Evaluation of the role of IL-6 gene polymorphism in determining response of HCV Egyptian patients to anti-HCV treatment

Thesis

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رسالة

توطئة للحصول على درجة الماجستير

فى الكيمياء الحيوية الطبية

مقدمة من

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بكالوريوس الطب و الجراحة

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Abstract

Background & Aims: HCV is the major etiological agent of liver disease worldwide. IL-6 is a cytokine that plays a role in immune defense against viruses. It had been demonstrated that polymorphism in the promoter region of the IL-6 (rs-1800795) gene locus polymorphism are correlated with treatment induced clearance of hepatitis C virus infection.

Methods: They are (90 patients) 86 males (95.6%) with mean age 51.5 ± 7.5 and 4 females with mean age 51.5 ±7.5 (4.4%).

All patients were collected from Electricity hospital in Cairo in the period from June 2015 to September 2015.

They was diagnosed using anti-HCV antibodies testing and confirmed by quantitative PCR testing. They received combination therapy Sovaldi (Sofosbuvir) 400mg and Olysio (Simeprevir) 90 mg once daily for a course of 12 successive weeks.

All patients were subjected to the following: DNA extraction from blood samples collected, quantitative PCR for HCV RNA using Taqman probe and genotyping of the IL6 polymorphism by real time polymerase chain reaction (qRT- PCR) using Applied Biosystem Step One instrument, USA.

Results: The distribution of the 3 genotypes (GG, GC & CC) showed predominance of GG genotype in (72.2%) of the sample size. Analysis of genotypes and linkage to response to treatment

revealed predominance of GG genotype among responders (71.6%). All analyses regarding genotype distribution and response to treatment showed non-significant pattern. This was in harmony with analysis of allele's frequency in relation to response to treatment that was also of non-significant pattern.

Conclusion: The concluded result is that IL-6 (rs-1800795) gene locus polymorphism has no role in determining response of HCV patients to combination therapy of Sofosbuvir and Simeprevir

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List of abbreviations

AFP……..Alpha-Feto Protein

ALT……..Alanine aminotransferase.

ANOVA……Analysis of Variance.

ART……..Anti-retroviral Therapy

AST……..Aspartate aminotransferase.

CBC……..Complete Blood Count

CD……Cluster of Differentiation

CHC……..Chronic hepatitis C

CNTF…….Ciliray Neurotropic Factor

CT-1……..Cardiotropin-1

DAA……..Direct Acting Antiviral

DDI……..Drug-Drug Interactions

DNA……..Deoxyribo-Nucleic Acid

FDA……..U.S. Food and Drug Administration

GFR……..Glomerular Filtration Rate

HBV……..Hepatitis B virus

HCC……..Hepatocellular carcinoma

HCV……..Hepatitis C virus

HHV-8…….human herpes virus 8

HIV……..Human immunodeficiency virus

HWE……Hardy-Weinberg Equation

IFNγ……..Interferon gamma

IL……..Interleukin

JAK–STAT……Janus family tyrosine kinase–signal transducer and activator of transcription

kDa……..kilo-Dalton

LIF……..Leukemia Inhibitory Factor

LMIC……..Low and Middle-Income Countries

mbIL-6R…….membrane-bound non signaling αIL-6 receptor

MSM……Men who have sex with men

NAT……..Nucleic Acid Test

NCCVH……National Committee for the Control of Viral Hepatitis

NFATc2……....Nuclear Factor of Activated T-cells2

NPN……..Neuropoietin

NS…….Non Structural protein

OSM……..Oncostatin M

OST……..Opioid Substitute Therapy

PCR……..Polymerase Chain Reaction.

PWID……People Who Inject Drugs

RANK……..Receptor Activator of Nuclear Factor k

Ras-MAPK……...mitogen-activated protein kinase

RNA……..Ribonucleic acid

SD…….Standard Deviation

sIL-R…….soluble Interleukin receptor

SNP……Single Nucleotide Polymorphism

SOCS……..Suppressor of Cytokine Signal

SVR……...Sustained virological response

TB …….Tuberculosis

Th…….….T helper lymphocyte

TLC……...Total Leucocytic Count

TNFα…….Tumour Necrosis Factor

TSH…….…..Thyroid stimulating hormone.

VEGF……Vascular Endothelial Growth Factor

vIL……..Viral Interleukin

WBC……..White Blood Cell Count

WHO……..World Health Organization

Introduction

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer, or life-threatening esophageal and gastric varices **(Ryan et al 2004).**

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, and transfusions. An estimated 150–200 million people worldwide are infected with hepatitis C **(Gravitz 2011)**. The existence of hepatitis C (originally identifiable only as a type of non-A non-B hepatitis) was suggested in the 1970s and proven in 1989 **(Houghton 2009)**.

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus. It is a member of the **Hepacivirus** genus in the family **Flaviviridae**. There are seven major genotypes of HCV, which are known as genotypes one to seven. The genotypes are divided into several subtypes with the number of subtypes depending on the genotype. It is estimated that 150–200 million people, or ~3% of the world's population, are living with chronic hepatitis C **(Mohd Hanafiah et al 2013)**.

About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases. During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection.

Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment **(Alter 2007).**

In Egypt the situation is quite worse. Egypt has a population of 62 million and contains the highest prevalence of hepatitis C in the world. Interestingly, genotype 4 represents over 90% of cases in Egypt. The major route of exposure appears to be due to injection therapy and inadequate infection control practices **(Mohamed 2004).**

Among those chronically infected, the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10–15% for men and ~1–5% for women **(Forton et al 2005).** The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1–4% per year. Rates of new infections have decreased in the Western world since the 1990s due to improved screening of blood before transfusion **(Ozaras and Tahan 2009)**.