Prevalence of Occult Hepatitis B Among HCV Patients Resistance to Antiviral Therapy

Thesis

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List of Abbreviations

AASLD	American Association for Study of Liver Diseases
ADV	Adefovir
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
anti-HBs	Hepatitis B surface antibody
AST	Aspartate aminotransferase
BCP	Basic core promoter
BMI	Body mass index
cccDNA	Covalently-closed-circular DNA
CBC	Complete blood count
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CT	Computerized Tomography
CTL	Cytotoxic T lymphocytes
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of Liver
EIAs	Enzyme immunoassay
ETV	Entecavir
FDA	Food and Drug Association
HAI	Histological activity index
HB	Haemoglobin
HBcAb	Hepatitis B core antibody
HBcAg	Hepatitis B core antigen

HBeAb	Hepatitis B e-antibody
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B Immune Globulin
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
IDUs	Injecting drug users
IFN- α	Interferon alpha
IFN-β	Interferon beta
IFN- γ	Interferon gamma
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INR	International normalized ratio
LMV	Lamivudine
MRI	Magnetic resonance imaging
mRNA	messenger ribonucleic acid
OBI	Occult hepatitis B infection
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction

PEG-IFN	Pegylated interferon
PLT	Platelets
PV	Portal vein
RBCs	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
SPSS	Statistical package for the social science software
SVR	Sustained virological response
TC	Total cholesterol
TGs	Triglycerides
TNF-α	Tumor necrosis factor alpha
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
UV	Ultraviolet
WBCs	White blood cells
WHO	World Health Organization

INTRODUCTION

Human hepatitis B virus (HBV) is a compact, partially double-stranded, enveloped, deoxyribonucleic acid (DNA) virus; member of the hepadnaviridae family, of approximately 3,200 nt. HBV infection is world wide spread and is considered a major public health problem, with an estimation of 350 million people chronically infected. The HBV replicates in the liver leading to hepatic dysfunction. Persistent HBV infection is associated with the development of chronic liver disease, including cirrhosis and hepatocellular carcinoma ***(Ganem and Prince, 2004)***.

Among the many viruses that are known to infect the human liver, hepatitis B virus and hepatitis C virus (HCV) are unique because of their prodigious capacity to cause persistent infection, cirrhosis, and liver cancer. HBV is noncytopathic viruse and thus immunologically mediated events play an important role in the pathogenesis and outcome of this infection ***(Guidotti and Chisari, 2006).***

As the treatment for chronic hepatitis C virus infection has improved over the last 2 decades, the number of patients for whom therapy fails has declined substantially. However, more than half of patients with HCV infections fail to achieve a sustained virological response (SVR) to pegylated interferon (PEG-IFN) and ribavirin (RBV) ***(Gara and Ghana, 2012).***

Subjects for whom combination therapy fails are a heterogeneous group and include individuals who experience virological breakthrough (detectable HCV RNA(ribonucleic acid) in serum during therapy after the achievement of an initial response) or virological relapse (the reappearance of HCV RNA in serum after the discontinuation of treatment and the achievement of an end of-treatment response) as well as individuals who fail to achieve an initial virological response [i.e., partial responders (≥2-log IU/mL decline in HCV RNA from the baseline to treatment week 12 but detectable HCV RNA at week 24) and null responders (≤2-log IU/mL reduction inHCV RNA from the baseline to treatment week 12] ***(Shiffman et al., 2007).***

The reasons for treatment failure are not well understood. Until recently, retreatment options were limited for persons for whom a PEG-IFN/RBV regimen failed. Studies evaluating retreatment with PEG-IFN and RBV yielded SVR rates of only 6% to 9% in partial and null responders and 33% in prior relapsers with an HCV genotype 1 infection ***(Jensen et al., 2009).***

In comparison with standard therapy, a higher dose of PEG-IFN as induction therapy had no effect on either the end-of treatment response rate or the SVR rate. However, extending therapy to 72 weeks resulted in a marginal increase in the SVR rate from 9% to 16%, primarily because of the prevention of

virological relapse. Similarly, a different preparation of interferon, consensus interferon, was minimally effective ***(Gara and Ghana, 2012).***

Occult hepatitis B virus (HBV) infection (OBI) is one of the most challenging topics in the field of viral hepatitis with its virological and clinical relevance being debated for more than 30 years. Initially described in the late 1970s, this form of hepatitis B infection has now been further characterised. In particular, in the last 10 years the application of highly sensitive molecular biology techniques has resulted in the elucidation of its virological features and possible clinical implication ***(Hollinger, 2008).***

Occult hepatitis B virus infection is characterized by the persistence of HBV DNA in the liver and serum of individuals negative for HBV surface antigen (HBsAg). Recent data demonstrated that occult HBV may exist in the hepatocytes as a free genome, its molecular basis being related to the long term persistence in the hepatocyte nuclei of the viral covalently-closed-circular DNA, a replicative intermediate that serves as template for gene transcription ***(Raimondo et al., 2007).***

The European Association for the study of the liver (EASL) defined occult hepatitis B virus infection (OBI) as the "presence of hepatitis B virus (HBV) DNA in the liver (with detectable or undetectable HBV DNA in the serum) of

individuals testing hepatitis B surface antigen (HBsAg) negative by currently available assays" ***(Ocana et al., 2011).***

On the basis of the HBV antibody profile, occult hepatitis B infection may be distinguished as:

a. Seropositive-OBI (anti-HBc and/or anti-HBs positive).

b. Seronegative-OBI (anti-HBc and anti-HBs negative).

In seropositive-OBI subjects, serum HBsAg may become negative either following the resolution of acute hepatitis B (thus, after a few months of HBsAg carriage) or after years of chronic HBsAg positive infection ***(Chen et al., 2002)***.

The seronegative-OBI cases might have either progressively lost the hepatitis B specific antibodies or theoretically, the individual may have been hepatitis B specific antibody negative from the beginning of the infection ***(Michalak et al., 2004).***

Occult HBV has important clinical implications such as transmission through blood transfusion, reactivation in the setting of immunosuppression and interference with hepatitis C treatment. To date, there is little date pertaining to the treatment of occult HBV outside of the setting of chemotherapy-induced HBV reactivation ***(Paul and Kenneth, 2010).***

The presence of occult hepatitis B, with its added deleterious effect, must always be considered in chronic hepatitis C patients especially those with flare in liver enzymes; HBsAg should not be used alone for the diagnosis of HBV infection ***(Selim et al., 2010).***

The probable impact of occult HBV in patients with chronic HCV infection has been previously investigated and the evidence suggests a possible correlation with lower response to anti-viral treatment, higher grades of liver histological changes, and also developing hepatocellular carcinoma. However, in the absence of conclusive results, further studies should be conducted to absolutely assess the impact of occult HBV contamination on the HCV related liver disease ***(Habibollahi et al., 2009).***