Pretreatment serum ferritin as a predictor of response to pegylated interferon and ribavirin therapy in patients with chronic hepatitis C infection

THESIS
Submitted for Partial Fulfillment of Master Degree in
Tropical Medicine

Presented by Ahmed Salah El Din Hassan M.B., B.Ch.

Under Supervision of
Professor Dr. Ahmed Abbas El-Khatib
Professor of Tropical Medicine
Faculty of Medicine
Ain Shams University

Dr. Ashraf Mohamed Al Breedy Lecturer of Tropical Medicine Faculty of Medicine Ain Shams University

> Faculty of Medicine Ain Shams University 2013





First and foremost thanks to ALLAH, the most merciful.

I wish to express my deepest appreciation and sincere gratitude to **Prof. Dr.Ahmed Abbas El Khattib,** Prof. of Tropical Medicine, Faculty of Medicine, AinShamsUniversity, for his continuous encouragement, kind supervision, valuable instructions and sincere advice which have been the main factors to complete this work. It was a great honor to me to work under his supervision.

Words can never express my deepest gratitude, appreciation and greatest respect to **Dr.Ashraf Mohamed El Breedy**, Lecturer of Tropical Medicine, Faculty of Medicine, AinShamsUniversity, for his close supervision, continuous guidance, great help and indispensable advice in every step of this work. He has generously devoted much of his valuable time, experience and effort for planning and supervision of this work and for presenting it in an ideal form.

I am also delighted to express my deep gratitude and thanks to all my dear professors and my colleagues that without their help, this work could not have been completed.

Last but not least, I would like to thank my mother, her support; encouragement, quiet patience and unwavering love were undeniably the bedrock upon which the past years of my life have been built. I would like to thank my father for his unconditional support, both financially and emotionally throughout my degree.

In particular, the patience and understanding shown by him. Their tolerance of my occasional vulgar moods is a testament in itself of their unyielding devotion and love.

Table of Contents

| Subject | Page no. |
|--|----------|
| Introduction | 1 |
| Aim of work | 4 |
| Review of Literature | 5 |
| Chapter 1: Hepatitis C virus | 5 |
| ➤ Chapter 2: Management of Hepatitis C virus | 38 |
| Patients and Methods | 81 |
| Results | 87 |
| Discussion | 107 |
| Summary | 119 |
| Conclusion and Recommendations | 122 |
| References | 124 |
| Arabic summary | |

List of tables

| Subject | Page no. |
|---|-------------|
| Table (1):Ishak scoring system | 33 |
| Table (2): Metavir scoring system | 34 |
| Table (3): Types of response to the combined therapy | 55 |
| Table (4): Comparison between the demographic data in rapid virological responders <u>vs.</u> non-responders. | 87 |
| Table (5): Comparison between patients with rapid virological response <u>vs.</u> non responders as regards the presence of diabetes and hypertension. | 88 |
| Table (6): Comparison between patients with rapid virological response <u>vs.</u> non responders as regards the type of interferon used. | 88 |
| Table (7): Comparison between liver profile indices in rapid virological responders <u>vs.</u> non responders. | 89 |
| Table (8): Comparison between the liver profile changes during treatment in rapid virological responders <u>vs.</u> non responders. | 89 |
| Table (9): Comparison between baseline hematological profile indices in rapid virological responders <u>VS.</u> non-responders. | 90 |

| Table (10): Comparison between the hematological profile | |
|--|----|
| changes during treatment in rapid virological responders <u>VS</u> .non responders | 90 |
| Table (11): Comparison between renal profile indices in rapid virological responders <u>vs.</u> non responders | 90 |
| Table (12): Comparison between ESR,thyroid profile, liver biopsy, and glucose profile, in rapid virological responders <u>VS.</u> non-responders. | 91 |
| Table (13): Comparison between baseline HCV RNA viral counts in rapid virological responders <u>VS</u> .non-responders. | 91 |
| Table (14): Comparison between Iron Profile indices in rapid virological responders <u>VS.</u> non-responders | 92 |
| Table (15): Comparison between Iron Profile changes during treatment in rapid virological responders <u>VS.</u> non-responders. | 92 |
| Table (16) :Comparison between the demographic data in early virological responders <u>vs.</u> non-responders. | 93 |
| Table (17) :Comparison between patients with early virological response <u>vs.</u> non-responders as regards the presence of diabetes and hypertension. | 93 |
| Table (18) :Comparison between patients with early virological response <u>vs.</u> non responders as regards the type of interferon used. | 94 |
| Table (19) : Comparison between the liver profile indices in early virological responders <u>vs.</u> non-responders. | 94 |

| Table (20) :Comparison between the liver profile changes during treatment in early virological responders <u>vs.</u> non- | 95 |
|---|-----|
| responders. | |
| Table (21) :Comparison between the renal profile indices in early virological responders <u>vs.</u> non responders | 96 |
| Table (22): Comparison between baseline hematological profile indices in early virological responders <u>vs.</u> non-responders. | 96 |
| Table (23): Comparison between the hematological profile changes during treatment in early virological responders <u>vs.</u> non-responders. | 97 |
| Table (24):Comparison between thyroid profile, Glucose profile, ESR and liver biopsy in early virological responders VS.non-responders. | 97 |
| Table (25): Comparison between baseline HCV RNA viral count in early virological responders VS.non-responders. | 98 |
| Table (26): Comparison between Iron Profile indices in early virological responders VS.non-responders. | 98 |
| Table (27): Comparison between Iron Profile changes during treatment in early virological responders VS.non-responders. | 99 |
| Table (28) :Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to demographic factors (using spearman correlation test) | 99 |
| Table (29) :Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to liver biopsy results (using spearman correlation test) | 100 |

| Table (30): Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to liver enzymes at different stages of treatment (using spearman correlation test). | 100 |
|--|-----|
| Table (31): Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to changes in liver enzymes during treatment (using spearman correlation test) | 101 |
| Table (32): Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to hemoglobin levels at different stages of treatment (using spearman correlation test) | 101 |
| Table (33): Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to serum iron levels at different stages of treatment (using spearman correlation test) | 102 |
| Table (34): Correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to Glucose profile (using spearman correlation test) | 102 |
| Table (35): Correlationbetween serum ferritin levelpeak during treatment and BMI (using spearman correlation test) | 102 |
| Table (36): Correlation between serum ferritin level peak during treatment and liver biopsy results (using spearman correlation test). | 103 |
| Table (37): Correlation between serum ferritin level peak during treatment and hemoglobin levels during treatment (using spearman correlation test). | 103 |

| Table (38): Correlation between serum ferritin levels changes during treatment and liver enzymes at different stages of treatment (using spearman correlation test). | 104 |
|--|-----|
| Table (39): Correlation between serum ferritin levels changes during treatment and serum iron levels at different stages of treatment (using spearman correlation test). | 104 |
| Table (40): Analysis of the cutoff value | 106 |

List of figures

| Subject | Page no. |
|---|----------|
| Figure (1):ROC curve analysis showing the diagnostic | |
| performance of Value of ferritin for discriminating early | 106 |
| virological responders at week 12 from non-responders | |

List of Abbreviations

| AIH | Autoimmune hepatitis |
|-------|--|
| ALT | Alanine Aminotransferese |
| ARFP | Alternate Reading Frame Protein |
| AST | Aspartate Aminotransferese |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CD | Cluster of differentiation |
| CHC | Chronic Hepatitis C |
| DC | Delta change |
| DNA | Deoxyribonucleic acid |
| ELISA | Enzyme-linked immunosorbent assay |
| EVR | Early virological response |
| FCH | Fibrosing Cholestatic Hepatitis |
| GGT | Gamma-glutamyl transpeptidase |
| HAV | Hepatitis A virus |
| HBV | Hepatitis B virus |
| HCC | Hepato cellular carcinoma |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| IFN | Interferon |
| IRES | Internal ribosome entry site |
| IL | Interleukin |
| MELD | Model for End-Stage Liver Disease |
| MPGN | Membranoproliferative glomerulonephritis |
| NAFLD | Non-alcoholic fatty liver disease |
| NIH | National Institute of Health |
| NS | Nonstructural |
| PCR | Polymerase Chain Reaction |
| RNA | Ribonucleic acid |
| RVR | Rapid virological response |

List of Abbreviations (cont.)

| SOC | Standard of care |
|-----|--------------------------------------|
| SVR | Sustained virological response |
| TGF | Transforming growth factor |
| Th1 | T- helper cells 1 |
| Th2 | T- helper cells 2 |
| TMA | Transcription-mediated amplification |
| ULN | Upper Limit of Normal |
| UTR | Untranslated region |



Introduction



Introduction

Hepatitis C virus (HCV) infection is a worldwide major health problem. Recent estimates indicate that approximately 130–210 million individuals, i.e. 3% of the world population, are chronically infected with HCV (Shepard et al., 2005 and Lavanchy, 2009). More than 90% of HCV isolates from Egyptian patients are of the genotype 4 variant, which is significant considering that Egypt has the highest worldwide prevalence, with 9% country wide and up to 50% in certain rural areas, due to specific modes of infection (Kamal and Nasser, 2008). Eventually, 20-50% of chronic HCV patient's progress to cirrhosis and 5-7% develop hepatocellular carcinoma within 10-20 years (Mohamed, 2004).

The current treatment for patients with chronic hepatitis C is the combined Ribavirin and Interferon-based therapies for 24 to 48 wk. Antiviral therapy for chronic hepatitis C has many goals; the primary goal is durable viral clearance as evidenced by the absence of HCV RNA in serum (virological response); the secondary goal is reduction of damage to the liver as determined by either persistently normal ALT levels (biochemical response) or improved liver biopsy, with the expectation that this will delay or prevent cirrhosis, HCC, the need for liver transplantation, and