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 world (10-20%) 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 a pleiotropic 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.

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

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.

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.

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

PATIENTS AND METHODS

Subjectsthis study is a prospective study consists of 57 patients with chronic hepatitis C to be treated with sofosbuvir (400 mg once per day) and simeprevir (150 mg once per day) for 3 months divided into:

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). And further divided according to SVR (Group 3).

Group (3): (SVR No. = 50) Negative HCV RNA after 12 weeks of cessation of treatment.

Group (4) (Controls group No. = 26) Included healthy subjects.

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 naive 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 a pre-requisite; however, collection of such data is encouraged if available at the time of presentation. And Exclusion criteria are:

- 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.

- 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.

Baseline IL-6 levels were significantly high in patients than control group (Table 2, figure 1).

As regard IL-6 levels before treatment were significantly higher in SVR than non-responders and After treatment IL-6 were significantly higher in non-responders than SVR (Table 3, figure 2).

No significance difference in IL-6 levels after treatment in non-responders group and IL-6 levels decrease significantly after treatment in SVR (Table 4, figure 3).

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 5).
Table 1 Demographic and laboratory data between SVR and non-responders.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Non-responders (No. = 4; 7.02%)</th>
<th>Group 3: (No. = 50; 87.72%) (SVR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean (± SD)</td>
<td>59.5 (±5.2)</td>
<td>49.9 (±7.87)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>0 (0%)</td>
<td>37 (74.0%)</td>
<td></td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>4 (100%)</td>
<td>13 (26%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Glucose mg/dl mean (± SD)</td>
<td>95.75 (12.97)</td>
<td>107.12 (53.22)</td>
<td>0.5</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL) mean (± SD)</td>
<td>11.1 (0.66)</td>
<td>14.07 (1.46)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Platelets (/µL) mean (± SD)</td>
<td>29500 (79372.54)</td>
<td>182960 (56603.51)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WBCs (/µL) mean (± SD)</td>
<td>5550 (806.22)</td>
<td>6306 (1747)</td>
<td>0.4</td>
</tr>
<tr>
<td>AST u/L mean (± SD)</td>
<td>44.75 (11.12)</td>
<td>55.44 (20.25)</td>
<td>0.3</td>
</tr>
<tr>
<td>ALT u/L mean (± SD)</td>
<td>98.5 (6.24)</td>
<td>55.56 (28.82)</td>
<td>0.005*</td>
</tr>
<tr>
<td>T. bil. mg/dL mean (± SD)</td>
<td>1.52 (0.39)</td>
<td>0.82 (0.29)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Albumin g/dL mean (± SD)</td>
<td>3.67 (0.15)</td>
<td>4 (0.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Creatinine mg/dL mean (± SD)</td>
<td>0.67 (0.22)</td>
<td>0.8 (0.17)</td>
<td>0.18</td>
</tr>
<tr>
<td>INR mean (± SD)</td>
<td>1.17 (0.05)</td>
<td>1.08 (0.06)</td>
<td>0.005*</td>
</tr>
<tr>
<td>AFP ng/mL mean (± SD)</td>
<td>6.12 (2.1)</td>
<td>9.06 (15.96)</td>
<td>0.88</td>
</tr>
<tr>
<td>TSH iu/mL mean (± SD)</td>
<td>2.37 (0.57)</td>
<td>1.75 (1.05)</td>
<td>0.25</td>
</tr>
<tr>
<td>Viral load (IU/mL) mean (± SD)</td>
<td>625750 (43496.2)</td>
<td>1661815 (2220344)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Patients (No. =57)</th>
<th>Group 4 (Controls)(No. =26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>IL-6 pg/mL</td>
<td>269.98 ± 78.63</td>
<td>180.73 ± 90-460</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Non-responders (No. = 4; 7.02%)</th>
<th>Group 3: (SVR) (No. =50; 87.72%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>IL-6 (Pg/mL before treatment)</td>
<td>230.5 ± 16.42</td>
<td>220-255</td>
<td>0.007*</td>
</tr>
<tr>
<td>IL-6 (Pg/mL after treatment)</td>
<td>164.5 ± 40.51</td>
<td>111-450</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Table 4 IL-6 levels in the same groups before and after therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: Non-responders (No. = 4; 7.02%)</th>
<th>Group 3: (SVR) (No. =50; 87.72%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>IL-6 (Pg/mL before treatment)</td>
<td>230.5 ± 16.42</td>
<td>220-255</td>
<td></td>
</tr>
<tr>
<td>IL-6 (Pg/mL after treatment)</td>
<td>164.5 ± 40.51</td>
<td>111-450</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 5 Correlations between IL-6 at baseline and other parameters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>r = 0.07</td>
<td>0.57</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>r = 0.07</td>
<td>0.62</td>
</tr>
<tr>
<td>Hemoglobin (gm/dL)</td>
<td>r = 0.003</td>
<td>0.98</td>
</tr>
<tr>
<td>Platelets (/µL)</td>
<td>r = -0.24</td>
<td>0.07</td>
</tr>
<tr>
<td>WBCs (/µL)</td>
<td>r = -0.06</td>
<td>0.64</td>
</tr>
<tr>
<td>AST (u/L)</td>
<td>r = 0.18</td>
<td>0.17</td>
</tr>
<tr>
<td>ALT (u/L)</td>
<td>r = -0.02</td>
<td>0.86</td>
</tr>
<tr>
<td>T. bil. (mg/dL)</td>
<td>r = 0.15</td>
<td>0.27</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>r = 0.08</td>
<td>0.54</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>r = 0.09</td>
<td>0.5</td>
</tr>
<tr>
<td>INR</td>
<td>ρ = -0.10</td>
<td>0.43</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>ρ = 0.05</td>
<td>0.71</td>
</tr>
<tr>
<td>TSH (iu/mL)</td>
<td>r = 0.08</td>
<td>0.56</td>
</tr>
<tr>
<td>Viral load (IU/mL)</td>
<td>ρ = 0.007</td>
<td>0.96</td>
</tr>
</tbody>
</table>

WBCs: white blood cells; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; T. bil.: Total bilirubin; INR: International Normalization Ratio; AFP: Alpha Feto Protien; TSH: Thyroid Stimulating Hormone.
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[10] and Afzal et al[11] 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 finding was in agreement with the results of El serafi et al[10] and Nattermann et al[11] who reported that IL-6 level greater than 2.15 pg/mL was significantly associated with SVR and could be considered as an independent predictor of EVR.

Also this finding was in agreement with the results of Faisal et al[12] and Nattermann et al[11] who reported that a higher level of IL-6 is significantly associated with SVR compared with a lower level. In contrast, Cotler et al[13] 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-α in human livers\(^2\).

STAT3 expression and activation are reduced in HCV-infected 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\(^3\).

Studies by Mohamed et al\(^2\) and Guzmán-n-Fulgenceo et al\(^3\) 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\(^4\), therefore, suppression of interferon-stimulated gene through activating IL6/SOCS3 signal results in resistance to IFN therapy.

In this study, there was negative correlation between IL-6 and platelets, white blood cells, alanine aminotransferase and INR and positive correlation with age, glucose, hemoglobin, aspartate aminotransferase, total bilirubin, albumin, creatinine, alpha feto protein, thyroid stimulating hormone and viral load however of non-significance.

Mohamed et al\(^3\) reported that There was a negative correlation between the serum levels of IL6 and AST and also between serum levels of TNFRI and ALT may indicate that the level of both marker reflect liver injury despite low levels of liver enzymes.

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\(^3\) 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.

ACKNOWLEDGMENT

The authors would thank Dr. Fatma Mohamed Abd El Salam, Dr. Naglaa El-Toukyh Ramadan El-Toukh, Dr. Amal Ahmed Mohamed who helped in conducting this study. And staff of the Tropical Medicine Department, and to the laboratory technicians, for their valuable efforts.

REFERENCES

15. El-Serafi TI, Awad MM, Tag-Eldeen LA. Effect of interleukin-6 and insulin resistance on early virological response of Egyptian chronic hepatitis C patients to combined pegylated interferon plus ribavirin therapy. \(\text{Egyptian Liver Journal}\) 2013; 3: 21–27
17. Faisal, A, Zytone AA, Gad Allah A, Dawood A. Predictors of


**Peer reviewer:** Nermine Ehsan