The effect of HBV coinfection on the sustained virological response in patients with chronic HCV treated with direct acting antivirals

Thesis

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List of Abbreviations

AASLD ---------- American association for the study of liver disease
ADV ---------- Adefovir dipivoxil
ALT---------- Alanine Transferase
AST---------- Aspartate Transferase
AUC ---------- Area Under Curve
CDC ---------- Center Disease Control
DAAs ---------- Direct Acting Antiviral Agents
DNA ---------- Deoxy Neuclic Acid
EASL ---------- European association for the study of liver disease
ETV ---------- Entecavir
FDA ---------- food&drug adminstration
GFR ---------- Glomerular Filtration Rate
HBsAg ---------- Hepatitis B Surface antigen
HBV ---------- Hepatitis B Virus
HCC ---------- Hepato Cellular Carcinoma
HCV ---------- Hepatitis C Virus
HIV ---------- human imunodefeciency virus
IL ---------- Interleukin
INFγ ---------- Interferone Gamma
INFα---------- Interferone Alpha
LAM ---------- Lamivudine
MHC---------- Major Histocompatibility Complex
NSB ---------- Non Structural Protein
PCR ---------- Polymerase Chain Reaction
PEG-INF ---------- pegylated interferon
RBV ---------- ribavirin
RNA ---------- Ribodeoxy Neuclic Acid
SOF ---------- Sofosbuvir
SVR ---------- Sustained Virological Response
TDF ---------- Tenofovir
Th ---------- T Helper Cell

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Introduction

Hepatitis C virus (HCV) is a globally prevalent pathogen and a leading cause of death and morbidity ***(Cooke et al, 2013).***

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable conditions and hygienic standards for invasive socioeconomic medical, dental, or paramedical procedures. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis. The large reservoir of chronic HCV infection established in the course of these campaigns remains likely to be responsible for the high prevalence of HCV morbidity and may be largely responsible for the continued endemic transmission of HCV in Egypt today ***(Colombo and Sangiovanni ,2002)***.

The prevalence rate of HBsAg in the Egyptian population was moderately high (10.1%); it was higher in the Upper Egypt (11.7%) than the Lower Egypt (8.0%) population and more frequent in young adults—especially those of Upper Egypt—and males than females in both populations ***(Liu et al, 2005)*** **.**

In patients with dual chronic hepatitis B and C infection, the clinical presentations and disease outcomes are usually more severe than in patients with single hepatotropic virus infection. Most studies have provided substantial evidence to support that dual HBV–HCV chronic infection increases the risk of fulminant hepatic failure, the progression of liver disease, and the development of HCC. Therefore, patients dually infected with hepatitis C and B need attention from the medical profession and require effective treatment. Data from clinical trials suggest that pegylated interferon (Peg-IFN) alfa plus ribavirin is effective in the clearance of HCV in dually infected patients with active hepatitis C ***(Chen et al, 1990), (Liaw et al, 2004)*** **.**

Sofosbuvir is clearly a breakthrough new medication for the treatment of patients with chronic hepatitis C. Sofosbuvir has a number of ideal properties, including

pangenotypic activity, once daily dosing, no meal restrictions, few adverse effects, minimal drug-drug interactions, high genetic barrier to resistance, good safety and efficacy in patients with advanced liver disease, and excellent sustained virologic response rates in patients with unfavorable baseline characteristics. In the new American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) hepatitis C guidelines, the combination of sofosbuvir plus peginterferon plus ribavirin is the recommended regimen for patients with genotype 1, 4,5, and 6 infection. In addition, for patients ineligible to receive interferon, the use of sofosbuvir in combination with ribavirin provides the first FDA approved all oral therapy for hepatitis C ***(Charlton et al, 2015)***

Caution must be taken with treatment of coinfected individuals, as exacerbations of liver disease after initiation of therapy have been described, likely due to loss of viral suppression from the successfully treated dominant virus ***(Crockett and Keeffe, 2005)***

In predominant HCV, standard combination treatment with pegylated interferon and ribavirin has proven equally effective in HBV/HCV-coinfected patients

as well as in HCV-monoinfected patients. The recently approved direct-acting antivirals combination treatments may definitely change the treatment protocols in the future although there is no experience with these drugs in dually infected patients until today ***(Konstantinou& Deutsch, 2015).***

Aim of the Study

This study aims to:

- Compare the sustained virological response rate in patients co infected with HCV & HBV to other group of treated patients for HCV mono infection.
- Study the impact of eradication of HCV on the natural history of HBV concomitant infection using the new arsenal of direct acting antivirals (DAAs).

Hepatitis C infection (HCV)

HCV is an enveloped virus with positive-sense RNA genome of 9.6 kb that encodes for a single polyprotein ***(Nelson et al., 2011)***. This single polyprotein can be cleaved by both viral and cellular proteases into 10 mature proteins including, structural (Core, E1, E2/p7) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins (Figure1).

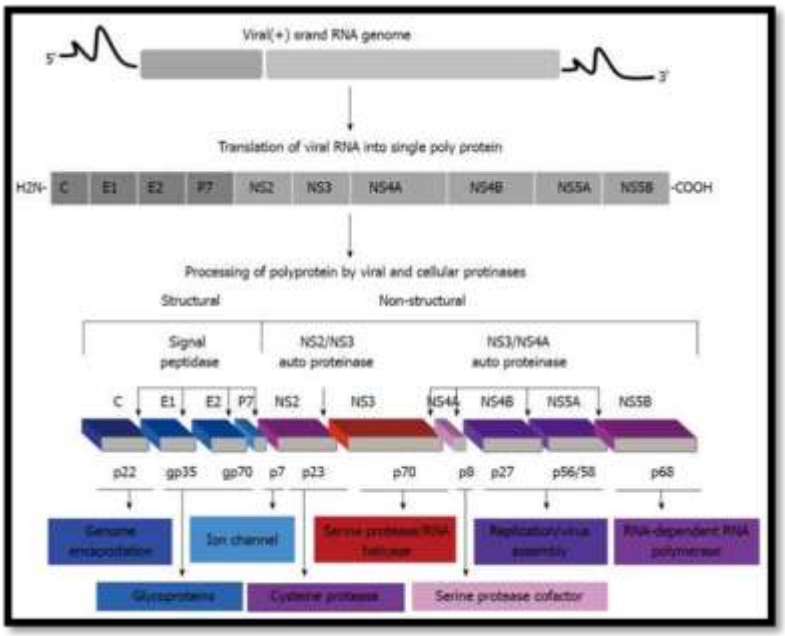

Figure (1): Hepatitis C virus genome. ***(Nelson et al., 2011).***

HCV has a high viral heterogeneity. According to the nucleotide divergence, there are at least six genotypes (HCV-1 to HCV-6), each of them containing a series of subtypes ***(Kuiken et al., 2009).***

HCV genotypes have a striking geographical and epidemiological distribution and genotype identification is clinically important to tailor the dosage and duration of treatment because of different patterns of the treatment response and, consequently, distinct therapeutic approaches are required for each genotype ***(Sy and Jamal., 2006).***

HCV subtypes 1a and 1b are the most common genotypes in the United States ***(Germer et al., 2006).*** The predominant subtype reported from Japan is subtype 1b, responsible for up to 73% of cases of HCV infection**.** HCV subtypes 2a and 2b are relatively common in North America, Europe and Japan and subtype 2c is found commonly in northern Italy ***(Cornberg et al., 2011).*** HCV genotype 4 appears to be prevalent in north Africa, Egypt and the Middle East genotypes 5 and 6 seem to be confined to South Africa and southeast Asia, respectively ***(Gededzha et al., 2012).***

Hepatitis C infection is now acknowledged as an issue of major public health importance for most countries in the world ***(Lavanchy et al., 2011)***. It is estimated that the global prevalence of HCV is approximately 2.8% (or 180 million people) of the total population ***(Hanafiah et al., 2013).***

The majority (50-80%) of infected individuals becomes chronic hepatitis which progressively develops into hepatosteatosis, liver fibrosis, liver cirrhosis and

ultimately to hepatocellular carcinoma (Fig. 2) ***(Zoulim et al., 2003).***

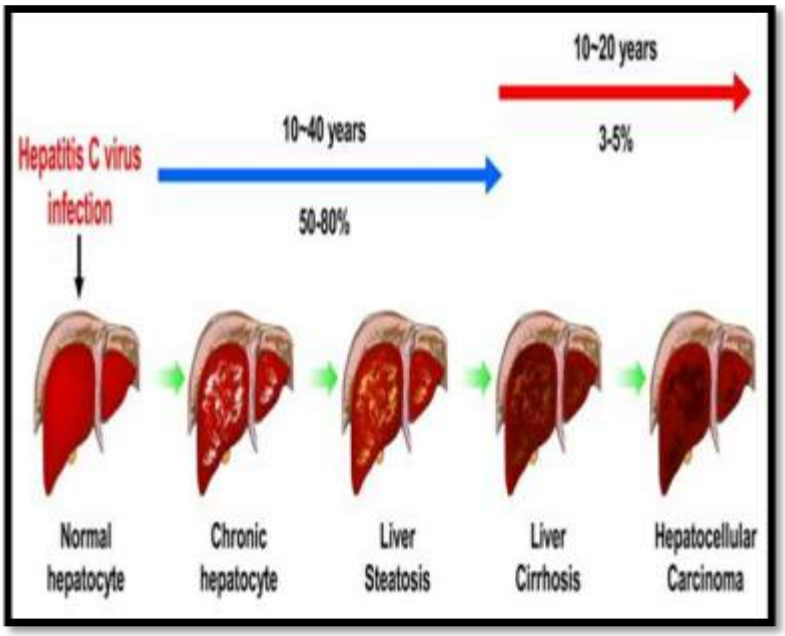

Figure (2): Course of HCV infection within the body. ***(Zoulim et al., 2003).***

Out of 100 people who contract the infection, 75–85% will develop chronic infection, 60–70% will develop chronic liver disease, 5–20% will develop cirrhosis over the course of their chronic infection, and 1–5% will die of complications including hepatocellular carcinoma (HCC) ***(Wise &Brenner., 2008).***

Signs and symptoms:

Hepatitis C infection causes acute symptoms in 15% of cases ***(Maheshwar&Garcia., 2008).*** Symptoms are generally mild and vague flu like symptoms including: