Serum Levels of AFP after Interferon-Based Therapy with Ribavirin for Genotype 4 Chronic HCV Patients

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بسم الله الرحمن الرحيم

(و قل اعملوا فسيرى الله عملكم و رسوله و المؤمنون و ستردون إلى عالم الغيب و الشهادة فينبئكم بما كنتم تعملون) صدق الله العظيم

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Shaimaa Mohamed Abdou

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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
- **AST :** Aspartate Aminotransferase
- **ANA:** Anti-Nuclear Antibody
- **ATP:** Adenosine Triphosphate
- **BMI:** Body Mass Index
- **bp:** base pair
- **CBC :** Complete Blood Picture
- **CD4+:** T-helper cell
- **CD8+:** Cytotoxic T cell
- **CLD:** Chronic Liver Disease
- **CHC :** Chronic Hepatitis C
- **CIFN:** Consensus Interferon
- **CTP :** Child-Turcotte-Pugh
- **DDB:**Dimethyl-4, 4'-dimethoxy-5,6,5',6'dimethylene dioxybiohenyl-2, 2'-dicarboxylate
- **DDW :** Digestive Diseases Week
- **dsRNA:** double-stranded RNA
- **EIA:** Enzyme Immunometric Assay
- **EVR:** Early Virological Response
- **ETR :**End of Treatment Response
- **FDA:** Food and Drug Administration
- **GFR :** Glomerular Filtration Rate
- **GGT:** Gamma glutamyl transaminase
- **GTP:** Gamma transpeptidase
- **HAART :** Highly Active Antiretroviral Therapy
- **HAI:** Histological Activity Index
- **Hb:** Hemoglobin

- **HBcAb:** Hepatitis B core antibody
- **HBsAg:** Hepatitis B surface antigen
- **HCC:** Hepatocellular carcinoma
- **HCV:** Hepatitis C virus
- **HDC:** Histamine dihydrochloride
- **HIV:**Human Immunodeficiency Virus
- **HP:** Hepatocyte Proliferation
- **HRP :** Horseradish peroxidase
- **HS:** Highly Significant
- **IFN:** Interferon
- **IL:** Interleukin
- **IU:** International Unit
- **IV:** Intravenous
- **IMPDH:** Inosine 5'-monophosphate dehydrogenase
- **IMU:** International Million Unit
- **INR:** International Normalized Ratio
- **IRES:** Internal Ribosome Entry Site
- **LCA:** Lectin Lens Culinaris Agglutin
- **LhRNAs :** long hairpin RNAs
- **LPS:** Lipopolysaccharide
- **MiRNA :** micro-RNA
- **MMP:** Matrix Metalloproteases
- **MMPD :** Merimepodib
- **mPEG:** Monomethoxy polyethylene glycol
- **mRNA:** Messenger RNA
- **NF Kappa B:** nuclear factor-Kappa B
- **NIH:** National Institute of Health
- **NK:** Natural Killer Cell
- **NS:** Non Structural
- **NSGCT:** Non-Seminomatous Germ Cell Tumours
- **NS5B:** Non structural 5 B
- **5'NTR :** 5' non translated region

- **PAT:** Parentral anti-schistosomal treatment
- **PCR:** Polymerase Chain Reaction
- **PEG-IFN :** Pegylated Interferon
- **PIs :** Protease Inhibitors
- **PO:** Per-oris.
- **PPV:** Positive Predictive Value
- **PT :** Prothrombin Time
- **RBCs:** Red Blood Cells
- **RIA:** Radioimmunoassay
- **RNA:** Ribonucleic acid
- **RNAi:** RNA interference
- **RTPCR:** Reverse-Transcription Polymerase Chain Reaction
- **RVR :** Rapid Virologic Response
- **SC :** Subcutaneously
- **SD :** Standard Deviation
- **SI :** Silymarin
- **siRNAs:** Small interfering RNAs
- **SOD:** Superoxide dismutase
- **STAT :** Specifically Targeted Antiviral Therapy
- **STAT –C :** Specifically Targeted Antiviral Therapy for Hepatitis C
- **SVR:** Sustained Virologic Response
- **Th1:** T – helper 1
- **Th2:** T – helper 2
- **TNF:** Tumour Necrosis Factor
- **TLR:** Toll-Like Receptor
- **Tα -1:** Thymosin alpha 1
- **ULN:** Upper limit of normal
- **WBC:** White Blood Cells

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Abstract

Key words:

AFP: Alpha feto-protein, HCC: Hepatocellular carcinoma,

HCV: Hepatitis C virus, PEG-IFN: pegylated interferon,

SVR: sustained virological response.

Aim: Compare changes in AFP levels before and after interferon treatment in responders and non-responders with liver histopathological changes and to verify the possibility of using AFP as a predictor of response to interferon-ribavirin therapy in chronic HCV genotype 4 patients.

Background and methods: HCV infection is a major health problem in Egypt and it is a major cause of chronic hepatitis and hepatic fibrosis that progresses in some patients to HCC. AFP has been widely used as a diagnostic marker for HCC. Elevated levels of AFP can be seen in chronic HCV.
This prospective study recruited 79 chronic HCV patients (genotype 4) who received treatment in the form of PEG-IFN alfa-2b 100 µg weekly and ribavirin 11mg/kg/day for 48 weeks then followed up by AFP level and liver biopsy.

Results: AFP level decreased in all patients with better results in SVR patients. Histopathological improvements occurred in most patients after treatment. Pre-treatment AFP was correlated with age, fibrosis , inflammation, transaminases, hemoglobin, platelet count and AFP difference.

Conclusions: AFP can be used as a good predictor for treatment response before starting treatment in chronic HCV genotype 4 patients.

Introduction

Chronic hepatitis C virus (HCV) infects approximately 170 million people world wide. It is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma and represents the most frequent cause for liver transplantation in the US and Europe ***(Lauer, 2001)*.**

Genotypes 1, 2 and 3 of the Hepatitis C virus (HCV) are widely distributed throughout Western countries and the Far East (Japan, China, Taiwan, and Thailand). Types 5 and 6 are mainly confined to South Africa and Southeast Asia, respectively, in contrast to type 4, which is predominant in the Middle East and Central Africa ***(Maertens, 1997).***

Hepatitis C virus (HCV) infection is a major health problem in Egypt, where the seroprevalence is 10-20-fold higher than that in the United States ***(Ray, 2000)***. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% among regions and demographic groups ***(Lehman, 2009).***

Pegylated interferon (PEG-IFN) plus ribavirin (RBV) therapy given for 48 weeks is established as the standard therapy for patients with chronic HCV infection with genotypes 1and 4 ***(NIH Consensus, 2002).*** This treatment has yielded overall sustained virological response (SVR) rates of 54% to 69% in randomized controlled phase III clinical trials ***(Zeuzem, 2005).*** However, response to treatment is not uniform across all populations ***(Dienstag, 2006b)*** and is dependent on various viral and host factors.

Alpha-fetoprotein (AFP) is α1-globulin secreted by fetal hepatocytes and in a small amount by other cells of the fetal gastrointestinal tract. Physiologically, in human adults an increased AFP level is present in the serum of pregnant women ***(Cedrone et al., 2000 and Chu et al.,2001).***

AFP has been widely used as a diagnostic marker for hepatocellular carcinoma (HCC).However, there are some patients showing continuous high AFP values but no evidence of HCC, and some studies have defined such patients as a high risk group for HCC ***(Murashima et al., 2006).***

In vitro study has shown that interferon (IFN) inhibits cell proliferation and enhances apoptosis as well as specific cytotoxic T-lymphocytes against HCC, resulting in direct anticancer actions. Since AFP is a significant predictor for HCC, therapeutic strategies for hepatitis C, e.g. long-term low-dose IFN treatment, may reduce hepatocarcinogenesis ***(Murashima et al., 2006).***

Hepatic progenitor cells (HPC) arise in the periportal region of the liver and may be responsible for liver regeneration. They express high levels of AFP, certain keratin markers, and GGT ***(Dabeva, 1993).***Their presence is related to the severity of fibrosis ***(Tsamandas et al., 2006)*** and their activation has been documented in parallel with cells associated with the development of fibrosis (stellate cells) ***(Yin et al., 2002).***Quite interestingly, HPC expression has recently been associated with response to treatment, being higher in non-responders and relapsers compared with responders ***(Tsamandas et al.,2006).***

Predictors of response to therapy serve as decision tools for physicians to help identify patients who are likely or unlikely to achieve an SVR, and to consider pre-treatment counseling in those patients with a reduced likelihood of successful therapy, perhaps sparing them the side effects and cost of therapy. Therefore, knowledge of predictors to these therapies is extremely valuable ***(Abdo, 2009).***