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ORIGINAL ARTICLE

Serum Interleukin-6 Concentration Associated with Response to Therapy for Chronic Hepatitis C Patients

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ABSTRACT

BACKGROUND: Egypt has the highest prevalence of hepatitis C virus (HCV) in the world. Interleukin 6 (IL-6) is a pleiotropic cytokine that increases in chronic HCV patients. IL-6 was suggested by several studies to play a major role in response to HCV therapy. However, its use for detection of response to SOF/SMV therapy is unclear.

AIM: to assess the possible role of IL-6 on response status of patients with HCV after treatment with sofosbuvir (SOF) and simeprevir (SMV) for 3 months and to find out the possibility of its use as predictor for HCV outcomes.

PATIENTS AND METHODS: Fifty seven patients with CHC were involved in this study. PCR for detection of viral activity was performed before treatment, after 4 weeks and 12 weeks from the beginning of treatment and according to the results of PCR, patients were divided into: (4Non-responders) and (53 Responders). Three months later after the end of treatment, PCR was repeated on Responders group and 50 developed Sustained Virologic Response (SVR). Patients groups were compared to Control group included 26 healthy subjects. The parameters measured included: CBC, Fasting Blood sugar, Liver function tests, including (Serum bilirubin "total and direct", Serum albumin and Prothrombin time and International Normalization Ratio (INR), ALT, AST and ALP, Viral markers including: hepatitis B surface antigen and hepatitis C antibody by ELISA, Kidney markers including serum Creatinine, á-feto protein by ELISA. IL-6 was measured using a commercially available Quantikine ELISA kit.

RESULTS: The Mean values of IL-6 level in responders and non-responders were 272.96 and 230.5pg/ml respectively. IL-6 levels decreased significantly after treatment in SVR group. The best cut-off point for IL-6 was 233 pg/ml with a sensitivity of 70% and a specificity of 75%.

CONCLUSION: Virological response during HCV therapy was associated with decrease in IL-6 level. IL-6 could be used for prediction of HCV response to SOF/SMV therapy.

Key words: Hepatitis C virus; SVR; Interleukin-6; HCV Therapy; Sofosbuvir and simeprevir

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INTRODUCTION

HCV is a leading cause of chronic liver diseases, cirrhosis and hepatocellular carcinoma as well as the most common indication of

liver transplantation in many countries[1].

Egypt has possibly the highest HCV prevalence in the world10-20% of the general population, Approximately 90% of Egyptian HCV isolates belong to a single subtype 4a which responds less successfully to interferon therapy than other genotypes[2].

The decision to treat patients with chronic hepatitis C depends on multiple parameters, including a precise assessment of the severity of liver disease and of its foreseeable outcome, the presence of absolute or relative contraindication to therapy and the patients willing to be treated[3].

Il-6 is apliotropic cytokine that plays a role in the acute phase response[4].

Il-6 is released from various cells, that is, Leukocytes, fibroblasts, endothelial cells and macrophages, in response to following systematic or local infection, tissue injury and inflammation[5].

As for the liver,Il-6 is produced mainly by kupffer cells[6] and induces the production of the acute phase proteins, C-reactive protein and haptoglobin[4].

Previous studies reported that serum Il-6 levels were increased, compared to healthy subjects, in patients with some liver diseases, such as chronic viral hepatitis due to HCV infection[6].

Previous results suggest that baseline levels of Il-6, as well as their decrease during treatment, are correlated to outcomes of HCV therapy in male patients. Further analyses of Il-6 may provide new strategies for difficult-to-treat CHC patients and prevention of hepatocarcinogenesis[7].

The aim of this work was to assess the possible role of IL-6 on response status of patients with HCV during treatment with SOF/SMV. Also we tried to use IL-6 as a predicting factor for response in patients with chronic HCV.

PATIENTS AND METHODS

Subjectsthis

This study is a prospective study consisted of 57 patients with chronic hepatitis C recruited from out-patients clinic Shebien El-Kom Teaching Hospital in the period from October 2015 to December 2015 to be treated with sofosbuvir (400 mg once per day) and simeprevir (150 mg once per day) for 3 months. PCR was performed before treatment, after 4 weeks, 12 weeks from the beginning of treatment and three months after the end of treatment to detect viral activity and according to the results of PCR, patients were further divided into the following groups:

Group (1): (Non-responders No. = 4): Positive Hepatitis C Virus (HCV RNA) after 12 weeks of treatment (the end of treatment).

Group (2): (Responders No. = 53): Negative HCV RNA after 12 weeks of treatment (the end of treatment). PCR was repeated in this group after 3 months to confirm total cure, 3 patients were missed from this group and 50 developed Sustained Virologic Response (SVR).

Patients groups were compared to Control group that included healthy subjects (No. = 26).

According to the national committee for control of viral hepatitis, Chronic HCV patient's candidate for combination therapy with sofosbuvir and simeprevir for 3 months and had the following inclusion criteria: Age from 18-70 years, HCV RNA positivity, Any Body Mass Index (BMI), Treatment naïve or treatment experienced and All fibrosis stages. Assessment of fibrosis is no more necessary. Performing liver biopsy or transient elastography (fibroscan) is not a pre-requisite; however, collection of such data is encouraged if available at the time of presentation. And Exclusion criteria are Direct serum bilirubin > 2 mg/dL, Serum albumin < 2.8 g/dL, International Normalization Ratio (INR) ≥ 1.7, Platelet count < 50000/mm^3, Ascites or history of ascites, Hepatic encephalopathy or history of Hepatic encephalopathy, Hepatocellular Carcinoma (HCC), except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI), Serum creatinine > 2.5 mg/dL. If creatinine is between 1.5 and 2.5 mg/dL, Glomerular Filtration Rate (GFR) should be calculated and should exceed 30 ml/min with favorable nephrological consultation, Extra-hepatic malignancy except after two years of disease-free interval and Pergnancy or inability to use effective contraception.

Laboratory and molecular investigations

Complete blood picture, Fasting Blood sugar, Liver function tests, including (Serum bilirubin "total and direct", Serum albumin and Prothrombin time and INR), Marker of liver injury: Alanine transaminase (ALT), Aspartate transaminase (AST) and Alkaline phosphatase (ALP), Viral markers including: hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV-Ab) by ELISA.

HCV polymerase chain reaction (PCR) before treatment, after 4 weeks, 12 weeks from the beginning of treatment and three months after the end of treatment, Kidney function tests including: serum Creatinine level, Serum á-feto protein by ELISA and Measurement of interleukin 6 (IL-6) levels before and after treatment by commercially available Quantikine enzyme linked immunosorbent assay (ELISA) kit.

Statistical analysis

All data were collected, tabulated and statistically analyzed using STATA/SE version 11.2 for Windows (STATA corporation, College Station, Texas). Continuous data were expressed as the mean ± SD and range, and categorical data were expressed as a number and percentage. The Student *t*-test (t) was used to compare two groups of normally distributed data. While, Mann-Whitney test (z) was used to compare two groups of nonparametric data. The Wilcoxon signed-rank test (z) was used to compare paired non-parametric data. Percent of categorical variables were compared using the Fisher's Exact Test.

Pearson correlation coefficient (r) and Spearman correlation coefficient (rho; ρ) were used to test for the correlation between estimated parameters.

Receiver Operating Characteristics (ROC) analysis was carried out to evaluate the diagnostic performance of IL-6 levels for response among patients. The best cutoff point and the corresponding sensitivity and specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Area Under the Curve (AUC) were estimated.

After the calculation of each of the test statistics, the corresponding distribution tables were consulted to get the "P" (probability value). Statistical significance was accepted at p value <0.05 (S). A p value <0.001 was considered highly significant (HS) while a p value > 0.05 was considered non-significant.

RESULTS

This study was conducted on fifty seven patients with chronic hepatitis C and twenty six healthy people as control group attending out-patients clinic Shebien El-Kom Teaching Hospital from October 2015 to December 2015. From these cases, Fifty three patients (92.9%) were diagnosed as responders to treatment with sofosbuvir and simeprevir and four patients (7.02%) were non responders to treatment. after 3 months of the end of treatment 50 (87.72%) of responding patients develop sustained virological response (SVR) and the other 3 patients were missed.

Table 1 Demographic and laboratory data between SVR and non-responders.

Variable	Group 1: Non-responders (No. = 4; 7.02%)	Group 3: (No. = 50; 87.72%) (SVR)	*P*
Age (years) mean (± SD)	59.5 (±5.2)	49.9 (±7.87)	0.02*
Male gender, n (%)	0 (0%)	37 (74.0%)	0.008*
Female gender, n (%)	4 (100%)	13 (26%)	
Glucose mg/dl mean (± SD)	95.75 (12.97)	107.12 (33.22)	0.5
Hemoglobin (gm/dL) mean (± SD)	11.1 (0.66)	14.07 (1.46)	<0.001*
Platelets /µL mean (± SD)	295000 (79372.54)	182960 (56603.51)	<0.001*
WBCs /µL mean (± SD)	5550 (806.22)	6306 (1747)	0.4
AST u/L mean (± SD)	44.75 (11.12)	55.44 (20.25)	0.3
ALT u/L mean (± SD)	98.5 (6.24)	55.56 28.82)	0.005*
T. bil. mg/dL mean (± SD)	1.52 (0.39)	0.82 (0.29)	<0.001*
Albumin g/dL mean (± SD)	3.67 (0.15)	4 (0.4)	0.12
Creatinine mg/dL mean (± SD)	0.67 (0.22)	0.8 (0.17)	0.18
INR mean (± SD)	1.17 (0.05)	1.08 (0.06)	0.005*
AFP ng/mL mean (± SD)	6.12 (2.1)	9.06 (15.96)	0.88
TSH iu/mL mean (± SD)	2.37 (0.57)	1.75 (1.05)	0.25
Viral load (IU/mL) mean (± SD)	625750 (433496.2)	1661815 (2220344)	0.72

WBCs: white blood cells; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; T. bil.: Total bilrubin; INR: International Normalization Ratio; AFP: Alpha Feto Protien; TSH: Thyroid Stimulating Hormone.

Table 2 Variations in baseline IL-6 between Patients and controls.

	Patients (No. =57)			Group 4 (Controls)(No. =26)			*P*
	Mean	± SD	Range	Mean	± SD	Range	
IL-6 pg/mL	269.98	78.63	111-450	180.73	79.54	90-460	< 0.001*

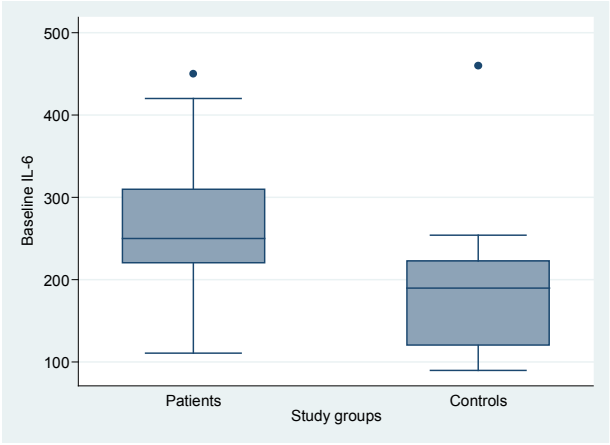

Figure 1 Variations in baseline IL-6 between patients and controls.

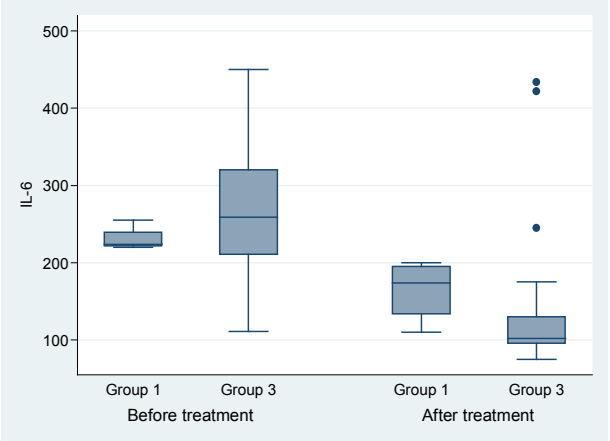

Figure 2 Il-6 levels between SVR and non-responders before and after therapy.

Table 3 Il-6 levels between SVR and non-responders before and after therapy.

Variable	Group 1: Non-responders (No. = 4; 7.02%)			Group 3: (SVR) (No. =50; 87.72%)			*P*
	Mean	± SD	Range	Mean	± SD	Range	
IL-6 (Pg/mL before treatment)	230.5	16.42	220-255	272.54	79.89	111-450	0.007*
IL-6 (Pg/mL After treatment)	164.5	40.51	111-450	125.76	69.38	75-434	0.02*
P	0.07			<0.001*			

Table 4 Correlations between IL-6 at baseline and other parameters.

Variable (No.= 57)	Correlation coefficient	*P*
Age (years)	r = 0.07	0.57
Glucose (mg/dL)	r = 0.07	0.62
Hemoglobin (gm/dL)	r =0.003	0.98
Platelets (/µL)	r = -0.24	0.07
WBCs (/µL)	r = -0.06	0.64
AST (u/L)	r = 0.18	0.17
ALT (u/L)	r = -0.02	0.86
T. bil. (mg/dL)	r = 0.15	0.27
Albumin (g/dL)	r = 0.08	0.54
Creatinine (mg/dL)	r = 0.09	0.5
INR	ρ = -0.10	0.43
AFP (ng/mL)	ρ = 0.05	0.71
TSH (iu/mL)	r = 0.08	0.56
Viral load (IU/mL)	ρ = 0.007	0.96

WBCs: white blood cells; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; T. bil.: Total bilrubin; INR: International Normalization Ratio; AFP: Alpha Feto Protien; TSH: Thyroid Stimulating Hormone.

Table 1 show the Demographic and laboratory data between SVR and non-responders as The mean age for SVR was younger than non-responders and the response to treatment tends to be more in males than in females. the Hemoglobin was significantly higher in SVR than non responders, The platelets was significantly higher in non responders than SVR. ALT, T. bil. and INR were significantly higher in non responders than SVR.

Baseline Il-6 levels were significantly high in patients than control

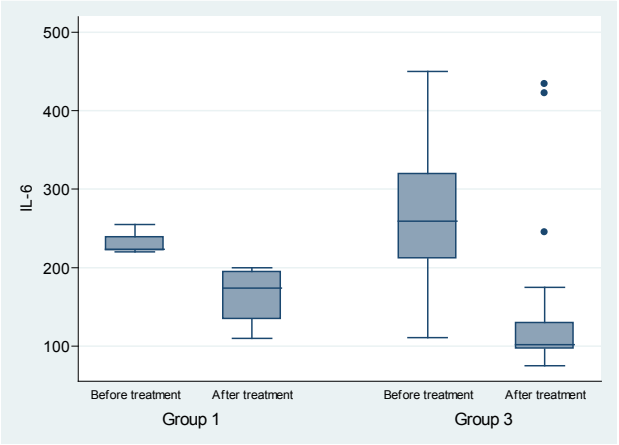

Figure 3 IL-6 levels in the same groups before and after therapy.

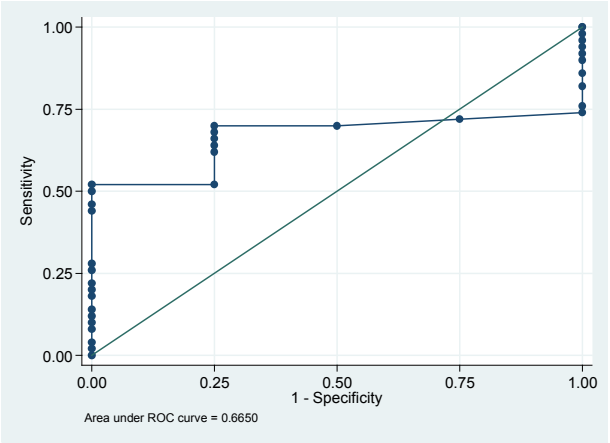

Figure 4 ROC for IL-6 for prediction of response (SVR) .

Table 5 ROC for IL-6 for prediction of response (SVR) .

Test	cutoff	Sensitivity	Specificity	PPV	NPV	AUC (95%CI)	Correctly classified
Il-6 (Pg/mL)	233 pg/Ml	70.00%	75.00%	97.20%	16.70%	0.6604 (0.512-0.818)	70.37%

group (Table 2, figure 1).

(Table 3, figure 2) illustrate comparison between IL-6 levels before and after treatment in non-responders and SVR groups. From which we can notice that there was significant decrease in IL-6 levels after treatment than before treatment in responders group. Surprisingly, No significant difference was obtained after treatment than before treatment in non-responders group.

Moreover the baseline levels (before treatment) of IL-6 were higher in responders than non-responders, whereas, its levels after treatment were lower in responders than non-responders. These results reflect the importance of IL-6 in predicting the consequences of HCV.

There was negative correlation between IL-6 and platelets, white blood cells, alanine aminotransferase and INR and positive correlation with age, glucose, hemoglobin, aspertate aminotransferase, total bilirubin, albumin, creatinine, alpha feto protein, thyroid stimulating hormone and viral load however of non-significance (Table 4).

ROC curve for IL-6 regarding prediction of response showed the best cut-off point at 233 pg/ml with a sensitivity of 70%, a specificity of 75% and a positive predictive value of 97.2 %, negative predictive value of 16.7 % and area under the curve 0.6604. (Table 5, figure 4).

DISCUSSION

Egypt is enduring a large HCV disease burden, and is likely to be the most affected nation worldwide by this infection[8].

There are a series of viral, host, and treatment characteristics that influence the likelihood of HCV treatment success and are useful when assessing the benefits and risks of therapy[9].

The introduction of direct-acting antiviral agents, in particular sofosbuvir (SOF), has revolutionized the treatment for chronic HCV. With SOF-based regimens, higher cure rates and shorter duration of treatment have been achieved. In early 2014, simeprevir (SIM) plus SOF, the first highly effective, interferon (IFN) sparing HCV treatment regimen, entered the clinical practice in the USA for the treatment of patients with HCV genotype 1 infection[10].

SMV is active against genotypes 1, 2, 4, 5 and 6. It is administered as a once-daily tablet orally and has demonstrated a favorable safety profile and limited drug drug interactions[11].

SMV/SOF combination therapy was more effective, better tolerated and associated with significantly fewer adverse events, compared with pegylated IFN-based regimens[12].

HCV infection can increase IL-6 production by altering the innate immune response by upregulating toll-like receptors (TLR4 and TLR2) in B cells, which will likely lead to an increased inflammatory response. The increased TLR4 and TLR2 expression is a result of increased transcription of the TLR4 and TLR2 genes and is mediated by the viral NS5A and core proteins, respectively[13].

This work aimed to study the association between IL-6 Levels and response to Sofosbuvir and Simeprevir in chronic hepatitis C virus patients.

In order to achieve this goal, this study was conducted on fifty seven patients with chronic hepatitis C and twenty six healthy people as control group attending Shebien El-Kom Teaching Hospital for treatment with sofosbuvir 400 mg once a day and simeprevir 150 mg once a day for 3 months from October 2015 to December 2015.

In this study, PCR was done for 57 patients with chronic HCV after 12 week of treatment with sofosbuvir and simprevir. 53 (92.98%) of patients develop response, and 4 (7.02%) of patients didn't develop response. after 3 months of the end of treatment 50 (87.72%) of responding patients develop sustained virological response (SVR) and the other 3 patients were missed.

El-Khayat *et al*[14] reported that The overall SVR rate was 95.7% (558 out of 583 patients). In total, SVR12 in naïve patients with mild fibrosis score (F1 and F2) was achieved in 98.9% (94/95) for F1 and 98.1% (105/107) for F2, while naïve patients with severe fibrosis (F3 and F4) achieved SVR of 97.7% (86/88) for F3 and (42/52) 80.8% for F4. SVR in patients with previous interferon treatment achieved in 100% (45/45) for patients with F1 and 98.7% (74/75) for F2. While 94.7% (72/76) in experienced patients with F3; and 88.9% (40/45) for F4 achieved SVR12.

In this study, Baseline IL-6 levels were significantly higher in patients than control group, this finding is in agreement with the result of El serafi *et al*[15] and Afzal *et al*[16] who reported that IL-6 levels were significantly higher in patients than control group.

In this study, responders who achieved SVR had significantly higher baseline IL-6 levels compared with those who did not before treatment and significantly lower after treatment.

This findings were in agreement with the results of El serafi *et al*[15], who reported that CHC patients who achieved early virological response (EVR) had significantly higher IL-6 levels compared with those who did not, and IL-6 level greater than 2.15 pg/mL was significantly associated with EVR and could be considered as an independent predictor of EVR.

Also this finding were in agreement with the results of Faisal *et al*[17] and Nattermann *et al*[18] who reported that a higher level of IL-6 is significantly associated with SVR compared with a lower level. In contrast, Cotler *et al*[19] reported that there was no significant difference in basal IL-6 levels between the groups of responders and non-responders to IFN therapy.

A possible explanation of this finding that IL-6 level could modulate the response to treatment by activation of STAT3 by phosphorylation in hepatic stellate cells and by promoting their survival and proliferation. Furthermore, IFN-a activates STAT3, followed by induction of a wide variety of antiviral and proapoptotic genes that may contribute to the antiviral and antitumor activities of IFN-a in human livers[20].

STAT3 expression and activation are reduced in HCVinfected livers. The HCV core protein has been shown to prevent phosphorylation of STAT3, which has been associated with resistance of HCV to IFN therapy. IL-6 can overcome HCV core-induced inhibition of STAT3 activation and phosphorylation[21].

Studies by Mohamed *et al*[22] and Guzma´n-Fulgencio *et al*[23] showed a significant higher level of serum IL6 in non-responders compared to responders after Peg-IFN-α and RBV therapy. They 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[24], therefore, suppression of interferon-stimulated gene through activating IL6/SOCS3 signal results in resistance to IFN therapy.

In this study, ROC for IL-6 for prediction of response show the best cut-off point for IL6 was 233 pg/ml with a sensitivity of 70%, a specificity of 75% and a positive predictive value of 97.2%, negative predictive value of 16.7% and the area under the curve was 0.6604.

El serafi *et al*[15], reported that IL-6 level greater than 2.15 pg/ml was significantly associated with response and could be considered as an independent predictor of response.

Conclusion: Virological response during HCV therapy with SOF/SMV was associated with a significant decrease in IL-6 level. IL-6 could be used for prediction of HCV response to SOF/SMV therapy.

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