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A STUDY ON INTERFERON APLHA RECEPTORS AND STAT1 AS THERAPY PREDICTORS IN HEPATITIS INFECTION

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Abstract:

Introduction: *Liver is a pivotal organ of the body and play very important role in the metabolism. If there is any problem in the liver then the herbs or different plants play an important role for the treatment of liver disorders.*

Objective of the study: *The main objective of the study is to analyze the interferon aplha receptors and STAT1 as therapy predictors in hepatitis infection.*

Methodology of the study: *This cross sectional study was conducted in hospital of Sialkot during September 2018 to January 2018. The purpose and benefits of the study were explained to each participant and informed written consent was obtained. By using non-probability convenience sampling, we enrolled treatment-naïve HCV mono-infected and HCV/HBV co-infected patients along with healthy controls. Out of the eligible patients, some were also positive with hepatitis B surface antigen (HbsAg) along with serum HBV-deoxyribonucleic acid (DNA) level.*

Results: *The demographic values of patient group and control group shows a significant difference. The data suggest clearly that CD4 count decreases in abnormal liver function. There were non-significant relationship present in diseased group treated with different therapies like interferon and glutathione as as $p<0.05$. The level of micronutrients become decreases in diseased group. Of the eligible 171(88%) patients, 86(50.3%) were also positive with HbsAg. The final study sample had 191 subjects. Of them, there were 20(10.5%) in group-1a, 35(18.3%) in group-2a, 65(34%) in group-1b and 51(26.7%) in group-2b.*

Conclusion: *It is concluded that hepatitis directly increase the liver enzymes even after receiving medication and other therapies. Expression rate of IFNAR-1 mRNA maybe useful index for predicting long-term efficacy of IFN therapy compared to STAT-1 and IFNAR-2. Replication of HBV-DNA is not the main factor leading to down-regulation of IFN-α receptors or STAT-1.*

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INTRODUCTION:

Liver is a pivotal organ of the body and play very important role in the metabolism. If there is any problem in the liver then the herbs or different plants play an important role for the treatment of liver disorders. There are a number of plants which shows hepatoprotective property. Hepatitis B and C viruses can lead to hepatocellular carcinoma and cirrhosis-related end-stage liver disease, which are potentially life-threatening liver diseases [1]. Hepatitis B and C need immediate worldwide attention as the infection rates are too high. More than 240 million people globally have chronic (long-term) liver infections. Every year, about 600,000 people die because of the acute or chronic consequences of hepatitis B, and more than 350,000 people die from hepatitis C-related liver diseases worldwide [2].

Hepatitis is a major public health problem and is endemic throughout the world especially in tropical and developing countries [3]. Hepatitis means inflammation of the liver. The liver is indispensable to our survival. It has synthetic, storage and detoxification functions. An abnormal LFT may signify a serious disease that can be identified only through further testing. These conditions include liver diseases, such as primary biliary cirrhosis (PBC), diseases of other organs such as Paget's disease of bone, and multi-organ diseases such as haemochromatosis [4]. However, the majority of people with an abnormal LFT in primary care settings will not have any such previously undetected disease [5]. They will have either no disease at all, or will be manifesting the effects of alcohol abuse or obesity. Due to shared mode of transmission, hepatitis C virus (HCV) /hepatitis B virus (HBV) co-infection represents significant public health issues worldwide. Owing to hepatotropic nature, HCV and HBV co-infection is common in highly endemic areas and among subjects with increased possibility of parental infections. HCV causes persistent infection in 60-65% of HCV mono infected and 70-80% of HCV/HBV co-infected patients. Signal transduction is mediated by rapid tyrosine phosphorylation of IFNAR-1 and JAK proteins, leading to activation of downstream STATs by phosphorylating critical serine and tyrosine residues [6]. STAT proteins are the key mediators of cytokine-induced gene expression and exert active role in anti-viral, anti-mycobacterial and anti-tumor responses against hepatitis. A recent review described multiple mechanisms related to JAK-STAT signaling pathway for modulation of HCV infection. Activated STAT-1 and STAT-2 bind IFN-regulatory factor 9 and form a heterotrimeric complex called IFN stimulated gene factor 3 (ISGF-3) [7]. Consequently, ISGF-3 binds to IFN-stimulated response elements in the promoters of IFN-stimulated genes, thereby activating transcription. IFN expression and STAT may be directly involved in response to therapy and pathogenesis of viral hepatitis [8].

Objective of the study

The main objective of the study is to analyze the interferon aplha receptors and STAT1 as therapy predictors in hepatitis infection.

METHODOLOGY OF THE STUDY

This cross sectional study was conducted in hospital of Sialkot during September 2018 to January 2018. The purpose and benefits of the study were explained to each participant and informed written consent was obtained. By using non-probability convenience sampling, we enrolled treatment-naïve HCV mono-infected and HCV/HBV co-infected patients along with healthy controls. Out of the eligible patients, some were also positive with hepatitis B surface antigen (HbsAg) along with serum HBV-deoxyribonucleic acid (DNA) level. Detailed history was taken from all patients with special reference to duration of hepatitis, mode of infection, previous history of jaundice, HBV or HCV infection. A thorough clinical examination was carried out and stigmata of chronic liver disease, hepatosplenomegaly, ascites, etc. if present were noted.

Blood investigation

It includes Hemoglobin (Hb), total leucocytes count (TLC), differential leucocytes count (DLC), platelet count, level of micronutrients and LFT were done in all patients. The LFT included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (SAP) and serum albumin. Abnormal values were defined as serum Bilirubin ≥1.5 mg/dl, ALT/AST≥50 IU/ml.

Statistical analysis

The data were sampled and entered into the SPSS worksheet for analysis. The alpha criterion was set at 0.05 (95% confidence interval [CI]). After constructing a 2×2 contingency table, chi-square without Yates correction was used to find the association between the potential risk factors and hepatitis status.

RESULTS:

The demographic values of patient group and control group shows a significant difference. The data suggest clearly that CD4 count decreases in abnormal liver

function. There were non-significant relationship present in diseased group treated with different therapies like interferon and glutathione as as $p<0.05$. The level of micronutrients become decreases in diseased group. Of the eligible 171(88%) patients, 86(50.3%) were also positive with HbsAg. The final study sample had 191 subjects. Of them, there were 20(10.5%) in group-1a, 35(18.3%) in group-2a, 65(34%) in group-1b and 51(26.7%) in group-2. The remaining 20(10.5%) were controls. Overall, 106 (55.5%) were male and 85 (44.5%) were female. Comparison of demographic and clinical characteristics among the groups was done.

Table 01: analysis of characteristics of patients and control.

Characteristics	Group 1 HCV mono-infected (n= 85)	Group 2 HCV/HBV co-infected (n= 86)	Group 3 Control (n = 20)
Mean Age, years	31.20 ± 5.04	36.33 ± 8.61	31.70 ± 6.78
Gender			
Male	47 (55.3%)	48 (55.8%)	11 (55%)
Female	38 (44.7%)	38 (44.2%)	09 (45%)
BMI, kg/m^2	23.32 ± 2.07	24.72± 1.81	22.60 ± 2.68
AST, U/L	45.20 ± 15.10	38.12 ± 8.56	26.55 ± 6.6
ALT, U/L	61.89 ± 20.44	65.07 ± 21.03	31.20 ± 7.19
HCV-RNA, >4×10^6 IU/ml	5.48 ± 1.2	5.84± 1.3	Not detected
HBV-DNA, >2×10^4 IU/ml	Not detected	4.18 ± 1.90	Not detected
IFNAR-1 mRNA	47 (55.29%)	63 (73.25%)	20 (100%)
IFNAR-2 mRNA	72(84.7%)	54 (62.7%)	20 (100%)
STAT-1	75 (88.23%)	54(62.7%)	14 (70%)

DISCUSSION:

The chemokine IL-8 is an important member of the chemokine CXC family. The key function of IL-8 is to attract polymorphonuclear cells to sites of tissue injury and inflammation. IL-8 is synthesized by several cell types, including monocytes, macrophages, Kupffer cells, hepatocytes, and hepatic stellate cells [7]. IL-8 levels are upregulated in the peripheral blood and liver, thereby indicating that increased tissue infiltration and macrophage-induced hepatic activation are mediated by the interaction between IL-8 and CXCR-1 during hepatitis C infection [1]. Damage to the structural integrity of liver is reflected by an increase in the level of serum transaminase because these are cytoplasmic in location and are released into circulation after cellular damage [9]. It is generally accepted that the toxicity of carbon tetrachloride depends on the cleavage of the carbon-chlorine bond to generate a trichloromethyl free radical, and this free radical reacts rapidly with oxygen to form a trichloro methyl peroxy radical, which may contribute to the hepatotoxicity and subsequent increase in hepatic enzymes [4].

Essential micronutrients are involved in many metabolic pathways in the liver, such as enzymatic functions and protein synthesis, oxidative damage and anti-oxidant defense, immunological competence, interferon therapy response regulations, and alterations of the virus genomes. Reactive oxygen species (ROS) have also been implicated in a number of hepatic pathologies in exacerbating liver diseases [10].

HCV is a major cause of chronic liver disease. HCV infection frequently leads to chronic hepatitis with increasing risk of developing liver cirrhosis and HCC.

Interferon with or without ribavirin is the only drug with proven efficacy in treating chronic HCV infections. Unfortunately, these therapeutic models maintain the rate of sustained virologic response (SVR) to approximately 10-40%. The effective advancement in the antiviral treatments against chronic hepatitis C is necessary [1].

CONCLUSION:

It is concluded that hepatitis directly increase the liver enzymes even after receiving medication and other therapies. Expression rate of IFNAR-1 mRNA maybe useful index for predicting long-term efficacy of IFN therapy compared to STAT-1 and IFNAR-2. Replication of HBV-DNA is not the main factor leading to down-regulation of IFN-α receptors or STAT-1. The distribution of micronutrients activities in blood may be an additional host-specific parameter with a predictive value for the responsiveness of patients to interferon therapy.

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