STUDY OF THE RELATIONSHIP BETWEEN THE PRESENCE OF HEPATITIS B CORE ANTIBODY IgG AND THE RESPONSE OF GENOTYPE-4 CHRONIC HEPATITIS C PATIENTS TO INTERFERON COMBINATION THERAPY

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LIST OF ABBREVIATIONS

anti-HBc	Anti hepatitis B core antibodies
BCP	Basic Core Promoter
BMI	Body mass index
cccDNA	covalently closed circular deoxyribonucleic acid
CHC	Chronic hepatitis C
DNA	Deoxyribonucleic acid
EIA	Enzyme immunoassay
ETVR	End treatment virologic response
EVR	Early virolgic response
HAI	Histologic activity index
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-Ab	Anti hepatitis C antibodies
HDV	Hepatitis D virus
HIV	Human immunodefficiency virus
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M

ISGs	Interferon-stimulated genes
NIH	National institute of health
NPV	Negative predictive value
NS	Non significant
OLT	Orthotopic liver transplantation
ORF	open reading frame
PCR	Polymerase chain reaction
PEG-IFN	Pegylated interferon
PPV	Positive predictive value
RNA	Ribonucleic acid
RT	Real time
S	Significant
SVR	Sustained virolgic response
TMA	Transcription-mediated amplification

INTRODUCTION

Hepatitis C virus (HCV) is a parenterally transmitted hepatotropic pathogen. HCV infection is a major health problem worldwide, frequently causing cirrhosis and liver cancer (***Amador-Canizares***, ***2006***).

Hepatitis C virus and hepatitis B virus (HBV) infections account for a substantial proportion of liver diseases worldwide. Because the two hepatotropic viruses share same modes of transmission, coinfection with the two viruses is not uncommon, especially in areas with a high prevalence of HBV infection and among people at high risk for parenteral infection ***(Zhihua et al., 2006)***.

There is no preventive vaccine against HCV. The current treatment of chronic hepatitis C is based on interferon alpha plus ribavirin which is generally effective in less than 50% of cases. HCV has evolved mechanisms for surviving in the host. Infection with multiple different HCV variants, as well as interaction with concurrent pathogens might be successful strategies for viral persistence (***Amador-Canizares***, ***2006***).

The presence of isolated anti-HBc antibodies has been reported in HBsAg-seronegative subjects which may be an indicator of occult hepatitis B, immunity of HBV after recovery or false anti-HBc test result. The presence of isolated anti-HBc antibodies

IgM may be an indicator of a window phase of acute HBV infection ***(Lok and McMahon, 2007)***.

The current study concerns only the presence of anti-HBc IgG antibodies in chronic hepatitis C patients.

Chronic hepatitis C (CHC) patients frequently have antibodies to hepatitis B core antigen (anti-HBc) indicative of prior HBV infection ***(Myers et al., 2003)***. Impact of previous HBV infection on hepatitis progression and response to interferon based therapy remains controversial ***(Kao et al., 2002)***. Many authors reported diminished response to interferon (IFN) therapy in anti-HBc seropositive CHC patients (***Santoro et al.***, ***1992; De et al.***, ***2000***; ***Sagnelli et al.***, ***2001***; ***Berberova et al.***, ***2003***), while others concluded that the presence of anti-HBc antibodies may not affect the outcome of interferon therapy (***Kao et al.***, ***2002***; ***Myers et al.***, ***2003***; ***Silva et al.***, ***2004***).

Sagnelli et al., (2001) reported poor response to IFN-α in CHC patients with negative hepatitis B surface antigen (HBsAg) and positive anti-HBc antibodies irrespective of HCV genotype. They suggested that isolated anti-HBc in hepatitis C patients might be explained by the fact that hepatitis C virus interferes with HBV replication. In such cases, low levels of HBV-

deoxyribonucleic acid (DNA) would remain in the hepatocytes, explaining the severity of the disease and its association with HCC as well as the poor response to interferon therapy (***Sagnelli et al.***, ***2001***).

In another study conducted by ***De et al., (2000)***, they concluded that one third of individuals with CHC have serological markers of HBV infection, independent of the prevalence of HBV infection in the general population. The response rate to IFN-α treatment in anti-HBc-positive individuals is reduced as compared to those without evidence of a previous HBV infection. This impaired response may be related to the persistence of HBV-DNA in the liver.

On the other hand, ***Myers et al., (2003)*** reported similar sustained virologic response (SVR) in anti-HBc seropositive and anti-HBc seronegative CHC patients to IFN-based therapy.

Also, ***Kao et al., (2002)*** reported comparable response to combination therapy against hepatitis C between patients with and without occult HBV.

AIM OF WORK

The current work aimed to evaluate the relationship between the response to interferon-ribavirin combination therapy and the presence of anti-HBc IgG antibodies in HBsAg seronegative chronic hepatitis C genotype-4 patients.

HEPATITIS C VIRUS

Hepatitis C virus is a member of the Falviviridae family, genus Hepacivirus (***Robertson et al., 1998)***. HCV is a 60 nm spherical enveloped single strand ribonucleic acid (RNA) of positive polarity genome composed of □10,000 nucleotides and a large open reading frame (ORF) (***Choo et al., 1991)***. There are six major groups or genotypes numbered 1 to 6, although some experts believe that there may be as many as eleven. These genotypes can differ up to 30% from each other in nucleotide sequence. Within each genotype, there are further divisions called subtypes and quasispecies ***(Bukh et al., 1995; Robertson et al., 1998)***.

Epidemiology

The estimated global prevalence of HCV infection is 2.2%, corresponding to about 130,000,000 HCV-positive persons worldwide (***Alter***, ***2007***). The highest prevalence (15%-20%) has been reported from Egypt (***Frank et al.***, ***2000***; ***Perz et al.***, ***2006***).

There are both geographic and temporal differences in the patterns of HCV infection (***Wasley and Alter***, ***2000***). In Egypt, the prevalence of infection increases steadily with age, and high rates of infection are observed among persons in all age groups

(Abdel-Aziz et al., 2000; Frank et al., 2000). This pattern of distribution of HCV infection in Egypt indicates an increased risk in the distant past followed by an ongoing high risk for acquiring HCV infection, although there are regional differences in average overall prevalence ***(Medhat et al., 2002; Perz et al., 2006)***. There has been an ongoing high risk of HCV infection for decades in Egypt and therefore the high magnitude of the current burden of HCV-related chronic disease is predicted to continue into the future (***Deuffic-Burban et al.***, ***2006***)

Different HCV genotypes prevail in different parts of the world (Box 1). Genotype-4a constitutes the majority of infection in Egypt (***Nguyen and Keeffe***, ***2005; Kamal and Nasser***, ***2008***).

Box (1): Geographical distribution of HCV genotypes

HCV Genotype	**Distribution**
1, 2, 3	Worldwide
4	Middle East, Africa
5	South Africa
6	Southeast Asia

Natural history and pathogenesis

Hepatitis C Virus transmission occurs primarily through exposure to infected blood. This exposure exists in the form of injectable drug use, blood transfusion and solid organ transplantation from infected donors before 1992, unsafe medical practices and occupational exposure to infected blood (***Pawlotsky***, ***2006***).

After acute infection, only a small proportion of patients recovers and test negative for HCV-RNA using standard diagnostic assays. Viral clearance from the liver, and possibly from other reservoirs, probably takes longer than viral clearance from the blood ***(Bigger et al., 2001)***. In general, prospective studies have shown that 60%–85% of HCV infected people develop chronic infection (***Muir***, ***2000***; ***Thomas et al.***, ***2000***).

The pathogenesis of chronic hepatitis and cirrhosis is thought to be immune mediated. The pathogenesis of hepatitis itself is not a direct cytopathic effect of HCV as it replicates in the cytoplasm of hepatocytes and the virus are released from the cell by budding. The most important sequels of chronic HCV infection are progressive liver fibrosis leading to cirrhosis and end-stage liver disease and hepatocellular carcinoma (HCC). HCC almost always develops on the background of liver cirrhosis in patients with chronic hepatitis C and rarely occurs in the