

HEMATOLOGICAL COMPLICATIONS OF CHRONIC HCV INFECTION AND ITS TREATMENT

Essay

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By

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ABSTRACT

Background/Aim: Hepatitis C virus (HCV) infection has been reported to cause many extrahepatic complications including hematological complications such as anemia, thrombocytopenia and leucopenia. Interferon-based regimens were reported to induce high incidence of hematological side effects with eventual dose reduction in 40 % of patients with consequent 10-20% reductions in the virological responses achieved. We conducted this research to explore information about these hematological adverse effects related to hepatitis C virus infection in addition to those related to combined antiviral therapy.

Methods: The current essay introduces formulation of problem, possible methods of interference to overcome it, via search on Medical database such as Pubmed, MD consult, Up to date and Medline for the period between 1999 and 2010.

Summary: Among non cirrhotic INF naive chronic HCV, anemia, thrombocytopenia and neutropenia were reported in about 40-50 %, 13-17% and 5-9% respectively, while in those receiving antiviral therapy they were detected in about 39%, 10-15% and 8-24% respectively. Hematopoietic growth factors including recombinant *erythropoietic growth factors* (rHuEPO) and Granulocyte colony-stimulating factor (G-CSF) were generally well tolerated and may be useful for managing hematological side effects of anti-HCV therapy. However, their positive impact on SVR is not substantiated by studies to date.

Conclusion: Hematological complications that occur with chronic HCV or with interferon based therapy are frequent. Careful monitoring of hematological indices in chronic HCV infection with identifying possible risk factors for the development of hematological complications is highly recommended.

Key words:

(Hepatitis C Virus - anemia, Thrombocytopenia, neutropenia, granulocyte colony- stimulating factor, erythropoietic growth factors)

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List of Abbreviations

Abbreviation	
AIHA	<i>Autoimmune hemolytic anemia</i>
ALT	<i>Alanine aminotransferase</i>
ANA	<i>Anti-nuclear antibody</i>
ANC	<i>Absolute neutrophil count</i>
ASH	<i>American Society of Hematology</i>
AST	<i>Aspartate aminotransferase</i>
CITP	<i>Chronic idiopathic thrombocytopenia</i>
COPD	<i>Chronic obstructive pulmonary disease</i>
DNA	<i>Double-stranded nuclear amino acid</i>
EMC	<i>Essential mixed cryoglobulinemia</i>
ESRD	<i>End-stage renal disease</i>
EVR	<i>End virological response</i>
FDA	<i>Food and Drug Administration</i>
G-CSF	<i>Granulocyte colony stimulating factor</i>
HB	<i>Hemoglobin</i>
HBV	<i>Hepatitis B Virus</i>
HCC	<i>Hepatocellular carcinoma</i>
HCV	<i>Hepatitis C Virus</i>
HIV	<i>Human Immunodeficiency Virus</i>
ICs	<i>Immune-complexes</i>
IFN	<i>Interferon</i>

IgM	<i>Immunoglobulin M</i>
IMPDH	<i>Inosine monophosphate dehydrogenase enzyme</i>
ITPase	<i>Inosine triphosphatase</i>
IVIG	<i>Intravenous immunoglobulins</i>
LDH	<i>Lactate dehydrogenase</i>
MALT	<i>Mucosa-associated lymphoid tissue</i>
MGUS	<i>Monoclonal gammopathy of uncertain significance</i>
MGN	<i>Membranous glomerulonephritis</i>
MPGN	<i>Membranoproliferative glomerulonephritis</i>
mRNA	<i>messenger ribonucleic amino-acid</i>
NHL	<i>Non Hodgkin lymphoma</i>
NIH	<i>National Institute of Health</i>
PCR	<i>Polymerase chain reaction</i>
PCT	<i>Porphyria cutanea tarda</i>
PEG- IFN	<i>Pegylated Interferon</i>
PET	<i>Positron-Emission tomographic scan</i>
PRCA	<i>Pure red cell aplasia</i>
PT	<i>Prothrombin time</i>
RBCs	<i>Red blood cells</i>
RBV	<i>Ribavirin</i>
RDW	<i>Red cell distribution width</i>
RF	<i>Rheumatoid factor</i>

RNA	<i>Ribonucleic amino-acid</i>
RVR	<i>Rapid virological response</i>
SNP	<i>Single nucleotide polymorphisms</i>
SVR	<i>Sustained virological response</i>
TCP	<i>Thrombocytopenia</i>
TIBC	<i>Total iron binding capacity</i>
TPO	<i>Thrombopoietin</i>
WHO	<i>World Health Organization</i>
WK	<i>Week</i>
WM	<i>Waldenstrom macroglobulinemia</i>

INTRODUCTION

Infection with hepatitis C virus (HCV) is an increasing epidemic with over 170 million people infected worldwide (**Purcell, Walker, 2008**). Infection with HCV persists in about 75% of cases and causes various degrees of liver inflammation and fibrosis; in time it may lead to cirrhosis and hepatocellular carcinoma (**Lauer, Walker, 2001**).

The primary aim of anti-HCV therapy is permanent eradication of the virus or a sustained viral response there by reducing the risk of progression to end-stage liver disease and improving quality of life. The most effective treatment for chronic HCV infection at present is the combination of pegylated interferon (PEG-IFN) α -2a or α -2b and ribavirin (RBV). Both drugs have a significant effect on virological and histological responses and provide a SVR rate of 40% up to 80% in patients with HCV genotypes 2 and 3 (**Davis et al., 2003**).

However, these drugs together with HCV itself have been reported to cause multiple hematological side effects that result in high rates of dose reduction and discontinuance of treatment. Among these are anemia, neutropenia and thrombocytopenia (**Dieterich, Spivak, 2008**). The SVR rate decreases dramatically when adherence to treatment is not optimal (**Castera et al., 2006**).

Management of these hematological side effects of antiviral therapy for HCV infection can be an important strategy for maximizing treatment outcomes.

AIM OF THE WORK

Our research aims to explore the hematological adverse effects related to hepatitis C virus infection in addition to those related to combined antiviral therapy and possible measures to overcome such adverse effects.

HEMATOLOGICAL COMPLICATIONS RELATED TO CHRONIC HEPATITIS C Virus INFECTION

Hepatitis C Virus Overview:

Egypt has the largest epidemic of hepatitis C virus (HCV) in the world. The overall prevalence positive for antibody to hepatitis C Virus in Egypt is, 14.7 %. HCV infects approximately 170 million individuals worldwide. Chronic HCV infection has been estimated to be responsible for approximately 250 000 to 350 000 deaths per year, essentially related to decompensation of cirrhosis, end-stage liver disease and hepatocellular carcinoma. **(El-Zanaty et al., 2009), (Purcell , Walker, 2008).**

HCV is a single-stranded RNA virus belonging to the Flaviviridae family, genus Hepacivirus. Six HCV genotypes (1-6) and a large number of subtypes (1a, 1b, 1c, etc.) have been identified **(Penin et al., 2004)**

The most prevalent genotype in Egypt is genotype 4. Hepatitis C virus genotype/subtype was determined in 129 HCV-infected patients residing in three governates in south Egypt: Assuit, Sohag, and Qena. Genotype 4a was detected in 80.6%, whereas 1g, 4n, 4o, 4f, and 4m were identified in 7.7%, 3.9%, 1.6%, 0.8%, and 0.8% of cases, respectively. **(Moustafa et al., 2009)**

The known modes of transmission of HCV infection include injection drug use, blood and blood products transfusion, organ transplantation, iatrogenic medical or dental exposure including needles or syringes, hemodialysis equipment play another

important role in this field. Also one should take in consideration sharing personal care items, body piercing and Tattoos, mother-to-child transmission as other well known methods of transmission. Regarding sexual transmission of HCV, it was recently proved to be rare. **(Lauer, Walker, 2001)**

Clinically, HCV infection can present either in an acute form or in a chronic one which may be complicated with liver cirrhosis or liver cancer **(Lauer et al., 2001)**.

Chronic Hepatitis C:

Is defined as; infection with hepatitis C virus persisting for more than six months. Clinically, it is often asymptomatic and it is mostly discovered accidentally (e.g. usual checkup). **(Villano et al., 1999)**.

Evidenced data suggest that among untreated patients, roughly one-third progress to liver cirrhosis in less than 20 years, another third progress to cirrhosis within 30 years. The remainder of patients appears to progress so slowly that they are unlikely to develop cirrhosis within their lifetimes. The NIH consensus guidelines state that the risk of progression to cirrhosis over a 20-year period is 3-20 percent. **(Zheng et al., 2002)**

Liver cancer can be linked to cirrhosis mostly due to viral etiology in over 80 percent of cases, according to the National Liver Foundation **(Rambusch et al., 2001)**.

Extrahepatic manifestations of HCV infection are varied and involve a number of organ systems. Physicians and patients should be aware of these signs and symptoms, and testing for