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Correlation between Serum Levels of TNFR and IL6 with Treatment Response to Pegylated Interferon and Ribavirin Therapy in Chronic Hepatitis C Egyptian Patients

Amal A Mohamed[1]*, Essam A Afifi[2], Rehab R EL-Awady[3], Sally M Aboelsayed[3], Fathia El- Halawany[4], Mohamed Saleh[5] and Hala H El Deeb[6]

[1]*Biochemistry Department, National Hepatology and Tropical Medicine Research Institute, Egypt*

[2]*Biochemistry Department, Faculty of Medicine (Boys), Al-AzharUniversity, Egypt*

[3]*Biochemistry Department, Faculty of Pharmacy (Girls), AL- Azhr University, Egypt*

[4]*Statistics Department, Faculty of Science (Girls), King AbdulazizUniversity, Jeddah*

[5]*Internal Medicine Department, National Hepatology and Tropical Medicine Research Institute, Egypt*

[6]*Clinical pathology Department, El Sahel Teaching Hosiptal, Egypt*

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***Corresponding author:** Amal, Consultant of Biochemistry and Molecular Biology, Biochemistry department, National Hepatology and Tropical Medicine Research Institute, Fom El-Khalig, Cairo,11796, Egypt, Tel: +201224847367; +201094918168; email: amalahmedhcp@yahoo.com

Abstract

Background: Hepatitis C virus (HCV) infects nearly 3%of the population worldwide and has emerged as major causative agent of liver disease, resulting in acute and chronic infections that can lead to intrahepatic lipid accumulation (steatosis) and progressive fibrosis of variable degrees and long–term progression to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Egypt has one of the highest HCV prevalence in the world (nearly 15% of the population). The combination of Pegylated interferon alpha (PEG-IFN α) and Ribavirin (RBV) is the approved and well accepted standard-of-care for chronic hepatitis C (CHC).It was reported that Interleukin 6(IL6) is associated with insulin resistance and interferon resistance, which may affect the outcome of antiviral treatment.

Patients and methods: This study was conducted on 70 subjects.

A. **Group I:** Included 20 healthy subjects aged 18-60 years old with no history of liver infection.

B. **Group II:** Involved 50 Egyptian adult patients with chronic hepatitis C virus type-4 (HCV-4) infection. All the patients were subjected to clinical assessment. Height and weight were determined at baseline and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (weight in kilograms/height in meters). Liver enzymes including ALT (alanine aminotransferase), AST (aspartate amino transferase), serum albumin (Alb), serum bilirubin including total bilirubin (T BIL), prothrombin time (PT), complete blood count (CBC), fasting blood sugar, Alpha fetoprotein (AFP) andQuantitative detection of HCV-RNA in serum by real-time PCR were measured. Serum concentrations of both Tumor necrosis factor Receptor I (TNFR1) and Interleukin 6(IL6) before and after treatment using a commercially available Quantikine enzyme linked immunosorbent assay.

Results: The Mean values of IL6 level in responders and non-responders were308.88and 405.33Pg/ml, respectively. The Mean values of TNFRI in responders and non-responders were 59.197and 59.611Pg/ml, respectively .Regarding IL6 level, there was a statistically significant difference between responders and non-responders (P=0.000). Regarding to TNFRI level there was no significant difference between responders and non-responders ($P < 0.05$). The best cut-off point for IL6 was ≤260 with a sensitivity of 84%, a specificity of 82.9% and a positive predictive value of 78.1 %, negative predictive value of 77.7 %.The best cut-off point for TNFRI was >33 with a sensitivity of 78%, a specificity of 65.71% and a positive predictive value of 78.1 %, negative predictive value of 22.2 %.

Conclusion: High serum level of IL-6 is associated with response failure to PEG-IFN/RBV therapy while TNFRI is not associated with the response to therapy. IL6 and TNFRI have a good predictive ability for the response to PEG-IFN α/ RBV and IL6 is a more sensitive and specific predictive factor than TNFRI

Keywords: Hepatitis C virus; Hepatocellular carcinoma; Pegylated interferon; Interleukin 6; Tumor necrosis factor Receptor I.

Introduction

Hepatitis C virus (HCV) infects nearly 3%of the population worldwide and has emerged as major causative agent of liver disease, resulting in acute and chronic infections that can lead to intrahepatic lipid accumulation (steatosis) and progressive fibrosis of variable degrees and long – term progression to cirrhosis, liver failure,and hepatocellular carcinoma (HCC)[1]. Egypt has one of the highest HCV prevalence in the world (nearly 15% of the population) [2]. The combination of Pegylated interferon alpha (Peg-IFN α) and Ribavirin (RBV) is the approved and well-accepted standard-of-care (SOC) for chronic hepatitis C (CHC) [3].

Cytokines are pleiotropic, regulatory molecules that elicit their effect by binding and activating specific cytokine-receptors. They produced by macrophages, T-cells and monocytes, platelets, endothelial cells and vascular smooth muscle cells [4]. The cytokine group is highly heterogeneous and consists of different types of molecules, such as the interleukins (ILs), the tumor necrosis factor (TNF) family, the interferons (IFNs), the chemokines, the transforming growth factor-b and others [5]. Cytokines are produced by a wide variety of cells, mainly the T helper 1(Th1) and T helper 2(Th2) cells. Th1 cells secrete pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, and TNF) whereas the Th2 cells secrete anti-inflammatory cytokines (e.g. IL-4, IL-5, IL-6, IL-10, and IL-13) [5,6]. Changes in various cytokine activities have been reported during HCV infection, while an imbalance of pro-inflammatory and anti-inflammatory cytokine production influences their immune pathogenesis. In particular, alterations in serum and intra hepatic Th1 and Th2 cytokine patterns play a critical role in viral persistence, as well as in host immune response, in liver damage and liver disease progression from chronic hepatitis to hepatocellular carcinoma [7,8]. Tumor necrosis factor-alpha has two receptors, which upon binding of TNF-α dissociate from the membrane of the target cells. The shedded receptors can be detected in serum assoluble TNF-α receptor I (sTNFRI, p55&CD120A) and soluble TNF-α receptor II (sTNFRII, p75& CD120B). They have a longer half-life than TNF-α itself [9]. In CHC, serum levels of TNF-α and both types of circulating sTNFR were not only increased in infected patients compared with controls, but also the levels of sTNFR correlated significantly with amino transferase levels and the histological severity of inflammation [10]. Interleukin 6 is a pleiotropic cytokine; it increased in various types of chronic liver disease, including CHC [11]. IL-6 has a dual effect; at some levels it acts as a defense mechanism (anti-inflammatory) but in chronic inflammation it is rather pro-inflammatory [12].

IL6 production was induced by monocytes through a TNF-α independent pathway and the increased level of IL6 in turn down regulated the production of TNF- α [13]. IL6 is associated with insulin resistance, iron metabolism and interferon resistance, which may affect the outcome of antiviral treatment [11]. Both Peg-IFN α and RBV have not only antiviral but also immune modulatory properties such as alteration of immune functions and T-helper1 (Th1(/T-helper2 (Th2) cytokine balance [14]. Increased Th2 and altered Th1 cytokine production have been associated with viral persistence and failure of antiviral treatment in CHC [15]. The aim of the present study is to assess the association of TNFR and IL6 concentrations with response to Peg-IFN and RBV for CHC patients.

Patients and methods

Subjects

This study was conducted on 70 subjects. Both adult males and females were included:

A. **Group I:** Included healthy subjects (n = 20, 12 males and 8 females), aged 18-60 years old with no history of liver infection, endocrine disorders, long term drug use, autoimmune hepatitis or alcohol consumption and all of them had completely normal liver function tests, normal liver ultrasounds and negative serological findings for viral and autoimmune liver diseases and diabetes.

B. **Group II:** Involved 50 Egyptian adult patients with chronic hepatitis C virus type-4 (HCV-4) infection. They were 16 females and 34 male patients aged 18-60 years old. The blood samples were collected from patients treated at National Hepatology& Tropical Medicine Research institute, Cairo, Egypt.

Treatment regimens

All patients with chronic HCV-4 were treated with a weekly subcutaneous injection of Pegylated interferon-alpha-2b (Peg-IFN-α-2b) at a dose of 1.5 mg/kg per week in combination with a weight-adjusted dose of oral ribavirin (RBV) (1000 mg/day for <75 kg, 1200 mg/day for > 75 kg) for 48 weeks. The inclusion criteria are adult men or women (18–60years old) with proven chronic hepatitis C genotype 4, elevation of aspartate aminotransferase and alanine aminotransferase levels, positive serum HCV-RNA by quantitative PCR, naive patients (not previously treated with any antiviral drugs including IFN, ribavirin and thymosin). The exclusion criteria are decompensated liver disease, histological evidence of hepatic cirrhosis diagnosed by hepatic histopathology, pregnant or nursing female, concomitant hepatic schistosomal infection (excluded by rectal snip and pathologically), alcohol intake, other etiologies of chronic hepatitis (e.g. auto- immune, hepatitis B virus infection and drug-induced liver injury), pre-existing anemia (Hb< 13 gm /dl in males and 12 gm /dl in females, Severe pre-existing psychiatric conditions, Antiviral or immunosuppressive therapy within the last 6 months, and presence of any chronic systemic illness(Thyroid disease ,Uncontrolled Diabetes mellitus , renal disease, Ischemic cardiovascular disease or hypertension). All the patients were subjected to clinical assessment. Height

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and weight were determined at baseline and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (weight in kilograms/height in meters). Abdominal Ultra sonography was done for all Participants.

Laboratory investigations

Liver enzymes including ALT (alanine aminotransferase), AST (aspartate aminotransferase), serum albumin (Alb), serum bilirubin including total bilirubin (T BIL), direct bilirubin (D BIL) international normalized ratio of prothrombin time (INR), white blood cells (WBC), hemoglobin (Hb), fasting blood sugar, thyroid stimulating hormone (TSH), Alpha fetoprotein (AFP) .

Molecular tests

Quantitative detection of HCV-RNA in serum by real-time PCR was performed for all patients and controls initially and repeated for the patients again after 48 weeks of treatment with (Peg-IFN-α-2b) +RBV. According to quantitative PCR value both the level of viremia and the response to the treatment can determined. Serum concentrations of both TNFR1 and IL6 were measured before and after treatment with (Peg-IFN-α-2b)+RBV using a commercially available Quantikine enzyme linked immunosorbent assay (ELISA) kit provided by (R&D Systems, USA) following the manufacturer's recommendations.

Statistical analysis

- Data were collected, checked, revised and entered the computer. Data analyzed by SPSS statistical package version 19. Excel computer program was used to tabulate the results, and represent it graphically.
- For the quantitative variables, which are normally distributed, independent t-test used to declare the significant difference between control and cases at P<0.05.
- Paired t-test used to declare the significant difference between before and after treatment at P<0.05.
- Pearson's correlation coefficient used to declare the significant correlation between the quantitative parameters within each group at P<0.05.
- Qualitative variables were expressed as count and percentages. Chi-square test for distribution used to show the significant difference between control and cases at P<0.05.

MedCalc creates a list of sensitivity, specificity, likelihood ratios, and positive and negative predictive values for all possible threshold values. MedCalc allows performing Receiver operating characteristic curve (ROC curve) analysis easily and accurately, the Area under the curve (AUC) with standard error (SE) and 95% confidence interval (CI), with automatic calculation of corresponding sensitivity and specificity.

Results

The Mean values of IL6 level in control, CHC patients before and after treatment were 251.2, 265.97 and 343.6 Pg/ml, respectively. There was no statistically significant difference between control and CHC patients before treatment (P =0.585) (Table 1), although there was a statistically significant increase in CHC patients after treatment compared to before treatment (P= 0.000) (P < 0.05) (Table 2). The Mean values of TNFRI level in control, CHC patients before and after treatment were 22.405, 76.394 and 59.346 Pg/ml, respectively. There was a statistically significant increase in CHC patients compared to controls (P =0.009) (Table 1) and a statistically significant decrease in CHC patients after treatment compared to before treatment (P= 0.000) (P < 0.05) (Table 2). Chronic hepatitis C patients before treatment showed significantly higher level of AST, ALT, AFP, TSH, WBC and significantly lower level of glucose, platelets when compared to control (P < 0.05) (Table 1). Chronic hepatitis C patients before treatment showed significantly higher level of AST, ALT, WBC, Hb, Alb, platelets and significantly lower level of Creatinine when compared to after treatment (P < 0.05) (Table 2).

At the end of the study, patients were subdivided according to the response to treatment into responders and non-responders. The Mean values of IL6 level in responders and non-responders were 308.88and 405.33Pg/ml, respectively while the Mean values of TNFRI in responders and non-responders were 59.197and 59.611Pg/ml, respectively. Regarding IL6 level, there was a statistically significant increase in non-responders compared to responders (P=0.000) (P < 0.05) (Table 3). Regarding TNFRI level there was no significant difference (P < 0.05) between responders and non-responders (P=0.984) (P < 0.05) (Table 3). Responders showed significantly lower level of AST, ALT, TSH, D BILL and significantly higher level of Alb when compared to Non-responders (P <0.05) (Table 3). There was a significant negative correlation between the serum levels of IL6 and AST (*P* = 0.004, r = -0.3997), also between serum levels of TNFRI and ALT (P = 0.0171, r = -0.33587). Receiver operating characteristic curve was plotted (Figure 1,2) to identify the best cut-off point for both IL6 and TNFRI to detect the difference between CHC patients before treatment and CHC patients after treatment plus control.

- The best cut-off point for IL6 was ≤260 with a sensitivity of 84%, a specificity of 82.9% and a positive predictive value of 78.1 %, negative predictive value of 77.7 %.
- The best cut-off point for TNFRI was >33 with a sensitivity of 78%, a specificity of 65.71% and a positive predictive value of 78.1 %, negative predictive value of 22.2 %.

Table 1: Comparison between control and chronic hepatitis C patients

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Variable	Control N=20		CHC before treatment N=50		P= value
	Mean	SE	Mean	SE	
IL6 (Pg/ml)	251.2	20.624	265.97	14.855	0.585
TNFRI (Pg/ml)	22.405	6.3556	76.394	12.4305	0.009*
ALT (IU/L)	32.1	1.961	59.18	2.772	0.000*
AST (IU/L)	35.2	2.384	62.62	3.424	0.000*
T BIL (g/dl)	0.856	0.0519	1.06	0.0579	0.049
D BIL(g/dl)	0.195	0.0352	0.254	0.0236	0.179
Alb (g/dl)	3.79	0.458	3.834	0.0461	0.578
INR (%)	1.198	0.0395	1.238	0.0253	0.402
Glucose (mg/dl)	110.6	3.639	99.24	2.44	0.014*
Hb (g/dl)	11.8	0.408	12.01	0.258	0.662
TSH (ng/dl)	2.77	0.243	3.67	0.107	0.000*
Serum AFP (ng/ml)	6.88	0.901	13.04	1.818	0.040
Creatinine(mg/dl)	0.966	0.368	0.972	0.022	0.889
Platelets	255100	14676.571	291.08	10.529	0.000*
WBC	5938.75	443.571	8024	197.299	0.000*
BMI	23.3	1.318	26.98	1.334	0.110

IL6: Interleukin 6; TNFRI: Tumor Necrosis Factor Receptor I; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TBil: Total Bilirubin; D.Bill: Direct Bilirubin; INR: International Normalized Ratio of Prothrombin Time of Blood Coagulation; Hb: Hemoglobin; Alb: Albumin; AFP: Alpha Fetoprotein; TSH: Thyroid Stimulating Hormone; BMI: Body Mass Index; WBC: white blood cells.

*P< 0.05.

Table 2: Comparison between chronic hepatitis C before and after treatment.

Variable	CHC before treatment N=50		CHC after treatment N=50		P= value
	Mean	SE	Mean	SE	
IL6 (Pg/ml)	265.97	14.855	343.6	10.921	0.000*
TNFRI(Pg/ml)	76.394	12.4305	59.346	9.812	0.000*
ALT (IU/L)	59.18	2.772	36.26	1.481	0.000*
AST (IU/L)	62.62	3.424	46.66	3.379	0.003*
T BIL(g/dl)	1.06	0.0579	2.97	1.1385	0.101
D BIL(g/dl)	0.254	0.0236	0.292	0.0384	0.379
Alb(g/dl)	3.834	0.0461	3.376	0.1478	0.004*
INR (%)	1.238	0.0253	1.24	0.0228	0.96
Glucose (mg/dl)	99.24	2.44	96.47	4.367	0.606
Hb (g/dl)	12.01	0.258	9.96	0.242	0.000*
TSH (ng/dl)	3.67	0.107	3.74	0.224	0.756
Serum AFP (ng/ml)	13.04	1.818	15.15	3.182	0.572
Creatinine (mg/dl)	0.972	0.022	1.088	0.0428	0.014
Platelets	291.08	10.529	210.34	6.539	0.000*
WBC	8024	197.299	5206.36	246.48	0.000*
BMI	26.98	1.334	24.42	1.09	0.184

IL6: Interleukin 6; TNFRI: Tumor Necrosis Factor Receptor I; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TBil: Total Bilirubin; D.Bill: Direct Bilirubin; INR: International Normalized Ratio of Prothrombin Time of Blood Coagulation; Hb: Hemoglobin; Alb: Albumin; AFP: Alpha Fetoprotein; TSH: Thyroid Stimulating Hormone; BMI: Body Mass Index; WBC: white blood cells.

*P< 0.05.

Table 3: Comparison between responders and non-responders after treatment.

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Variable	Responders N=32		Non-responders N=18		P= value
	Mean	SE	Mean	SE	
IL6 (Pg/ml)	308.88	19.488	405.33	19.488	0.000*
TNFRI (Pg/ml)	59.197	16.9365	59.611	16.9365	0.984
ALT (IU/L)	32.53	1.286	42.89	2.856	0.000*
AST (IU/L)	36.56	2.738	64.61	6.122	0.000*
T BIL (g/dl)	2.478	1.1665	3.844	2.4284	0.57
D BIL(g/dl)	0.2	0.0291	0.456	0.0813	0.001*
Alb (g/dl)	3.628	0.1719	2.928	0.2464	0.021*
INR (%)	1.247	0.0294	1.227	0.0367	0.675
Glucose (mg/dl)	91.98	5.391	104.47	7.251	0.172
Hb (g/dl)	9.47	0.345	10.34	0.259	0.237
TSH (ng/dl)	3.34	0.27	4.47	0.344	0.014*
Serum AFP (ng/ml)	14.88	4.134	15.63	5.065	0.911
Creatinine (mg/dl)	1.066	0.0511	1.128	0.0779	0.492
Platelets	206.84	7.777	216.56	11.948	0.482
WBC	5444.62	304.989	4782.78	410.335	0.201
BMI	20.62	0.938	31.17	1.57	0.000*

IL6: Interleukin 6; TNFRI: Tumor Necrosis Factor Receptor I; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; TBil: Total Bilirubin; D.Bill: Direct Bilirubin; INR: International Normalized Ratio of Prothrombin Time of Blood Coagulation; Hb: Hemoglobin; Alb: Albumin; AFP: Alpha Fetoprotein; TSH: Thyroid Stimulating Hormone; BMI: Body Mass Index; WBC: white blood cells.

*P< 0.05.

Table 4: Area under the curve of IL6.

IL6	AUC	St. error	P (Area =0.5)	95%CI (Confidence interval)
	0.812	0.0408	<0.0001	0.731 to 0.878

Table 5: ROC curve values of IL-6.

ROC values	Il6 ≤ 260Pg/ml
Sensitivity (%)	84
Specificity (%)	82.86
AUC	0.812
PPV	78.1 %
NPV	77.7 %

Table 6: Area under the curve of TNFRI.

TNFRI	AUC	St. error	P (Area =0.5)	95% CI (Confidence interval)
	0.716	0.047	<0.0001	0.627 to 0.795

Table 7: ROC curve values of TNFRI.

ROC values	TNFRI>33 pg/ml
Sensitivity (%)	78
Specificity (%)	65.71
AUC	0.716
PPV	78.1 %
NPV	22.2 %

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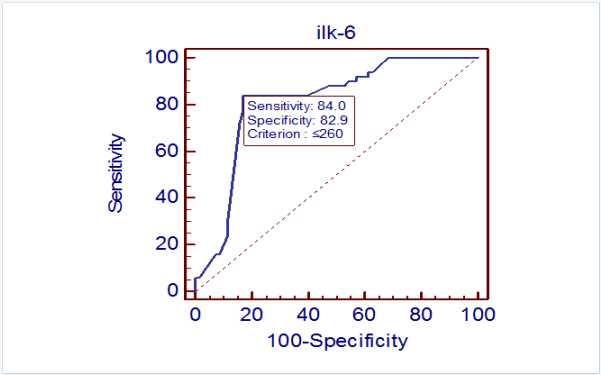

Figure 1: Receiver operating characteristics (ROC) curve to define the best cut off toIL6.

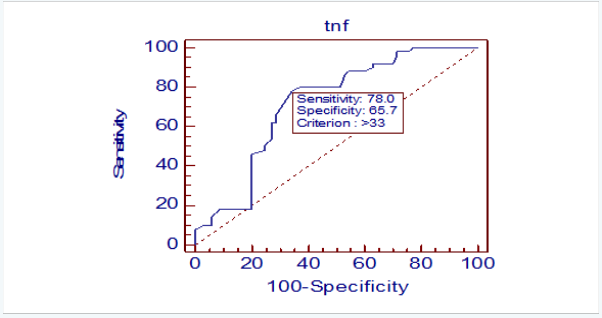

Figure 2: Receiver operating characteristics (ROC) curve to define the best cut off.

Discussion

Chronic hepatitis C is characterized by inflammatory liver disease of variable severity and increased risk of developing cirrhosis, liver failure and hepatocellular carcinoma [16]. Hepatitis C virus is hepatotropic, noncytopathic virus and liver injury induced by the virus is mainly mediated by the host immune response against the virus-infected cells and by the production of inflammatory cytokines [17]. TNF-α is aTh1 cytokine while IL6 is considered as Th2 cytokine [18]. Both Peg IFN- α and RBV have not only antiviral but also immune modulatory properties such as alteration of immune functions and Th1 (IL-2&IFN-γ) / Th2 (IL-4&IL10) cytokine balance [14,19]. Increased Th2 and altered Th1 cytokine production have been associated with viral persistence and failure of antiviral treatment in CHC [15].

In this study we measured the serum levels of both IL-6(as a Th1 cytokine) and TNFRI (receptor for TNF-α which is a Th2 cytokine) in responders and non- responders of CHC patients after treatment with Peg-IFN-α and RBV for 48 weeks. Also we measured the level of these cytokines in HCV patients and healthy controls. IL-6 is a pleiotropic cytokine that exerts its complex biological activities through different mechanisms [20]. Elevated levels of IL-6 have been associated with morbidity and disease activity in a variety of chronic diseases [21] as well as in chronic hepatitis, liver cirrhosis and hepato cellular carcinoma [22]. In our study serum IL-6 level was different in HCV patients than in healthy controls but these differences were not statistically significant. This agrees with Mourtzikou, et al. [8], who showed that there was no statistically significant difference inIL-6 level between CHC patients and controls. In contrast Falasca, et al. [23], reported that IL-6 was higher in the HCV group than in controls.

Our study showed a significant higher level of serum IL6 in non-responders compared to responders after 48 week of starting the treatment. This agrees with Guzma´n-Fulgencio, et al. [24] who showed association between high levels of IL-6 and IL-10 (Th2cytokines) with non-response to Peg-IFN-α and RBV in HIV/HCV confected patients after 72 week of starting the treatment. Also agrees with Ueyama, et al. [11] who showed that Serum IL-6 levels correlate with resistance to treatment of chronic hepatitis C infection with Peg-IFN-α and RBV and he explained this correlation by that IL6 promotes suppressor of cytokine signaling 3 (SOCS3) expressions which suppress the JAK-STAT pathway and inhibits the formation of interferon-stimulated gene [25]. Therefore, suppression of interferon-stimulated gene through activating IL6/SOCS3signal results in resistance to IFN therapy. On the other hand, our results disagree with both Awad, et al. [26] and Faisal, et al. [27] who both reported that Serum the IL-6 level is significantly higher in responders and can used as independent predictor to response to therapy. They explained the increased level of IL6 with response by that IL-6 has been shown to activate STAT3 by phosphorylation in hepatic stellate cells and promote their survival and proliferation. Activation of STAT3 is followed by induction of a wide variety of antiviral and proapoptotic genes that may contribute to the antiviral and antitumor activities of IFN in human livers and that IL-6 can overcome HCV core-induced inhibition of STAT3 activation and phosphorylation, improving the response rate [28,26].

In our study there was a significantly lower level of AST and ALT in responders compared to non-responders agreeing with Yoneda, et al. [15] who reported that AST is one of the independent factors related to SVR. This disagrees with Faisal, et al. [27] who demonstrates that there was no significant difference in AST and ALT levels between responders and non-responders. Also our results disagree with Pockros, et al.[29] who reported that there was no significant difference in ALT level between responders and non-responders. In liver physiology TNF- α has a dual effect due to its capacity to induce both hepatocyte cell death and hepatocyte proliferation. Circulating TNF- α levels increase HCV infection and they are associated with severity of hepatic inflammation, fibrosis, and liver injury. Moreover, they are also elevated in patients with HCC [30].

Kallinowski, et al. [31], reported a significant enhancement of TNF-α and both receptors (TNFRI &TNFRII) in CHC patients compared with controls. This agrees with our results that show

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a significant higher level of serum TNFRI in HCV patients than controls. In contrast Cubillas, et al. [32] assessed the level of TNFR expression in peripheral blood mononuclear cells (PBMCs) and they reported that there was a similar level of TNFRI mRNA in PBMC in HCV patients and controls. Mouraet al. [33] reported that there was no an association between plasma levels of sTNFR with virological response (after 12 and 24 weeks of treatment). This agrees with our results that showed no significant difference in serum TNFRI between responders and non-responders (after 48 weeks of treatment). Also agrees with Abdo et al. [34] who reported that after 24 weeks of treatment there was no correlation between TNF-α (itself)and INF-γ immuno histochemical expression with response to therapy. Par, et al. [35] reported that patients with RVR (after 4 weeks of treatment) were associated with an increased baseline IL6 and TNF-α production by TLR-4 activated monocytes this disagrees with our results that showed that after 48 weeks of treatment there was no significant difference in serum TNFRI between responders and non-responders and that IL6. Also in contrast to our results Lio, et al. [36] reported that low TNF-α and high IL-10 were associated with resolved HCV infection using gene polymorphism technique. This finding supported by Larrea, et al. [37] who found that high levels of TNF-α might play a role in resistance to interferon therapy.

There was a negative correlation between the serum levels of IL6 and AST (P = 0.004, r = -0.3997) and also between serum levels of TNFRI and ALT (P = 0.0171, r = -0.33587)may indicate that the level of both marker reflect liver injury despite low levels of liver enzymes. Ueyama, et al. [11], reported that Serum IL-6 is correlated with treatment resistance to PEG-IFN/RBV therapy, especially in male patients and that IL-6 is associated with insulin resistance (obesity and diabetes mellitus) and iron metabolism. This agrees with our results that showed a statistically significant increase of both IL6 and BMI in non-responders but disagrees in the part of male patients as there was no statistically significant difference between male and female before or after treatment regarding both IL6 and TNFRI levels. The association between IL6 and obesity because IL6 is an adipokine (polypeptide secreted by adipose tissue and store triglyceride in hepatocytes as well as in adipocytes) and it is, involved in the development of metabolic syndrome and is correlated with increasing visceral fat in humans [38].

Conclusion

High serum level of IL-6 is associated with response failure to PEG-IFN/RBV therapy while TNFRI is not associated with the response to therapy.

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