TMA | : Transcription-Mediated Amplification |
| TSH | : Thyroid-Stimulating Hormone |
| VLDL | : very low-density lipoproteins |
| WBCs | : White Blood Cells |
| WHO | : World Health Organization |
| Wk | : Week |

List of Tables

| Eable No | v. Citle Page No. |
|--------------------|---|
| Table (1): | Extrahepatic manifestations of chronic hepatitis C infection |
| Table (2): | Types of cryoglobulinemia21 |
| Table (3): | Child-Pugh classification of severity of liver disease |
| Table (4): | Serum-based tests recommended in the clinical practice for the detection of significant fibrosis |
| Table (5): | Approved HCV DAAs in Europe in 2016 and ribavirin |
| Table (6): | Relevant definitions for HCV treatment 37 |
| Table (7): | Interferon-ribavirin drug information 44 |
| Table (8): | Common adverse events during therapy with peg-interferon α -2b or -2a plus ribavirin |
| Table (9): | Incidence of most reported IFN α-induced psychiatric side effects |
| Table (10): | Guidelines for adjusting therapy for CBC changes |
| Table (11): | Adverse event profile associated with telaprevir and boceprevir in therapy-naïve patients in clinical studies |
| Table (12): | Adverse Events (All Grades and without Regard to Causality) Reported in ≥15% of Subjects with HCV in Any Treatment Arm 66 |

| Table (13): | Potentially Significant Drug Interactions: Alteration in Dosage or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interactiona |
|--------------------|--|
| Table (14): | Approved HCV drugs in the 69 |
| Table (15): | Treatment recommendations70 |
| Table (16): | Treatment recommendations (for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PagIFN-α and ribavirin (RBV) |
| Table (17): | Comparison between all groups as regards gender |
| Table (18): | Comparison between all groups as regards age |
| Table (19): | Baseline of laboratory investigations114 |
| Table (20): | Comparison between patients and control groups regarding abdominal ultrasonography116 |
| Table (21): | Baseline Liver Biopsy Activity and fibrosis according to metavir score |
| Table (22): | Laboratory investigations after 12 weeks 117 |
| Table (23): | Comparison between baseline of TLC and at week 12 in Early virological Responder and Null responder |
| Table (24): | Comparison between baseline of Neut and at week 12 in Early virological Responder and Null responder |

| Table (25): | Comparison between baseline of haemoglobin concentration at week 12 in Early virological Responder and Null responder |
|--------------------|---|
| Table (26): | Comparison between baseline of PLT and at week 12 in Early virological Responder and Null responder |
| Table (27): | Comparison between baseline of ALT and at week 12 in Early virological Responder and Null responder |
| Table (28): | Comparison between baseline of PCR and at week 12 in Early virological Responder and Null responder |
| Table (29): | Comparison between baseline of Neopterin and at week 12 in Early virological Responder and Null responder |
| Table (30): | Correlation between serum neopterin and different parameters in the studied groups 126 |
| Table (31): | Roc curve between patient and control group as regards neopterin |
| Table (32): | ROC curve between Early virological Responder and Null responder |

List of Figures

| Figure No | . Citle | Page No. |
|---------------------|--|----------|
| Figure (1): | Hepatitis C virus (HCV) model st and genome organization | |
| Figure (2): | HCV-coding proteins and representative direct-acting aragents (DAAs) | ntiviral |
| Figure (3): | Countries by the majority genotype across all associated studies | |
| Figure (4): | Natural History of HCV Infection | 16 |
| Figure (5): | Schematic representation of categories | |
| Figure (6): | Graphic display of virological resp RVR, rapid virological response | |
| Figure (7): | Time course of interferon-asso adverse events | |
| Figure (8): | Genomic organization of HCV | 54 |
| Figure (9): | Molecular structure of the HCV Norotease | |
| Figure (10): | Structure of the HCV NS5B polymerase and binding sites | |
| Figure (11): | Biosynthesis of neopterin derivati human monocytes/macrophages | |
| Figure (12): | Molecular structure of Neopterin | 91 |
| Figure (13): | Comparison between baseline of and at week 12 in Early viro Responder and Null responder | logical |

| Figure (14): | Comparison between baseline of Neut and at week 12 in Early virological Responder and Null responder |
|---------------------|---|
| Figure (15): | Comparison between baseline of HB% and at week 12 in Early virological Responder and Null responder |
| Figure (16): | Comparison between baseline of PLT and at week 12 in Early virological Responder and Null responder |
| Figure (17): | Comparison between baseline of ALT and at week 12 in Early virological Responder and Null responder |
| Figure (18): | Comparison between baseline of PCR and at week 12 in Early virological Responder and Null responder |
| Figure (19): | Comparison between baseline of Neopterin and at week 12 in Early virological Responder and Null responder125 |
| Figure (20): | AUC (area under curve) for neopterin to predict HCV diseased patien |
| Figure (21): | The cutoff value of neopterin to predict sensitivity and specificity of neopterin level in between HCV diseased patients and control |
| Figure (22): | The AUC (area under curve) for neopterin to predict HCV disease from neopterin levels of the patients |
| Figure (23): | The cutoff value of neopterin to predict the difference between EVR and null responder sensitivity and specificity from neopterin levels of HCV diseased patients |