Assessment of Hematological Side Effects of Combined Pegylated Interferon & Ribavirin in Treatment of HCV in Egypt

Thesis

Submitted for partial fulfillment of Master Degree in Tropical Medicine

By

Mostafa Abdelfattah Ismail Ahmed

M.B.B.CH

Assiut University

Supervised by

Professor Doctor/ Eman Mahmoud Fathy Barakat

Professor of Tropical Medicine
Faculty of Medicine - Ain Shams University

Doctor / Runia Fouad El-Folly

Assistant Professor of Tropical Medicine
Faculty of Medicine - Ain Shams University

Doctor / Adham Mohamed Hamdan EL-Nakeeb

M.D. Tropical Medicine
Head of Hepatology & Gastroenterology Department
Sohag Center of Cardiac and Digestive System
Specialized Medical Centers, Ministry of Health and Population

Ain Shams University

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Mostafa Abdel Fattah

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List of Abbreviations

AA	Amino acid
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
Anti HBC	Hepatitis(B) core antibody
AST	Aspartate aminotransferase
CDC	Centers for disease control and prevention.
CHF	Congestive heart failure
CITP	Chronic idiopathic thrombocytopenia
CLD	Chronic liver disease
CTL	Cytotoxic t-lymphocytes
DAA	Direct acting antiviral
ECG	Electrocardiogram
ETR	End of treatment response
EVR	End virological response
FDA	Food and drug administration
GP	Glycoprotein
Hb	Hemoglobin
HBs Ag	Hepatitis (B) surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HCWs	Health care workers
HD	Haemodialysis
HIV	Human Immunodeficiency Virus
IDUs	Intra venous drug users
IFN	Interferon
IRES	internal ribosome entry site
IVIG	Intravenous immunoglobulins

NI	Nucleoside inhibitors
NK	Natural killer
NNI	Non nucleoside inhibitors
ORF	Open reading frame
PAMPs	pathogen-associated molecular patterns
PAT	Parentral antishistosomal therapy
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PEG-IFN	Pegylated Interferon
PEG-rhMGDF	Pegylated recombinant human megakaryocyte growth and development factor
PI	Protease inhibitors
PT	Prothrombin time
RBCs	Red blood cells
RBV	Ribavirin
RDW	Red cell distribution width
RNA	Ribonucleic amino-acid
RVR	Rapid virological response
SNPs	Single nucleotide polymorphisms
SOC	Standard of care
SVR	Sustained virological response
TCP	Thrombocytopenia
TIBC	Total iron binding capacity
TNF	Tumor necrosis factor
TPO	Thrombopoietin
TSH	Thyroid stimulating hormone
UTR	Untranslated region
WBC	White blood cell
WHO	World Health Organization

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Specialized Medical Centers, Ministry of Health and Population
Faculty of Medicine

Ain Shams University

2011

Introduction:

Hepatitis C virus (HCV) infection is a global health problem, with an infection rate of 3% of the world's population equating to 170-200 million individuals ***(WHO, 2009).*** Egypt has the highest prevalence of hepatitis C in the world, reaching 13% of the population equating to an estimated 10 million anti-HCV-positive persons ***(Deuffic-Burban, 2006; Mohamed, 2004).***

Almost 90% of HCV infections are caused by genotype 4, which is the major cause of the high prevalence of liver cirrhosis, hepatocellular carcinoma and liver transplantation in the country ***(Ezzat et al., 2005; Kamal et al., 2008)***

The currently recommended combination therapy of pegylated IFN and ribavirin (1000–1200 mg/ day) for 48 weeks increased SVR rates to almost 40% ***(Kamal and Nasser, 2008).*** Larger controlled well-designed randomized clinical trials reported higher SVR rates ranging between 48 and 79% in patients receiving PEG-IFN a-2b plus ribavirin (800–1200 mg/day) for 48 ***weeks (Ferrenci and Laferl, 2008; Jessner et al., 2008; El-Zayadi et al., 2005).***

Sustained virologic response rates in chronic hepatitis C genotype 4 are better than those achieved in genotype 1 ***(Kamal et al., 2008; Ferrenci et al., 2008; El-Zayadi et al., 2005).***

In patients with chronic hepatitis C, the on-treatment response at weeks 4 and 12 of pegylated interferon plus ribavirin combination therapy may be used to predict the probability of a sustained virologic response (SVR) ***(Jensen et al., 2006).***

Unfortunately, peg-interferon plus ribavirin therapy can be associated with side effects, some of which may lead to dose reductions, premature discontinuation of the drug, and subsequent treatment failure ***(Sulkowski et al., 2004).*** IFN induced thrombocytopenia and leucopenia is common whereas anaemia is more a sequela of combination therapy with ribavirin (***Russo and Fried, 2003; Fried et al 2002).***

Thrombocytopenia is mild in most cases, amounting to a decrease in peripheral platelet count of 10–50% but, when severe, can lead to bleeding complications (***Soza et al., 2002; Wang et al, 2000***) and discontinuation of IFN therapy (***McHutchison et al., 2002***).

Absolute neutrophil and lymphocyte counts typically decrease by 30–50% of baseline values during IFN therapy but this is usually not associated with infection ***(Schmid et al., 2005)***.

The main mechanism leading to cytopenia during IFN therapy seems to be bone marrow suppression by IFN- (***Russo and Fried, 2003***). This suppressive action can be observed for pluripotent progenitor cells of all lineages (***Soza et al., 2002***). Immune mediated haematological toxicity and capillary sequestration of platelets and white blood cells (***Wang et al., 2000***) have been proposed as additional causes for severe thrombocytopenia and leucopenia during IFN therapy.

Ribavirin is associated with dose-dependent hemolytic anemia, which occurs in a considerable proportion of treated patients (***Sulkowski et al., 2004).*** Although treatment related

side effects can make therapy unpleasant, most do not necessarily lead to disruption or discontinuation of therapy. However, hemolytic anemia associated with ribavirin frequently leads to ribavirin dose reductions. Indeed, in a peg-interferon alfa-2a pivotal trial, it was reported that patients receiving peg-interferon alfa-2a plus ribavirin had a median maximal decrease in hemoglobin of 3.7 g/dL, and this resulted in a ribavirin dose modification in 22% of patients ***(Fried et al., 2002).***

Retrospective analyses of patients receiving combination therapy with ribavirin and interferon alfa-2b confirm the frequent occurrence of anemia. More than 50% of patients experienced a decrease in hemoglobin of 3.0 g/dL ***(Sulkowski et al., 2004),*** and, in another study, by 24 weeks of treatment ribavirin dose reduction was required in 27.6% of patients, with a mean maximal decrease in hemoglobin of 4.0 g/dL (***Takaki et al., 2004***).

Khuroo and Dahab, (2004) confirmed the importance of adequate ribavirin dosing, with higher SVR rates in patients receiving PEG-IFN-a in combination with high-dose (1000–1200 mg/day) than low-dose (800 mg/day) ribavirin. The traditional approach to hematologic toxicity has been reducing the dose of the offending antiviral; however, lower doses also may reduce treatment efficacy ***(Davis et al., 2003).***

The use of epoetin alfa (Epogen) at a dose of 40,000 units subcutaneously once per week is effective in increasing the hematocrit level in patients receiving treatment and in reducing

the number of patients who require reductions or discontinuations of their ribavirin ***(Afdhal et al., 2004).***

Interferon-induced neutropenia may put the patient at increased risk for bacterial infections, although other data suggest this risk is small (***Soza et al., 2002).***

Granulocyte colony-stimulating factor (G-CSF) treatment may prove useful in increasing the white blood cell count, and a reasonable approach is to maintain the neutrophil count above 500 per μL (0.5×10^9 per L). Studies clarifying the optimal dose and the levels of neutropenia at which to intervene are not yet available. Most of the increased risk of infection is confined to those with liver cirrhosis, suppressed immune systems, or profound neutropenia. The use of G-CSF or epoetin alfa will substantially increase the overall cost of treatment. Treatment-induced thrombocytopenia usually is mild and rarely leads to clinically significant bleeding ***(Ward and Kugelmas, 2005).***

In Egypt, the availability and cost of treatment for hepatitis C in is quite prohibitive. It is thus very important to optimize treatment to increase the chances of a sustained virologic response. Early prediction and management of adverse events is thus crucial for therapy adherence and better outcome. The frequency of hematologic adverse events has not been previously studied in chronic hepatitis C genotype 4 patients and no predictors for interferon induced anemia, leucopenia or thrombocytopenia have been identified in those patients.

Aim of The Work

The current study is designed to assess:

1- The incidence and prevalence of hematological side effects of combined pegylated interferon and ribavirin during treatment of Hepatitis (C) virus infection.

2- The impact of hematological side effects of combined pegylated interferon and ribavirin on ETR, RVR, EVR and SVR during treatment of Hepatitis (C) virus infection.