PATIENTS AND METHODS: Serum concentrations of Interleukin 6 (IL6) was measured before and after treatment using a commercially available Quantikine enzyme linked immunosorbent assay in fifty seven patients with chronic hepatitis C treated with sofosbuvir and simeprevir for 3 months.

RESULTS: The Mean values of IL6 level in responders and non-responders were 272.96 and 230.5 pg/mL respectively. IL-6 levels decrease significantly after treatment in SVR. 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%.

CONCLUSION: Virological response during HCV therapy was associated with decrease in IL-6 level.

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

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INTRODUCTION: Egypt has the highest prevalence of (HCV) in the world. Interleukin 6 is a pleiotropic cytokine that increased in chronic hepatitis C patients. IL-6 was suggested by several studies to play a major role in response to HCV therapy.

AIM: 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.
endothelial cells and macrophages, in response to following systematic or local infection, tissue injury and inflammation\(^\text{[9]}\). As for the liver, IL-6 is produced mainly by kupffer cells\(^\text{[9]}\) and induces the production of the acute phase proteins, C-reactive protein and haptoglobin\(^\text{[9]}\).

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\(^\text{[9]}\).

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\(^\text{[7]}\).

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

**Study design**

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).
- **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 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:

- Performing liver biopsy or transient elastography (fibroscan) is not available Quantikine enzyme linked immunosorbent assay (ELISA) kit.
- 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.
- 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.

### RESULTS

The aim of this study 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.

#### 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 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 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, aspartate 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.

| 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 (53.22)                    | 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 bilirubin; 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     |
|-------------------------|-------------------|---------------------------|-------|
| IL-6 pg/mL              | Mean ± SD         | Range                     | Mean ± SD | Range | <0.001* |
|                         | 269.98 ± 78.63    | 111-450                   | 180.73 ± 79.54 | 90-460 |       |

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.

| Variable                | Group 1: Non-responders (No. = 4; 7.02%) | Group 3: (SVR) (No. = 50; 87.72%) | P     |
|-------------------------|----------------------------------------|-----------------------------------|-------|
| IL-6 (Pg/mL) before treatment | Mean ± SD | Range | Mean ± SD | Range | 0.007* |
| IL-6 (Pg/mL) after treatment | 164.5 ± 40.51 | 111-450 | 125.76 ± 69.38 | 75-434 | 0.02* |

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

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

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

Table 5 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                | p = -0.10               | 0.43  |
| AFP (ng/mL)        | p = 0.05                | 0.71  |
| TSH (IU/mL)        | r = 0.08                | 0.56  |
| Viral load (IU/mL) | p = 0.007               | 0.96  |

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 order to achieve this goal, this study was conducted on fifty patients.

**DISCUSSION**

Egypt is enduring a large HCV disease burden, and is likely to be the most affected nation worldwide by this infection\(^9\).

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, simprevir (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\(^9\).

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\(^11\).

SIM/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 NSSA 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 \textit{et al} 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 \textit{et al}\(^9\) and Afzal \textit{et al}\(^9\) 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 \textit{et al}\(^9\) and Nattermann \textit{et al}\(^9\) who 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-α 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\(^4\) and Guzmán-n’Fulgenceo et al\(^5\) 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 genes\(^6\), therefore, suppression of interferon-stimulated gene through activating IL6/SOCS3 signal results in resistance to IFN therapy.

In this study, there was a 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.

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**REFERENCES**

1. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci.* 2006; 3(2): 47-52. Epub 2006 Apr 1. [PMID: 16614742]; [PMCID: PMC1415841]
2. Rahman El-Zayadi A1, Abaza H, Shawky S, Mohamed MK, Selim OE, Badran HM. Prevalence and epidemiological features of hepatocellular carcinoma in Egypt-a single center experience. *Hepatol Res.* 2001 Feb; 19(2): 170-179. [PMID: 11164741]
3. Chevaliez S, Pawlotsky JM. Hepatitis C virus serologic and virologic tests and clinical diagnosis of HCV-related liver disease. *Int J Med Sci.* 2006; 3(2): 35-40. Epub 2006 Apr 1. [PMID: 16614740]; [PMCID: PMC1415842]
4. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J.* 1990 Feb 1; 265(3): 621-36. [PMID: 1689567]; [PMCID: PMC1133681]
5. Sehgal PB. Interleukin-6: a regulator of plasma protein gene expression in hepatic and non-hepatic tissues. *Mol Biol Med.* 1990 Apr; 7(2): 117-30. [PMID: 2188060]
6. Oyanagi Y, Takahashi T, Matsui S, Takahashi S, Boku S, Takahashi K, Furukawa K, Arai F, Asakura H. Enhanced expression of interleukin-6 in chronic hepatitis C. *Liver.* 1999 Dec; 19(6): 464-72. [PMID: 10661679]
7. Ueyama M, Nakagawa M, Sakamoto N, Onozuka I, Funako Y, Watanabe T, Nitta S, Kiyohashi K, Kitazume A, Murakawa N, Nishimura-Sakurai Y, Sekine-Osajima Y, Itsui Y, Azuma S, Kakinuma S, Watanabe M. Ochanomizu-Liver Conference Study Group. Serum interleukin-6 levels correlate with resistance to treatment of chronic hepatitis C infection with pegylated-interferon-α2b plus ribavirin. *Antivir Ther.* 2011; 16(7): 1081-91. [PMID: 22024524]; [DOI: 10.3851/IMP1864]
8. Mohamoud YA, Muntaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis.* 2013 Jun 24; 13: 288.; [DOI: 10.1186/1471-2334-13-288.]; [PMID: 23799878]; [PMCID: PMC3702438]
9. Brok JI, Gluud LL, Gluud C. Meta-analysis: ribavirin plus interferon vs. interferon monotherapy for chronic hepatitis C - an updated Cochrane review. *Aliment Pharmacol Ther.* 2010 Oct; 32(7): 840-50. [PMID: 20839385]
10. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rahbinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JT, Favery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beumont M, Jacobson IM. Simprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naivepatients: the COSMOS randomised study. *Lancet.* 2014 Nov 15; 384(9956): 1756-65. [PMID: 25078309]; [DOI: 10.1016/S0140-6736(14)61036-9]. Epub 2014 Jul 28.
11. Abdel-Ghaffar TY, Sira MM, El Naghi S. Hepatitis C genotype 4: The past, present, and future. *World J Hepatol.* 2015 Dec 8; 7(28): 2792-810. [PMID: 26668691]; [PMCID: PMC4670951]; [DOI: 10.4254/wjh.v7.i28.2792]
12. Hézode C, Fontaine H, Dorival C, Zoulam F, Larrey D, Canva V, De Ledinghen V, Poynard T, Samuel D, Bourliere M, Alric L, Raabe JJ, Zarski JP, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Chazouilleres O, Abergel A, Guyader D, Metivier S, Tran A, Di Martino V, Causse X, Dao T, Lucidarme D, Portal I, Cacoub P, Gournay J, Grando-Lemaire V, Millot P, Attali F, Portanges T, Rosa I, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Cerrat F, Bronowicki JP; CUPIC Study Group. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype infection and cirrhosis. *Gastroenterology.* 2014 Jul; 147(1): 132-142.e4. [PMID: 24704719]; [DOI: 10.1053/ j.gastro.2013.03.051]. Epub 2014 Apr 3.
13. Feldmann G, Nischalke HD, Nattermann J, Banas B, Berg T, Teschedorff C, Schmiegel W, Dührsen U, Halangk J, Iwan A, Sauerbruch T, Caselmann WH, Spengler U. Induction of interferleukin-6 by hepatitis C virus core protein in hepatitis C-associated mixedcryoglobulinemia and B-cell non-Hodgkin's lymphoma. *Clin Cancer Res.* 2006 Aug 1; 12(15): 4491-8. [PMID: 16899594]; [DOI: 10.1158/1078-0432.CCR-06-0154]
14. El-Khayat HR, Foud YM, Maher M, El-Amin H, Mohammed H. Efficacy and safety of sofosbuvir plus simprevir therapy in Egyptian patients with chronic hepatitis C: a real-world experience. *Gut.* 2016 Aug 10. pii: gutjnl-2016-312012. [PMID: 27511197]; [DOI: 10.1136/gutjnl-2016-312012]
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. *Egyptian Liver Journal* 2013; 3: 21–27
16. Aflal N, Abbas S, Ahmed A, Arif M, Javeed K. Effect of hepatitis C virus on C-reactive protein and interleukin-6 in hemodialysis patients. *Iran J Kidney Dis.* 2011 Jul; 5(3): 182-6. [PMID: 21525578]
17. Faisal, A, Zytoon AA, Gad Allah A, Dawood A. Predictors of

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Mohamed AA et al. IL-6 and Hepatitis C Patients

Early Virological Response of Viral Hepatitis C to Combination Therapy with Pegylated Interferon Plus Ribavirin. *American Journal of Clinical Medicine Research*. 2013; 4: 54-60

18. Nattermann J1, Vogel M, Berg T, Danta M, Axel B, Mayr C, Bruno R, Tural C, Klausen G, Clotet B, Lutz T, Grünhage F, Rausch M, Nischalke HD, Schewe K, Bieneck B, Haerter G, Sauerbruch T, Rockstroh JK, Spengler U; Kompetenznetz HIV/AIDS. Effect of the interleukin-6 C174G gene polymorphism on treatment of acute and chronic hepatitis C in human immunodeficiency virus coinfected patients. *Hepatology*. 2007 Oct; 46(4): 1016-25. [PMID: 17668881]; [DOI: 10.1002/hep.21778]

19. Cotler SJ1, Reddy KR, McConne J, Wolfe DL, Liu A, Craft TR, Ferris MW, Conrad AJ, Albrecht J, Morrissey M, Ganger DR, Rosenblate H, Blatt LM, Jensen DM, Taylor MW. An analysis of acute changes in interleukin-6 levels after treatment of hepatitis C with consensus interferon. *J Interferon Cytokine Res*. 2001 Dec; 21(12): 1011-9. [PMID: 11798458]; [DOI: 10.1089/107999001317205132]

20. Gao, B. Cytokines, STATs, and liver disease. *Cell Mol Immunol* 2005; 2(2): 92–100. [PMID: 16191414]

21. Larrea E, Aldabe R, Molano E, Fernandez-Rodriguez CM, Ametzazurra A, Civeira MP, Prieto J. Altered expression and activation of signal transducers and activators of transcription (STATs) in hepatitis C virus infection: in vivo and in vitro studies. *Gut*. 2006 Aug; 55(8): 1188-96. Epub 2005 Aug 24. [PMID: 16120756]; [PMCID: PMC1856287]; [DOI: 10.1136/gut.2005.070060]

22. Mohamed AA, Afifi EA, El-Awady RR. Correlation between Serum Levels of TNFR and IL6 with Treatment Response to Pegylated Interferon and Ribavirin Therapy in Chronic Hepatitis C Egyptian Patients. *Virol Curr Res*. J 2015; 1(2).

23. Guzmán-Fulgencio M1, Jiménez JL, Berenguer J, Fernández-Rodríguez A, López JC, Cosín J, Miralles P, Micheloud D, Muñoz-Fernández MA, Resino S. Plasma IL-6 and IL-9 predict the failure of interferon-α plus ribavirin therapy in HIV/HCV-coinfected patients. *J Antimicrob Chemother*. 2012 May; 67(5): 1238-45. Epub 2012 Jan 31. [PMID: 22294644]; [DOI: 10.1093/jac/dkr595]

24. Gale M, Foy E. Evasion of intracellular host defense by hepatitis C virus. *Nature* 2005; 436(7053): 939-945. [DOI: 10.1038/nature04078]

Peer reviewer: Nermine Ehsan