IMPACT OF SERUM LEVELS OF AFP ON RESPONSE TO TREATMENT IN GENOTYPE 4 CHRONIC HCV PATIENTS

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ABSTRACT

Therapy of chronic hepatitis C has greatly improved in recent years, especially with the addition of ribavirin to interferon and with the use of PEG-IFN with ribavirin. Although AFP is used as a diagnostic marker of HCC, mild elevation can be seen in virus related acute and chronic hepatitis.

Aim of work: To detect the relation between the level of AFP in chronic HCV patients and degree of fibrosis and inflammation of the liver and to use AFP to predict SVR to combined interferon therapy.

Participants and methods: 175 chronic HCV patients: 91 patients received PEG-IFN α2b and ribavirin and 84 patients received IFN α2b and ribavirin for 48 weeks, for them routine investigations, serum AFP level and liver biopsy prior to treatment were done.

Results: High serum AFP is correlated with older age, low serum albumin level, low platelet count, higher stage of fibrosis and high HAI index, AFP appears as an additional tool to predict SVR to combined IFN therapy.

Key words: AFP – treatment of HCV – Predictors of response to HCV treatment.

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Aisha El-Sharkawy

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LIST OF ABBREVIATIONS

- **AASLD:** American Association for the Study of Liver Diseases
- **AFP:** Alpha fetoprotein
- **AFP-L :** Alpha fetoprotein-lectin
- **ALT:** Alanine aminotransferase
- **DDB:** Dimethyl-4, 4'-dimethoxy-5,6,5',6'dimethylene dioxybiohenyl-2, 2'-dicarboxylate
- **dsRNA:** double-stranded RNA
- **EVR:** early virological response
- **GGT:** Gamma glutamyl transaminase
- **GTP:** Gamma transpeptidase
- **HAI:** Histological activity index
- **HBcAb:** Hepatitis B core antibody.
- **HBsAg:** Hepatitis B surface antigen
- **HCC:** Hepatocellular carcinoma
- **HCV:** Hepatitis C virus
- **HDC:** Histamine dihydrochloride
- **HP:** Hepatocyte proliferation
- **IFN:** Interferon
- **IL:** Interleukin
- **IMPDH:** inosine 5'-monophosphate dehydrogenase
- **IMU:** International million unit
- **INR:** International normalized ratio
- **IRES:** internal ribosome entry site
- **LCA:** lectin lens culinaris agglutin
- **LPS:** Lipopolysaccharide

- **MMP: Matrix metalloproteases**
- **mPEG: monomethoxy polyethylene glycol**
- **mRNA: Messenger RNA**
- **NF Kappa B: nuclear factor-Kappa B**
- **NIH: National Institutes of Health**
- **NK: Natural killer cell**
- **NS: Non sructural**
- **NSGCT: non-seminomatous germ cell tumours**
- **NS5B: Non structural 5 B**
- **PEG-IFN: Pegylated interferon**
- **PPV: positive predictive value**
- **RIA: radioimmunoassay**
- **RNA: Ribonucleic acid**
- **RNAi: RNA interference**
- **RTPCR: reverse-transcription polymerase chain reaction**
- **siRNAs: Small interfering RNAs**
- **SOD: superoxide dismutase**
- **SVR: sustained virologic response**
- **Th1: T – helper 1**
- **Th2: T – helper 1**
- **TNF: Tumour necrotic factor**
- **Tα -1: Thymosin alpha 1**

INTRODUCTION

Hepatitis C is a major cause of liver related morbidity and mortality worldwide and represents a major public health problem ***(Alberti and Benvegnu, 2003).*** Chronic infection occurs in 50-80% of cases and eventually leads to cirrhosis and hepatocellular carcinoma ***(Pawlotsky, 2004).*** Genotype distribution varies considerably from country to country, with genotype 4 prevailing in Africa and the Middle East ***(Hoofnagle, 2002).***

Egypt has possibly the highest HCV prevalence worldwide ***(Pybus et al., 2003).*** Overall prevalence of antibody to HCV in the general population is around 15-20% ***(Frank et al., 2000)***. The overall prevalence of anti-HCV antibody in semirural and rural Egyptian communities was 20.7%, and the prevalence in each type of communities was 23% and 17.9% respectively ***(Zakaria et al., 2000).***

Arthur et al. (1997) found that HCV seroprevalence in different governorates ranged from zero to 38%. The seroprevalence of HCV increased with age, from 19% in persons 10 – 19 years old to about 60% in persons 30 years and older ***(Darwish et al., 2001)*.**

Therapy of chronic hepatitis C has greatly improved in recent years. Rates of sustained virological response have increased significantly in the late 1990s with the addition of ribavirin to interferon and have further

improved more recently with the use of PEG-IFN again in combination with ribavirin ***(Alberti and Benvegnu, 2003).***

Alberti et al. (1993) confirmed that pretreatment alanine aminotransferase (ALT) and γ-glutamyl transpeptidase levels tend to be lower in responders. ***Poynard et al. (1998)*** reported five factors associated with a favorable response: genotype 2 or 3, viral load less than 2 million copies per ml, age less than 40 years, minimal fibrosis on biopsy, and female sex.

Alpha fetoprotein (AFP) is a typical onco-developmental glycoprotein with one aspargine N-linked oligosaccharide ***(Katsuko et al., 1993)***. It is synthesized mainly in fetal life by yolk sac and in trace amounts by the fetal GIT. It is therefore normally present in the fetus and disappears a few weeks after birth. AFP forms one third of the total fetal plasma proteins. Carrying out most of the functions described to albumin in the adult life ***(Kaneko et al., 2001)*** .The normal adult serum AFP concentration does not exceed 6ng/ml ***(Greenberg, 1990).***

Significant synthesis of AFP commences again when some adult cell becomes transformed to cancer cells, AFP is also produced by the differentiated adult hepatocytes. The differentiation of the cancer cells and genetic depression of protein synthesis would explain the AFP production by cancer cells ***(Johnson, 2001).***

AFP and liver ultrasonography are the most widely used tools for screening of hepatocellular carcinoma ***(Barletta et al., 2005).***

Serum AFP values are elevated among patients with advanced HCV. Factors associated with raised AFP include severity of liver disease, female gender and black race. Serum AFP levels decline during antiviral therapy ***(Di Bisceglie et al., 2005).***

In patients with chronic HCV, elevated serum AFP levels were significantly correlated with lower serum albumin levels, advanced fibrosis/cirrhosis and genotype 1b infection ***(Chu et al., 2001).***