THE EFFECTS OF INTERFERON ON CARDIAC FUNCTIONS IN PATIENTS WITH HEPATITIS C VIRUS

Thesis

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List Of Abbreviations

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ATP	Adenosine triphosphate
BMI	Body mass index
CD	Cluster of differentiation
CHC	Chronic hepatitis C
CHF	Chronic heart failure
CVB3	coxsackie virus b3
DM	Diabetes mellitus
ECG	Electrocardiography
EDD	End diastolic dimension
EF	Ejection fraction
ESD	End systolic dimension
EVR	Early virological response
FDA	Food and Drug Administration
FS	Fractional shortening
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
IHIT	The Inhibition of Hepatocarcinogenesis by Interferon Therapy
IRES	Internal ribosome entry site

IVS	Interventricular septum
LDL	Low-density lipoprotein
LPs	Late potentials
MHC	Major histocompatibility
MR	Mitral regurge
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute of Health
NS	Non-structural
ORF	Open reading frame
PKC	Protein kinase C
SAECG	Signal-averaged electrocardiography
SCID	Severe combined immune deficiency
SD	Standard deviation
SPECT	Single photon emission computed tomography
SR-BI	Scavenger receptor BI
SVR	Sustained viral response
TNF	Tumor necrosis factor
US	United States
UTR	Untranslated region
WHO	World Health Organization

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INTRODUCTION

Hepatitis C virus (HCV) infects approximately 170 million individuals worldwide. Chronic HCV infection has been estimated to be responsible for approximately 25000 to 350000 deaths per year, essentially related to decompensation of cirrhosis, end stage liver disease and hepatocellular carcinoma. Prevention of HCV infection complications can be achieved by antiviral therapy based on the use of a combination of pegylated interferon (IFN) alfa and Ribavirin, that yields a sustained eradication of infection in 40% to 50% of cases *(NIH, 2002).*

IFN is particularly effective in the treatment of chronic active hepatitis in patients who are positive for hepatitis C virus antibody. On the other hand, IFN is known to induce cardiac adverse effects *(Sonnenblick et al., 1991)* such as cardiac dysfunction, cardio-myopathy *(Cohen et al., 1988)* various kinds of arrhythmias *(Martino et al., 1987)* and sudden cardiac death *(Dickson, 1982).*

Although clinical trials which evoke these cardiac events are not documented; in conjugation with these reports, study revealed that, human

recombinant interferon Alfa induced conduction slowing and ventricular arrhythmias in isolated and in vivo rat hearts *(Odashiro et al., 2002).*

Increased prevalence of positive serum anti-HCV has been found in patients with DM *(Ozyilkan et al., 1994)*. *Simo et al. (1996)* showed a significantly higher prevalence rate of positive serum anti-HCV in diabetic patients.

Chen et al. (2006) evaluated serum anti-HCV and hepatitis B surface antigen (HBsAg) among type 2 DM patients. They reported a higher seroprevalence of HCV infection among patients with type 2 DM (6.8%) than in control group (2.6%); they found a 2.8 times higher risk of hepatitis C in Chinese patients with type 2 DM. Their results are consistent with previous reports indicating the possible association between type 2 DM and chronic hepatitis C.

AIM OF THE WORK

The aim of this study is to investigate the effect of interferon alfa therapy on left ventricular systolic and diastolic functions in patients with chronic hepatitis C.

HEPATITIS C INFECTION

Hepatitis C is caused by a small RNA virus that is included in the flaviviridae family and has been classified as the sole member of the genes hepacivirus *(Robertson et al., 1998).*

The World Health Organization (WHO) estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. For example, Frank et al reported that Egypt has the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy *(Frank et al., 2000).*

This has led to a mean prevalence of HCV antibodies in persons in Egypt of 22%. In the United States approximately 4 million people are infected, most less than 50 years old. In Greece the estimated prevalence is 1-2% of the general population, one of the higher ones in Europe *(Gogos et al., 2003).*

The magnitude of the problem becomes even more evident if we consider that in the US there are nearly 10,000 deaths annually due to HCV related

diseases, with HCV also being responsible for nearly half of all hepatocellular carcinoma (HCC) cases, with the high risk of developing HCC since the development of cirrhosis is 3-4% per year *(Davis et al., 2003)*.

As a result HCV-cirrhosis has become the most common indication for liver transplantation in the US, accounting for 35-40% of all cases *(Szabo et al., 2003)*.

Routes of transmission

Hepatitis C may spread through blood and blood products, sexual contact, and vertically. There are also "occasional" infections, which account for as many as 40% of all chronic hepatitis C cases. They can be diagnosed as such when the source of infection is unknown. Blood infection may result from a blood transfusion or an organ transplant, it may occur during invasive diagnostic procedures (e.g., organ biopsies, endoscopic examination). There are approximately 10^5 to10^7 viral particles in 1 ml of blood of an infected patient with the chronic form of the disease, and up to10^9/ml in about 15% of patients. The quantity of the virus in body fluids and tissues is much lower *(Juszczyk, 2003).*

The prevalence of antibodies to HCV in Intravenous drug users is high and significantly higher than in the case of HBV and HIV *(Bolumar et al., 1996)*. Various studies *(Thomas et al., 2000; Van-Ameijden et al., 1993)* indicate that there is a relationship between HCV antibodies, the duration of drug use and the prevalence of HIV and HBV infection.

When a donor of an organ transplant is an HCV-infected person, a transmission of the virus occurs in 50% of patients. When immunotherapy is included into the treatment of a patient infected with HCV following transplantation, a chronic or fulminant form of hepatitis C frequently occurs *(Juszczyk, 2001)*.

The infection can also be acquired through an occupational exposure to blood, basically in health care workers, but also policemen, city guards, and penitentiary workers. The HCV infection can also be the result of perinatal exposure. The routes of transmission from a mother to a child and the timing of the contraction are still unclear. It is not known whether contracting the disease could occur during pregnancy, at birth, after delivery or while breastfeeding. There is no evidence as yet for

transmission through mother's milk. More commonly, the infection of a child takes place in acute hepatitis C in the third trimester of pregnancy, and when accompanied by HIV infection. It should be highlighted that just after birth the anti-HCV antibodies can be detected in child's blood (persisting even up to 1.5yrs), passively transmitted from the mother; this phenomenon is of no significance in pathogenesis of HCV infection *(Herrine et al., 2006).*

Sexual transmission as a route of HCV infection is estimated to occur in 2 to 27% of patients, depending on the study; on average no more than15% of such cases are approved as most probable. The rate of infected individuals' correlates with the number of sexual encounters, with prostitutes and intravenous drug users being the most commonly affected. Variable epidemiological data are reported for homosexuals *(Juszczyk, 2003).*

The intrafamilial transmission rates are significantly higher between sexual partners than among other household members who do not have sexual contact. Transmission to children is significantly low *(Saltoglu et al., 1998).*

Natural history of HCV: