Impact of Anti-Hepatitis C Therapy on Cardiac rhythm

Thesis

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Mohamed Medhat Awad

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List of Abbreviations

Abb.	Full term
2-h PG	*Two hours plasma glucose .*
ALT	*Alanine aminotransferase.*
AST	*Aspartate aminotransferase.*
bpm	*Beat per minute.*
CYP	*Cytochrome P450.*
DAA	*Direct-acting antiviral.*
DM	*Diabetes mellitus.*
ER	*Endoplasmic reticulum.*
ELISA	*Enzyme-linked immunosorbent assay.*
FDA	*Food and drug administration.*
FPG	*Fasting plasma glucose.*
GFR	*Glomerular filtration rate.*
Hb_{A1c}	*Glycosylated hemoglobin .*
HRV	*Heart rate variability.*
HCV	*Hepatitis C virus.*
HCC	*Hepatocellular carcinoma.*
IFN	*Interferon.*
IQR	*Inter-quartile ranges.*
NS	*Non structural.*
OGTT	*Oral glucose tolerance test.*
P-gp	*P-glycoprotein.*
PEG-IFN	*Pegylated interferon.*
PACs	*Premature atrial contractions.*
PVCs	*Premature ventricular contraction.*
RIBA	*Recombinant immunoblot assay.*
RNA	*Ribonucleic acid.*
SD	*Standard deviation.*
SDDN	*The standard deviation of the average normal-to-normal intervals.*
SPSS	*Statistical package for social science.*

List of Abbreviations (Cont...)

Abb.	Full term
SVR	*Sustained virologic response.*
Vs.	*Versus.*

INTRODUCTION

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease in many countries. HCV infection causes highly variable long term side effects, ranging from minimal histological changes to extensive fibrosis and cirrhosis and that could be also associated with hepatocellular carcinoma (HCC). Cirrhosis is considered a late stage of hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules **(Messina et al., 2015).**

Interferon (IFN)-based anti-HCV treatment were having many side effects and couldn't be tolerated by patients with advanced cardiac conditions , so there was a need for evolving HCV treatment into more tolerable medication with less side effects . It was evolving from IFN-based therapy to direct-acting antiviral (DAA) agents **(Petta et al., 2019).**

With the introduction of novel IFN-free highly efficient and well tolerated anti-HCV combination therapies, the issue of causal relationship between HCV infection and cardiac disease may finally be resolved since these new highly anti-HCV-specific drugs lack the complex non-specific side-effects upon cardiac functions which have always confounded interpretation of treatment results **(Kohli et al., 2014).**

Although DAAs are in progressive development and some have got breakthrough therapy status by the U.S. Food and Drug Administration (FDA), Recent retrospective studies, case reports and post marketing reports suggest that some of

novel DAAs that target different steps in the HCV life cycle and were developed for the treatment of chronic HCV infection may cause a toxic systemic effects including toxic cardiomyopathy **(Sherman et al., 2013).**

Treatment with Sofosbuvir-based regimens is associated with a rate of serious adverse events of less than 5%. . It was reported that cases of severe brady-arrhythmia have occurred during treatment with Sofosbuvir in a study done from January 2 to December 31, 2014 **(Hélène et al., 2015).**

The patho-physiological mechanism underlying this potential adverse event during treatment with Sofosbuvir is not clear. However, the potential cardiac toxicity of Sofosbuvir-containing regimens suggests the need for caution with the use of such regimens, including review of other medications, consideration of risk factors for brady-arrhythmias, and possibly monitoring (e.g., Holter ECG recordings) of cardiac rhythm during the initiation of therapy **(Hélène et al., 2015).**

Aim of the Work

The aim of the present study was to assess the impact of Anti-HCV infection therapy on cardiac rhythm using 24 hours Holter monitoring.

IMPACT OF ANTI-HEPATITIS C THERAPY ON CARDIAC RHYTHM

Hepatitis C virus infection:

The overall burden of HCV infection is about 170 to 200 million individuals, which represents more than 3% of the world's population **(Strader et al., 2004),** with annual 3 to 4 million newly diagnosed patients with HCV infection. So it resembles a major health problem being one of the leading causes of chronic liver diseases **(Kamal et al., 2008).**

HCV infection, while a serious infection on its own, it leads to more severe complications. It is estimated that about 20% of chronic HCV-infected patients develop cirrhosis within duration of 10 to 20 years, whereas other patients develop liver cancer within the course of 20 to 40 years. HCV is the cause of about half of the cases of primary liver cancer in the developed world **(Elzayadi et al., 2005).**

In Egypt, the situation is even more critical. Because Egypt has one of the highest prevalence for HCV in the whole world with even a higher prevalence comparing to countries has a similar socioeconomic situation and hygienic conditions **(Kamal et al., 2008).**

The distribution of HCV infection is highly variable, with the prevalence in individual countries ranging from <1% to >10%.

The highest prevalence has been reported in Africa and the Middle East and the lower ones in the Americas, Australia and Northern and Western Europe. In Africa, the highest prevalence of HCV infection has been reported in Egypt and Cameroon (>10%) **(Hajarizadeh et al., 2013).**

The first nationwide survey with a representative sample for HCV antibody testing done in Egypt was in 2008, that Egyptian Demographic Health Survey was carried out on 11126 women and men aged 15-59 years. The blood samples were tested by a third generation enzyme-linked immune-sorbent assay (ELISA) to detect the HCV antibody at the central laboratory in Cairo. Sero-positive patients were tested for HCV RNA. Results showed HCV antibody prevalence was 14.7% **(Guerra et al., 2012)**.

Prevalence was highest in lower Egypt (Nile Delta), followed by upper Egypt, then by urban governorates (Cairo, Alexandria, Port-Said, and Suez), and then by frontier governorates (17.5%, 14.7%, 9.5% and 3.8% respectively). Increased HCV antibody prevalence was shown with increasing age, in males and in rural areas. Decreased HCV antibody prevalence was shown with increasing educational level and wealth, but the prevalence was increased with increasing number of people in the same household. Previous history of blood transfusion, parenteral anti-schistosomiasis treatment, contaminated syringes and female circumcision were all associated with HCV infection in univariate analysis **(Guerra et al., 2012)**.

In 2015, a national Egyptian health issue survey was

conducted to describe the prevalence of HCV infection in Egypt. A multistage probability sampling approach was used, similar to the national demographic survey conducted in 2008. In the 15–59-year age groups, the prevalence of HCV antibody was found to be 10% and that of HCV RNA to be 7%. In children, 1–14 years old, the prevalence of HCV antibody and HCV RNA were 0.4% and 0.2% respectively. Approximately, 3.7 million persons have chronic HCV infection in the age group 15–59 in 2015. An estimated 29% reduction in HCV RNA prevalence has been seen since 2008, which is largely attributable to the aging of the group infected 40–50 years ago during the mass schistosomiasis treatment campaigns. Prevention efforts may have also contributed to this decline, with an estimated 75% decrease in HCV incidence in the 0–19 year age groups over the past 20 years **(Kandeel et al., 2017)**.

Hepatitis C virus infection and chronic hepatitis:

Acute HCV infection refers to the initial 6 months of infection and might or might not include clinical signs or symptoms. Symptomatic acute HCV infection is observed in 15–30% of patients infected with the virus, occurs within 5–12 weeks of HCV exposure and lasts 2–12 weeks. Symptomatic acute HCV infection is often mild, involving nonspecific symptoms such as lethargy and myalgia, but jaundice might also be observed **(Kandeel et al., 2017).**

Many extra-hepatic manifestations have been associated with HCV infection such as oral cancer, lichen planus, membranous glomerulonepritis, auto immune diseases like

autoimmune thyroiditis and mixed cryoglobulinemia, etc. HCV is a hepatotropic virus however it has tropism for other tissues against from the liver and that was proved by being isolated from the myocardium of patients with myocarditis and cardiomyopathy, so it is included among the cardio-tropic viruses **(Sanchez et al., 2008).**

Up to 50% of patients with late stages of cirrhosis have features of cardiac dysfunction. The term "cirrhotic cardiomyopathy" has been used to describe those patients who are characterized as having normal to increased cardiac output and contractility at rest, but with a blunted response to pharmacologic, physiologic or pathologic stress. Patients may also have electrophysiological abnormalities. It is thought to be related to both portal hypertension and cirrhosis **(Zardi et al., 2010)**.

Initial infection with HCV is characterized by the detection of virus in the blood within 2–14 days of exposure, increases in the levels of liver-associated serum enzymes (that is, Alanine aminotransferase (ALT) and Aspartate amino-transferase (AST) and the gradual appearance of HCV-specific antibodies within 20–150 days of exposure. Although patients with symptomatic acute HCV are often detected, the majority of patients is asymptomatic and is therefore missed as a diagnosis of acute HCV, which is often based on anti-HCV antibody sero-conversion **(Hajarizadeh et al., 2013).**

Virologic diagnosis and monitoring of HCV infection are based on the use of serologic assays detecting specific anti-HCV antibodies (including anticore antibodies) or

preferentially by proof of viremia and thereby infection using assays that can detect, quantify or characterize the components of HCV viral particles **(Quan et al., 2015)**.

Subsequent assays following detection of specific anti-HCV antibodies were developed to reduce the rate of false positivity in anti-HCV testing. A positive antibody reaction should be confirmed with either a confirmatory antibody assay such as recombinant immunoblot assay (RIBA) or molecular assays which are more sensitive than serological assays for HCV. Although HCV RNA detection assays are more sensitive and allow viral load quantification and genotyping **(Quan et al.,2015)** but still HCV antigen detection can serve as a cheaper alternative and might be the first next step following a positive antibody test **(Afdhal et al., 2014).**

Hepatitis C virus (HCV) :

HCV is a single-strand RNA virus belonging to the Flaviviridae family **(Kamal et al., 2008)**. Its open-reading frame encodes ten structural proteins (viral capsid and envelope) and non structural (NS) proteins (required for viral replication) **(Lam et al., 2012).**

NS proteins are vital components of the replication complex that HCV needs to replicate the viral genome **(Lee et al., 2011).**

HCV has six genotypes, which can each be split into multiple subtypes. The global distribution of HCV genotypes is