EVALUATION OF SOME SEROLOGICAL MARKERS IN TESTING THE PROGRESSION OF HEPATIC FIBROSIS IN CHRONIC HCV PATIENTS

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Abstract

Background: HCV is a major health problem worldwide including Egypt. Fibrosis is the major complication of HCV infection and has a significant influence on the response to antiviral therapy. ***Aim:*** evaluation of some non-invasive markers in testing progression of hepatic fibrosis after treatment with *Viscum album* in patients with chronic HCV. ***Methods:*** 20 patients were divided into two groups: group 1 received viscum and group 2 received viscum plus Ribavirin. Changes in viral load, P3NP, Fibrotest-Actitest, AFP, liver and kidney functions were followed for 6 & 12 months. ***Results:*** Follow-up showed a decrease in all liver enzymes in Group1, and only ALT in Group 2. Viral response was associated with low initial levels of GGT, AFP, CK, P3NP, and viral load combined (100% sensitivity and specificity). Higher APRI/P3NP, FIB-4, FIBROQ and Fibrotest values distinguished the presence of significant fibrosis - in a descending order. ***Conclusion:*** APRI/P3NP is a reliable and relatively cheap marker for fibrosis, and the viral response could be predicted in patients with initial low levels of viral load, GGT, AFP, CK, and P3NP combined. Viscum could be used safely with other anti-HCV compounds.

Keywords: HCV, Viscum album, P3NP, fibrotest-actitest

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1-Introduction

Hepatitis C is comparable to a 'viral time bomb'. The WHO estimates that about 200 million people, 3% of the world's population, are infected with hepatitis C virus (HCV) and 3 to 4 million persons are newly infected each year ***(WHO, 2009).***

Egypt has the highest known country-wide prevalence of HCV in the world, with an estimated 8-10 million people have been infected by the virus. It is believed that 85% of the patients with HCV will develop chronic hepatitis as determined by persistent viremia, abnormal liver enzymes and histology. Over 10 to 30 years, about 20% of those with chronic hepatitis C will progress to fibrosis followed by cirrhosis and hepatocellular carcinoma leading to death ***(Miller &Abo-Raddad, 2010)***

Hepatic fibrosis, the result of imbalance of fibrogenesis and fibrolysis, is a reversible wound healing response characterized by accumulation of extracellular matrix (ECM). Ultimately hepatic fibrosis leads to cirrhosis, an irreversible state, characterized by nodule formation and organ contraction ***(Manning & Afdhal, 2008).*** Fibrotic response leads to all the complications of

end-stage liver disease, including portal hypertension, ascites, encephalopathy, synthetic dysfunction, and impaired capacity. Thus, fibrosis is deleterious both by its direct effects on cellular function as well as its mechanical contribution to increased portal resistance ***(Coon et al., 2007).***

Liver biopsy has been the gold standard marker of staging activity of fibrosis. But being invasive, it carries risks, besides it disagrees with many patients. So there is a clinical need for non-invasive measurement of liver fibrosis both to evaluate stage of liver fibrosis and to monitor the effect of therapy on fibrogenesis and fibrolysis ***(Poynard et al., 2007b).***

Recently, various serum biomarkers and laboratory tests have been proposed as surrogates of liver histology. Notably, non-invasive serum biomarkers, when combined, may reduce by 50%–80% the number of liver biopsies needed for correctly classifying hepatic fibrosis ***(Sebastiani et al, 2011).***

The staging of liver fibrosis in the present study was done according to the recently described sequential algorithm for fibrosis evaluation (SAFE), which detects significant fibrosis (≥F2 by METAVIR) and cirrhosis (F4)

by combining the AST-to-platelet ratio index (APRI) and Fibrotest-Fibrosure ***(Sebastiani et al., 2009& 2011)***

FIB-4 marker combines biochemical variables (platelet count, AST, and ALT) with age. It has reasonably good accuracy for predicting advanced fibrosis in patients with chronic HCV (***Sterling et al., 2006; Vallet-Pichard et al., 2007).***

Fibro-quotient (FibroQ) is a novel noninvasive index for predicting liver fibrosis. It combines sex, age, AST, ALT, platelet count, PT and INR. It had reasonably good accuracy for predicting significant fibrosis (F2-F4) and cirrhosis in patients with chronic HCV ***(Hsieh et al, 2009)***.

FibroTest and ActiTest (FT-AT), are noninvasive blood tests that combine the quantitative results of six serum biochemical markers, α_2-macroglobulin, haptoglobin, apolipoprotein A_1, bilirubin, gamma glutamyl transpeptidase (GGT), and ALT, with the patient's age and gender (***Lau-Corona et al., 2009***). They were found to have high diagnostic value for fibrosis and necroinflammatory histological activity. They provide an alternative for assessing liver status without the associated risk of an invasive procedure ***(Morali et al., 2007).***

Amino-terminal type III procollagen (P3NP) has been reported to serve as non-invasive serologic marker of liver fibrosis in hepatitis and cirrhosis and thereby reduce the need for repeated liver biopsies ***(Carey &Carey, 2010)***.

Due to failure of interferon therapy and the high rates of side effects a strong movement towards complementary and alternative medicine (CAM) for chronic HCV infection has been accepted worldwide ***(Azzam et al., 2007).*** Botanicals are the most popular type of CAM treatment (***Gui et al., 2006).***

Viscum album (mistletoe), a semi-parasitic woody perennial plant, is commonly found on oak and other deciduous trees. European mistletoe extracts possess various biological activities, such as immunoadjuvant activities, induction of various cytokines, and enhancement of natural killer (NK) cell activity ***(Lee et al., 2009).*** The advantage of viscum therapy is the absence of side effects and its low cost effectiveness. Therefore, viscum therapy could be an alternative therapy to patients who did not respond to standard therapy or those with relative or absolute contraindication to interferon therapy ***(Bloksma, 1982).***

2-Review of Literature

2.1. Hepatitis C Virus

Hepatitis C virus remains a large health care burden to the world. Incidence rates across the world fluctuate and are difficult to calculate given the asymptomatic, often latent nature of the disease prior to clinical presentation ***(Derbala et al., 2006; Sy & Jamal, 2006)***. The WHO estimates that about 200 million people, 3% of the world`s population are infected with HCV and from 3 to 4 million persons are newly infected each year. HCV is responsible for 50–76% of all liver cancer cases, and two thirds of all liver transplants in the developed world ***(WHO, 2009)***.

High incidence of hepatic morbidity and mortality result from the late complications of HCV infection, which include chronic hepatitis, cirrhosis, and hepatocellular carcinoma ***(Strickland et al., 2002; El-Zayadi et al., 2005)***.

2.1.1. History of HCV

For many years, hepatitis A and hepatitis B virus were thought to be the major causative agents of hepatitis, including cases of transfusion-associated hepatitis. However, even after the establishment of prevention and diagnostic methods for these hepatitis viruses, transfusion-associated hepatitis continued to occur, and these cases were recognized as non-A,

non-B hepatitis. Although the causative agent of parenteral non-A, non-B hepatitis was considered to be an unknown virus, this virus proved to be very difficult to identify. In 1989, after a large number of trials were conducted in order to find this new virus, Chiron's group finally succeeded in cloning part of the genome of the virus that came to be known as the hepatitis C virus ***(Kato, 2001).***

2.1.2. Epidemiology of HCV Infection:

Prevalence:

The estimated worldwide prevalence of HCV infection is about 200 million individuals worldwide ***(WHO, 2009)***. Region- or country-specific overall prevalence does not necessarily reflect the risk for spread of HCV because this risk is not homogenous either between or within most countries. Age-specific HCV prevalence rates are more variable, and their patterns provide clues to geographic and temporal differences in the risk for acquiring HCV infection ***(Alter, 2002).***

Hepatitis C Virus Projections Working Group (2002) reported that vastly different countries, including Australia, Italy, Japan, Spain, Turkey, and the United States, belong to regions of the world that have similar estimated average prevalence rates of HCV infection (1.0% to 1.9%).

2.1.3. HCV IN EGYPT:

Egypt has the highest known country-wide prevalence of HCV in the world, with an estimated 8-10 million people have been infected by the virus, ranging from 6 to 28% with an average of approximately 13.8% in the general population ***(Miller & Abo-Raddad, 2010)***. The prevalence of HCV infection also increases steadily with age, but high rates of infection are observed among persons in all age groups ***(Abdel-Aziz et al., 2000)***. Genotype 4 is the most common genotype of HCV and its response to treatment is still a controversy ***(Kamal et al, 2011).***

The origin of the HCV epidemic in Egypt has been attributed to intravenous schistosomiasis treatment in rural areas in the 1960s-80s ***(Frank et al., 2000).*** As schistosomiasis was traditionally the most important public health problem and infection with *Schistosoma mansoni* the major cause of liver disease. From the 1950s until the 1980s, the Egyptian Ministry of Health undertook large control campaigns using intravenous tartar emetic, the standard treatment for schistosomiasis, as community-wide therapy ***(Frank et al., 2000)***. This commendable effort to control a major health problem unfortunately established a very large reservoir of HCV in the country. By the mid-1980s, the effective oral drug, praziquantel, replaced tartar emetic as treatment for schistosomiasis in the entire country. This both reduced schistosomal transmission and