Early on-treatment response as a predictor of sustained virological response in genotype 4 HCV naïve Egyptian patients treated with peginterferon plus ribavirin

Thesis

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Abstract

Background and Study Aims: Effect of peginterferon and ribavirin treatment on chronic hepatitis C virus infection has early been established. However, predictors of treatment success need more elucidation. The present study is directed to estimate the importance of rapid virological response, and other host and viral factors as predictors of sustained virological response in genotype 4 hepatitis C virus naïve Egyptian patients treated with 48 weeks of pegylated interferon and ribavirin.

Patients and Methods: A total of 111 naïve patients with chronic hepatitis C genotype 4 were randomly assigned to 48 weeks of either peginterferon-alpha-2a (180 μg/week) or peginterferon-alpha-2b (1.5 μg/Kg/week) plus weight based oral ribavirin with a 24-week follow-up. The endpoint was the sustained virological response.

Results: Overall, sustained virological response was achieved by 85 patients (70.2%), while 26 patients relapsed (21.5%). Rapid virological response occurred in 95 patients where 77 of them achieved SVR (84.6%) and 14 of them relapsed (15.4%). According to Metavir score, F_3 stage significantly affects sustained virological response compared to stage F_1 with an OR 5.9 (95% CI: 1.1-31.0) and compared to F_2 with an OR 7.2 (95% CI: 1.3-40.9).

Conclusion: Rapid virological response is an independent factor affecting sustained virological response. Also, low pretreatment fibrosis stage is a predictor of sustained virological response.

Keywords: Rapid virological response; sustained virological response; peginterferon; ribavirin

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List of abbreviations

Abbreviations	*Meaning*
AASLD	American Association for the Study of Liver Disease
AFP	Alpha Fetoprotein
AHC	Acute Hepatitis C
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ARF	Alternate Reading Frame
AST	Aspartate aminotransferase
b-DNA	Branched DNA
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCG	Cysteine- Cysteine-Glycine
CD4, CD81	Cluster of differentiation 4 and 81
CDC	Center for Disease Control and Prevention, USA
CHC	Chronic hepatitis C
DM	Diabetes Mellitus
DNA	Deoxy ribonucleic acid
E1&E2	Envelope protein 1 and 2
ECG	Electrocardiogram
EIA	Enzyme Immunoassay
ELISA	Enzyme linked immunosorbent assay
ETR	End of Treatment Response
EVR	Early Virological Response
F	Frame shift
GGT	Gamma Glutamyl Transpeptidase
HAART	Highly Active Antiretroviral Therapy
HALT-C	Hepatic C Antiviral Long term Treatment Against Cirrohsis
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	HepatoCellular Carcinoma
HCV	Hepatitis C Virus
HCV Abs	Hepatitis C virus antibodies
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
I.M	Intramuscular
IASL	International Association for the Study of the Liver
IFNα	Interferon Alfa
INR	International Normalized Ratio
ISDR	Interferon-α Sensitivity Determining Region

Abbreviations	*Meaning*
IU	International Unit
LEL	Large Extracellular Loop
NIH	National Institute of Health
NPV	Negative Predictive Value
NS	Non-Structural protein
NS2,NS3,NS4,NS5	Non Structural proteins 2, 3, 4, 5
P7	Protein 7
PCR	Polymerase Chain Reaction
PEG-IFN	Pegylated Interferon
PPV	Positive Predictive Value
PT	Prothrombin Time
RBCs	Red Blood Cells
RBV	Ribavirin
RIBA	Recombinant ImmunoBlot Assay
RNA	Ribonucleic acid
RT-PCR	Real time polymerase chain reaction
RVR	Rapid Virological Response
S.C	Subcutaneous
SD	Standard Deviation
SEL	Small Extracellular Loop
SVR	Sustained Virological Response
TMA	Transcription-Mediated Amplification
TSH	Thyroid-Stimulating Hormone
WBCs	White Blood Cells
WHO	World Health Organization
Wk	Week
Yr	Year
MMWR	Morbidity and Mortality Weekly Report

Introduction

INTRODUCTION

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) and is a major problem throughout the world. Approximately 500 million persons are living with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, which contribute to nearly 1 million deaths annually ***(CDC, 2012).***

Egyptian Ministry of Health annual report (2007) and El Kady et al. (2009) revealed that Egypt has the highest prevalence of HCV infection worldwide (15%) and interestingly genotype 4 represents over 90% of cases.

Chronic hepatitis C infection may result in serious sequelae, such as end-stage cirrhosis, hepatocellular carcinoma (HCC), need for liver transplantation and premature death ***(Perz et al., 2006).***

Both the National Institute of Health (NIH) and the American Association for the Study of Liver Disease (AASLD) have reported that the most efficacious treatment for this disease is the combination of weekly subcutaneous injections of long-acting pegylated-interferon (PEG-IFN) alfa and oral daily ribavirin, as such, this regimen represents the current standard of care ***(Fried et al., 2002).***

The standard duration of therapy in patients with genotype 4 infection is 48 weeks. This results in an SVR of 40% to 79% ***(Diago et al., 2004; Kamal et al., 2005).***

Early assessment of viral kinetics during treatment accurately predicts response to therapy and provides additional information about how to individualize treatment ***(Ferenci et al., 2005)***. Consequently, duration of therapy may be shortened for patients who respond rapidly and extended for those who respond slowly. Shortened courses of treatment may be useful if adverse effects or costs are an issue and are particularly valuable in patients who experience substantial adverse effects that may pose a health risk if treatment is continued. Thus, Rapid virological response (RVR) provides complementary information and represents a key opportunity to individualize treatment and improve the benefit/risk ratio of therapy. RVR, defined as an undetectable serum HCV RNA level at week 4 of treatment ***(Poordad et al., 2008)***.

Review of Literature