Interleukin-28B Gene polymorphism in Egyptian patients with chronic hepatitis C infection related liver diseases

Thesis submitted in Partial fulfillment of the M.D Degree in infectious diseases and endemic hepatogastroenterology

BY

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2012

Acknowledgement

First of all, Thanks to **GOD**, without his will, nothing could have been achieved.

My gratitude to **Prof. Dr.Hosny Salama** Professor of Tropical Medicine, Cairo University, for his support and endless advices and help. He gave me much of his time, experience and support, his valuable comments and collaboration were the causes to complete this work properly.

I would like to thank **Prof. Dr. Eman Medhat** Professor of Tropical Medicine, Cairo University, for her effort, kindness, and generous help, without her help this work could not be done.

I would like to thank **Prof. Dr. Abdel Rahman Zekri** Professor of immunology and virology, national cancer institute for his effort, time, and insight advices.

I would like to appreciate the great effort of **Dr Rasha Ahmad**, assistant professor of tropical medicine, to finish this work.

To all my professors, and colleagues to whom I have the honor to belong, to who taught and advised me, who gave me their confidence, who trained me and pushed me forwards.

Abstract

Background/Aims: Polymorphism at the IL28B gene may modify the course of hepatitis C virus (HCV) chronic infection. Our aim was to study the influence of IL28B rs12979860 gene polymorphism on the biochemistry and pathology of HCV-induced disease in the clinical course from mild chronic hepatitis C to hepatocellular carcinoma.

Methods: We have determined the rs12979860 single nucleotide polymorphism (SNP) upstream IL28B gene in three groups of Egyptian patients with HCV-induced chronic liver disease: 1) 119 patients with biopsy-proven chronic hepatitis C, to analyze its relation with biochemical and histological features; 2) 66 patients with HCV-related liver cirrhosis and 3)71 patients with hepatocellular carcinoma. Their results were compared to the results of 48 normal persons.

Results: No relation was found between the analyzed SNP and METAVIR scores for necroinflammation and fibrosis, and there were no differences in the distribution of the analyzed SNP between hepatocellular carcinoma and untreated chronic hepatitis C patients.

Conclusion: The IL28B rs12979860 polymorphism doesn’t correlate with the histological staging or severity of liver fibrosis in chronic hepatitis C and doesn’t correlate with the incidence of hepatocellular c Interleukin 28B - HCV - Liver cirrhosis - Hepatocellular carcinoma

Key Words:

arcinoma in the Egyptian patients.

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List of abbreviations

ALT	Alanine aminotransferase
APOE	Apolipoprotein E
AST	Aspartate aminotransferase
BCLC	Barcelona-Clinic Liver Cancer
BMI	Body mass index
CCR **CXCR** **CXCL** **CCL**	Chemokine receptor
CD	Cluster of differentiation
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CPTA1	Carnitine palmitoyltransferase 1A
CTL	Cytotoxic T lymphocytes
DAAT	Directly acting antiviral treatment
DNA	Deoxyribonucleic acid
EVR	Early virologic response rates
FasL	Fas ligand
GWAS	Genome wide association study
HAART	Highly active antiretroviral therapy
HALT-C	Hepatitis C antiviral long term treatment against cirrhosis
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HapMap	Haplotype map
HRS	Hepatorenal syndrome
IDUs	Injecting drug users
IFN	Interferon
IL	Interleukin

IL28B	Interleukin 28B
IL- 10Rβ	interleukin-10 receptor β chain
IL-28Rα	interleukin-28 receptor α chain
ISG	IFN-stimulated gene
Jak	Janus kinase
KIR2DL3	Killer cell immunoglobulin-like receptor 2DL3
LDLR	Low-Density Lipoprotein Receptor
MIP	Macrophage inflammatory protein
MMPs	Matrix metalloproteinases
NHANES	National Health and Nutrition Examination survey
NK	Natural killer
PEG-IFN	Pegylated interferon
PMN	polymorphonuclear leucocytes
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virological response
SBP	Spontaneous Bacterial Peritonitis
SNP	single nucleotide polymorphism
SOCS-3	Suppressor of cytokine signaling 3
STAT	Signal Transducers and Activators of Transcription
SVR	Sustained virological response
TGFβ1	Transforming growth factor beta 1
Th1	T helper 1
TNF	Tumor necrosis factor
Tyk	Tyrosine kinase
VDR	Vitamin D receptor

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Introduction

Several immunological factors have been implicated in determining disease outcomes in hepatitis C virus (HCV) infections ***(Rehermann, 2009)***. Approximately 30% of individuals clear the infection naturally, whereas the remaining 70% develop chronic disease that may result in liver cirrhosis (LC) and/or hepatocellular carcinoma ***(Morgan, 2011)***. Therefore, identification of the factors involved in persistent HCV infections may lead to the development of effective prognostic tests and hence improved treatment management or to the development of novel antiviral agents. Although the role of the adaptive immune response has been well documented, other evidence supports a role for the innate immune system in regulating disease progression in HCV infection ***(zekri et al., 2010)***. More recent evidence to support a role for the innate immune system in HCV outcomes, has come from a series of studies on SNPs in the IL28B gene region which predicts spontaneous and type 1 IFN induced clearance of HCV infections. Multiple genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) near the IL28B gene (encoding IFN-λ3) to be strongly associated with spontaneous and treatment-induced clearance of HCV infections ***(Rauch et al., 2010).*** One of these SNPs, rs12979860 was pivotal in predicting the resolution of HCV infections ***(Thomas et al., 2009).*** The SNP rs12979860 is found ~ 3 kb upstream from the IL28B gene. Little is known about the IFN λ family, but evidence is mounting to support a role for them in the immune response to viral infections ***(Chevaliez and Hezode, 2010).*** Therefore, associations made between IL28B variants and HCV clearance in large-scale genetic studies provides an exciting mechanistic link between innate immunity and viral clearance. Chronic HCV patients (CHC) can be roughly categorized into patients with a very slow disease progression and patients with rapid progression into LC and HCC. The factors controlling the pathobiology of HCV disease are either viral or host related. No apparent differences between the pathobiology of HCV genotypes was reported until Mihm et al. identified a relationship between hepatic steatosis and HCV genotype 3 infections ***(mihm, 2010)***.

This relationship was subsequently confirmed by comparing patients infected with genotype 3 and those infected with other genotypes. However, Genotype 4a represents more than 93 % of chronic HCV patients in Egypt ***(Elkady et al., 2009)***

AIM OF THE WORK

The aim of this trial is to:

- To assess the allelic and genotypic frequencies of the IL-28B rs12979860 C/T polymorphism in patients with chronic HCV infection at various stages of the disease in comparison to healthy control subjects
- To verify whether this polymorphism is an independent predictor of the degree and progression of fibrosis in chronic hepatitis C
- To verify whether this polymorphism is an independent predictor of incidence of HCC
- To investigate the interaction between the IL-28B rs12979860 C/T polymorphism and other factors known to influence the evolution of chronic hepatitis C

<u>Chapter One</u>

Natural history of HCV infection

The natural history of hepatitis C is quite varied. There are some inherent drawbacks in studying natural history. First, it is difficult to ascertain the exact time of acquirement of infection; second, primary infection is commonly asymptomatic and last, disease progression is slow.

Natural history data reported in the literature vary according to the type of study (retrospective vs. prospective). Different study populations also result in different predictions about natural history ***(Hourigan et al., 1999)*** (patients attending liver clinic vs. blood donors vs. community-based studies vs. post-transfusion cohorts).

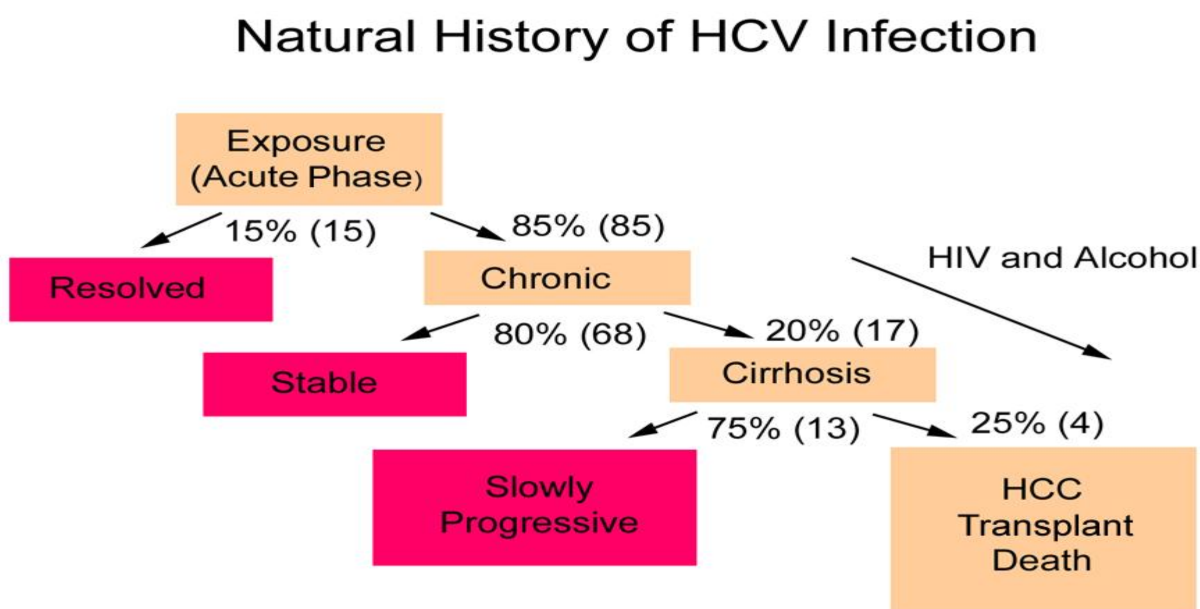

Fig (I): **Natural history of HCV infection** ***(Hourigan et al., 1999)***

A- Acute hepatitis C virus infection:

Acute hepatitis C virus (HCV) infection is infrequently diagnosed, because the majority of acutely infected individuals are asymptomatic. In the transfusion setting, where acute onset of HCV infection has been best documented, 70–80%