HISTOPATHOLOGICAL FINDINGS IN LIVER BIOPSY IN RELATION TO VIROLOGICAL RESPONSE IN CHRONIC HEPATITIS C PATIENTS RECEIVING COMBINED THERAPY

"A thesis Submitted in Partial Fulfillment of the MD of Tropical Medicine"

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List of Abbreviations

AKT	Protein Kinase B (PKB), is a serine/threonine-specific protein kinase
ANOVA	Analysis Of Variance
BOC	Boceprevir
CD	Cluster of differentiation
cEVR	Complete early virological response
CLDN	Claudin
DAAs	Directly Acting Antiviral Agents
DNA	Deoxyribonucleic acid
EC1	First extracellular loop
ETR	End of treatment response
EVR	Early virological response
FDA	Food and Drug Administration
HCV	Hepatitis C Virus
HCV RNA	Hepatitis C Virus Ribonucleic Acid
IFN	Interferon
IFN a2a	Interferon alpha 2 a
IFN a2b	Interferon alpha 2 b
LB	Liver Biopsy

MEK	Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase Kinase
MKK6	MAPK (Mitogen-Activated Protein Kinase) Kinase
NCCVH	National Committee for the Control of Viral Hepatitis
NS	Non structural protien
PASW	Predictive Analytics Software
PegIFN/RBV	Pegylated interferon and Ribavirin
pEVR	Partial Early Virological Response
PI	Protease Inhibitors
PKR	Protein kinase R
RNA	Ribonucleic Acid
RT-PCR	Real Time Polymerase Chain Reaction
SOC	Slandered Of Care
SVR	Sustained Virological Respond
TVR	Telaprevir
WBC	White Blood Cells
WK 12	Week 12

CHAPTER ONE: INTRODUCTION

In the nearly 50 years since Menghini popularized the use of percutaneous needle biopsy , microscopic evaluation of the liver has remained an important modality in the diagnosis and management of patients with liver disease. For patients suffering from chronic hepatitis, defined as ‘‘inflammation of the liver continuing without improvement for 6 months or longer’’, liver biopsy has been considered the ‘‘gold standard’’ of diagnosis, the most direct way of visualizing the necroinflammatory and architectural status of the liver **(Tagaya, 2012)**

There are three primary reasons for performing a liver biopsy: it provides helpful information on the current status of the liver injury, it identifies features useful in the decision to embark on therapy, and it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices. The biopsy is assessed for grade and stage of the liver injury, but also provides information on other histological features that might have a bearing on liver disease progression. The grade defines the extent of necroinflammatory activity, while the stage establishes the extent of fibrosis or the presence of cirrhosis **(Alswat et al., 2010)**

Several studies have demonstrated the antifibrinogenic action of interferon, which is not related to antiviral and anti-inflammatory effects; furthermore, it provokes histological improvement even in virological non-responders **(Shepherd et al., 2007; Ingiliz et al., 2012)**.

The treatment of HCV4 is affected by many Host/Virus factors that must be precisely evaluated and optimized before treatment initiation.**(Esmat et al., 2013)**.

Aim of the work

In this study we will discuss the relation between the histopathological findings in liver biopsy and their impacts on sustained virological response in patients infected by hepatitis c virus who are receiving pegylated interferon and ribavirin.

CHAPTER TWO: HEPATITIS C OVERVIEW

2-1 Epidemiology

An estimated 2%-3% of the world's population is living with hepatitis C virus (HCV) infection, and each year, >350 000 die of HCV-related conditions, including cirrhosis and liver cancer. The epidemiology and burden of HCV infection varies throughout the world, with country-specific prevalence ranging from <1% to >10%. In contrast to the United States and other developed countries, HCV transmission in developing countries frequently results from exposure to infected blood in healthcare and community settings. Hepatitis C prevention, care, and treatment programs must recognize country-specific epidemiology, which varies by setting and level of economic development **(Averhoff et al., 2012)**.

Egypt has the largest burden of HCV infection in the world, with a 10% prevalence of chronic HCV infection among persons aged 15–59 years. The hepatitis C epidemic in Egypt began during 1960–1980, when mass campaigns were conducted to control schistosomiasis through parenteral antischistosomal therapy administered by health-care workers using improperly sterilized glass syringes. HCV transmission is ongoing in Egypt, and incidence rates have been estimated at 2.4 per 1,000 person-years (165,000 new infections annually). In 2008, nearly 15% of

the population aged 15–59 years had antibodies to HCV (anti-HCV), and 10% (approximately 5 million persons) had chronic HCV infection; overall, an estimated 6 million Egyptians had chronic HCV infection in 2008. Prevalence of chronic HCV infection in Egypt is higher among men than women is (12% and 8%, respectively), increases with age (reaching >25% among persons aged >50 years), and is higher among persons residing in rural versus urban areas (12% versus 7%). Primary modes of HCV transmission include unsafe injections, other inadequate infection control practices, and unsafe blood transfusions. HCV transmission also occurs among injection-drug users in Egypt .**(Centers for Disease Control and Prevention, 2012)**.

Given the high burden of viral hepatitis in Egypt, in 2006, the Egyptian Ministry of Health and Population established the National Committee for the Control of Viral Hepatitis (NCCVH). By April 2008, this committee had developed a National Control Strategy for Viral Hepatitis, which called for effective surveillance, enhancements in prevention to reduce the incidence of hepatitis B virus and HCV infection and expanded access to care and treatment for those with chronic infection. To date, implementation largely has been limited to the care and treatment component of the strategy; a national network of 23 viral

hepatitis facilities has been established to provide viral hepatitis care and treatment at a substantially reduced cost. Facilities are located throughout Egypt and within 100 kilometers of every Egyptian city and village, allowing greater access to care and treatment. Each facility is directed by a trained hepatologist to ensure that care and treatment standards are met and provides a full spectrum of care **(Centers for Disease Control and Prevention, 2012)**.

HCV is an RNA virus known to infect humans and chimpanzees, causing a similar disease in these two species. There are six HCV genotypes (genotypes 1 to 6), many subtypes (a, b, c, etc.), and approximately 100 different strains (1, 2, 3, and so forth) based on the sequence heterogeneity of the HCV genome. Genotypes 1 to 3 are widely distributed globally, with genotypes 1a and 1b accounting for 60% of infections worldwide. Genotype 1a is predominantly located in northern Europe and North America, whereas genotype 1b is predominantly found in southern, Eastern Europe, and Japan. Genotype 2 is less common than genotype 1 and it is found more frequently in Europe than in North America. Genotype 3 is endemic to South-East Asia, and genotype 4 is characteristic of the Middle East, Egypt, and central Africa. Genotype 5 is almost exclusively found in South Africa, and genotype 6 is primarily

distributed in Asia. The impact of the viral genotype on the pathogenesis of liver disease remains a subject of controversy, but the influence of the genotype on the response to interferon-based therapy is established. Genotype 1 is generally associated with a poorer response to therapy, whereas genotypes 2 and 3 have responses that are more favorable. Genotype 4 seems to have an intermediate response **(Jang & Chung, 2011)**.