SUSTAIND VIROLOGICAL RESPONSE IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS GENO TYPE4 INFECTION TREATED BY ACOMBINATION THERAPY OF INTERFERON AND RIBAVIRIN

Thesis

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LIST OF ABBREVIATIONS

HCV	**:**	Hepatitis C virus
IDU	**:**	Intravenous drug use
RNA	**:**	Ribo Nuclic Acid
HIV	**:**	Human Immnodefecincy virus
HBV	**:**	Hepaliti B virus
ELISA	**:**	Enzyme linked immno sorbant assay
PCR	**:**	Polymerase chain reation
IFNS	**:**	Interferons
IL10R2	**:**	Inter lueckin 10`recopter 2
PKR	**:**	Protein kinase R
ISGS	**:**	Interferon stimulating genes
MHC	**:**	Major histocompitability complex
TLR	**:**	Toll like receptor
ds RNA	**:**	Double standed ribo nuclic acid
rt PCR	**:**	Real time poly merase chain reaction
TMA	**:**	Transcreption mediated amplification
RIBA	**:**	Ribavirin
PEG	**:**	Poly ethelyne glycol
RSV	**:**	Respiratory syncytial virus
CSF	**:**	Cerebro- spinal – fluid
RBCS	**:**	Red blood cells
ATP	**:**	Adenosine triphosphate
E1	**:**	Envelope glycoprotien 1
E2	**:**	Envelope glycoprotien2
IRES	**:**	Internal ribosome entery site
NS2	**:**	Non structural protien 2
KDA	**:**	Kilo Dalton

ARFP	**:**	Alternate reading frame protein
CDC	**:**	Center for diseases control and prevention
AIDS	**:**	Acquired immunodeficiency syndrome
ISGs	**:**	Interferon stimulated genes
JEV	**:**	Japanes encephalitis virus
DEN2	**:**	Dengue type 2 virus
HCMV	**:**	Human cytomegalo virus
KSHV	**:**	Kaposi sarcoma herpes virus
HHV8	**:**	Human herpes virus 8
EBV	**:**	Epestien Bar virus
EBVNA1	**:**	Epestien Bar virus nuclar antigas
HPV	**:**	Human papilloma virus `
GTP	**:**	Guanosine tri phosphate
HCC	**:**	Hepato cellular carcinoma
FDA	**:**	Food and drug administration
ALT	**:**	Alanine transaminase
RVR	**:**	Rapid viral response
ANC	**:**	Absolute neutrophil count
EVR	**:**	Early viral responses
SVR	**:**	Sustained viral response
ETR	**:**	End of treatment response
CYP3A4	**:**	Cytochrome p3a4

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INTRODUCTION

Hepatitis C

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 and Ray, 2004).***

HCV is spreads primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions. An estimated 130–200 million people worldwide are infected with hepatitis C ***(Gravitz, 2011).***

The virus persists in the liver in about 85% of those infected. This persistent infection can be treated with medication: the standard therapy is a combination of peginterferon and ribavirin, with either boceprevir or telaprevir added in some cases. Hepatitis C is the leading cause of liver transplantation, though the virus usually recurs after

transplantation. Egypt is one of the countries with particularly high rates of infection (22%) ***(Wilkins et al., 2010).***

Chronic infection

About 80% of those exposed to the virus develop a chronic infection (***Davis GL, 2011)***. Hepatitis C after many years becomes the primary cause of cirrhosis and liver cancer ***(Ray and Thomas, 2009).*** About 10–30% of people develop cirrhosis over 30 years ***(Wilkins et al., 2010 and Davis GL, 2011).*** Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma, a rate of 1–3% per year, ***(Wilkins et al., 2010 and Davis GL, 2011).*** Hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma worldwide liver cancer ***(Ray and Thomas, 2009).***

Liver cirrhosis may lead to portal hypertension, ascites, easy bruising or bleeding, varices, jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy. It is a common cause for requiring a liver transplant ***(Nicot, 2004).***

Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40-80% of these clear with treatment

(Torresi et al., 2011 and Ilyas and Vierling, 2011). In rare cases, infection can clear without treatment (***Davis GL, 2011).***

Medications

As of 2010, treatments consists of a combination of pegylated interferon alpha and the antiviral drug ribavirin for a period of 24 or 48 weeks, depending on HCV genotype (***Davis GL, 2011).*** When combined with ribavirin, pegylated interferon-alpha-2a may be superior to pegylated interferon-alpha-2b, though the evidence is not strong ***(Awad et al., 2010).*** Improved outcomes are seen in 50–60% of people (***Davis GL, 2011).*** Combining either boceprevir or telaprevir with ribavirin and peginterferon alfa improves antiviral response for hepatitis C genotype 1 ***(Foote et al., 2011); Smith et al., 2011 and Ghany et al., 2011).*** Adverse effects with treatment are common, with half of people getting flu like symptoms and a third experiencing emotional problems.[10] Treatment during the first six months is more effective than once hepatitis C has become chronic ***(Nicot, 2004).***

Interferon

Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses,

bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors. IFNs belong to the large class of glycoproteins known as cytokines. Interferons are named after their ability to "interfere" with viral replication within host cells. IFNs have other functions: they activate immune cells, such as natural killer cells and macrophages; they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus. Certain symptoms, such as aching muscles and fever, are related to the production of IFNs during infection..All interferons share several common effects; they are antiviral agents and can fight tumors. Some of those treated with interferon have a sustained virological response and can eliminate hepatitis virus. The most harmful strain—hepatitis C genotype I virus—can be treated with a 60-80% success rate with the current standard-of-care treatment of interferon-α, ribavirin and recently approved protease inhibitors such as Telaprevir (Incivek) or Boceprevir (Victrelis) ***(Ge et al., 2009)*.**

Biopsies of patients given the treatment show reductions in liver damage and cirrhosis. Control of chronic hepatitis C by

IFN is associated with reduced hepatocellular carcinoma ***(Ishikawa, 2008)***.

Polyethylene glycol is added to make the interferon last longer in the body. Initially used for production of PEGylated interferon-alpha-2b (Pegintron), approval for PEGylated interferon-alpha-2a (Pegasys) followed in October 2002. These PEGylated drugs are injected once weekly, rather than administering three times per week, as is necessary for conventional interferon-alpha. When used with the antiviral drug ribavirin, PEGylated interferon is effective in treatment of hepatitis C; at least 75% people with hepatitis C genotypes 2 or 3 benefit from interferon treatment, although this is effective in less than 50% of people infected with genotype 1 (the more common form of hepatitis C virus in both the U.S. and Western Europe) ***(Jamall et al., 2008; NIH Consensus Statements, State-of-the-Science Statements, 2002 and Sharieff et al., 2002)***.

The most frequent adverse effects are flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning, and depression. Erythema, pain and hardness on the spot of injection are also frequently observed. IFN therapy causes