International Journal of Microbiology and Immunology Research Vol. 3(2), pp. 020-028, March 2015
Available online at http://academeresearchjournals.org/journal/ijmir
ISSN 2327-7769 ©2015 Academe Research Journals

Full Length Research Paper

Pre-treatment of serum ferritin in prediction of early virologic response in patients with Chronic Hepatitis C receiving pegylated interferon and ribavirin combination therapy

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Accepted 1 March, 2015

Many studies have been performed on the role of serum ferritin in the pathogenesis and treatment of Chronic Hepatitis C (CHC). Serum iron and serum ferritin have been suggested as predictors of therapeutic response to IFN therapy. However, the correlation between serum ferritin level and therapeutic response to IFN and RBV combination therapy remains controversial. This study aims to assess the value of pretreatment serum ferritin as a predictor of early virological response in CHC patients receiving a combination therapy of Pegylated-Interferon and Ribavirin. This study was conducted on 96 naive patients with CHC virus infection genotype 4. All patients were subjected to full history taking, and thorough clinical examination. Continuous monitoring of the liver profile and serum ferritin level was done. However, quantitative monitoring of the HCVRNA was done at 4 and 12 weeks of the treatment by the PCR. It was observed that 64 patients (66.6%) achieved early virological response (EVR), 54 of which (56.2%) achieved RVR at week 4. The level of pretreatment serum ferritin was lower in patient who achieved EVR. Serum ferritin increased significantly during the first 12 weeks of therapy in the EVR group when compared to the non EVR group. Our study pointed out that lower pretreatment serum ferritin levels and its increase during the course of treatment was associated with EVR in CHC patients receiving PEGINF and Ribavirin combination therapy.

Key words: Hepatitis C, fibrosis, ferritin, interferon.

INTRODUCTION

Chronic hepatitis C (CHC) is one of the most significant infectious diseases being a leading cause of liver-related morbidity and liver transplantation worldwide (Lange et al., 2012). The conventional treatment regimen for CHC includes pegylated interferon (PEG-IFN) combined with ribavirin (Barut et al., 2012). Recently, direct antiviral agents (DAAs) such as protease inhibitors, nucleoside, non-nucleoside HCVpolymerase inhibitors, and HCV nonstructural (NS) 5A protein inhibitors have been either added to the PEGINF/RIB combination therapy or put in new combinations. Some of these new DAAs showed significant improvement in the SVR and some are still under wider research projects.

Several host and viral factors contribute to SVR in the combination treatment. The host factors include younger age, male gender, body weight, race, liver histology, platelet count, LDL cholesterol values, gamma-glutamyl transpeptidase values, baseline alanine aminotransferase level and insulin resistance (Lukasiewicz et al., 2010). The viral factors include amino acid substitutions in the IFN sensitivity determining region of the HCV nonstructural 5A (NS5A) protein and in the HCV core,

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HCV genotype, baseline viral load (Yada et al., 2010), viral level and IL28B CC genotype predict SVR.

Iron is an essential substrate for the growth of all organisms, and may facilitate viral replication. Iron may act in synergism with hepatitis C virus (HCV) to accelerate the progression to cirrhosis and liver carcinoma. It has been previously observed that serum iron indices and liver iron deposition are frequently raised in patients with chronic viral hepatitis (Distante et al., 2002).

Elevated serum ferritin levels may reflect a systemic inflammatory state as well as increased iron storage, both of which may contribute to an unfavorable outcome of chronic hepatitis C (CHC). Therefore, many studies have performed on the role of serum ferritin and its genetic determinants in the pathogenesis and treatment of CHC (Lange et al., 2012).

Studies on CHC showed that serum ferritin is a useful marker for assessing disease duration and progression. Significant rise in ferritin levels has been observed during treatment with interferon. Consequently, specific role was suggested for interferon in the synthesis or secretion of ferritin (Barut et al., 2012).

Many recent studies suggested new predictors of therapeutic response to IFN therapy as serum iron and serum ferritin. However, the correlation between serum ferritin level and therapeutic response to IFN and RBV combination therapy remains controversial (Yada et al., 2010).

The present study was designed to assess the value of pretreatment serum ferritin as a predictor of early virological response in CHC patients receiving combination therapy of pegylated-Interferon and Ribavirin.

MATERIALS AND METHODS

Patients

The present study was conducted on 96 treatment naive patients with chronic HCV, genotype 4, who received PEG INF + Ribavirin combination therapy, and followed in the outpatient clinics of Hepatology and Gastroenterology, a department in Ain Shams University Hospitals over a period of one year. The patients were included in the study according to the following criteria:

Inclusion criteria

1. Adult patients aged 20 to 60 years with chronic HCV (+ve HCV Ab by ELISA and detectable HCVRNA by PCR).
2. Liver fibrosis stages < F6 according to HAI, modified Ishak (Shiha and Zalata, 2011).
3. Patients with body mass index <30.
4. Patients with hemoglobin >10g/dl, platelets >100000/mm^3 and leukocyte count >2000/mm^3.

Exclusion criteria

1. Patients excluded from treatment with interferon therapy such as decompensated liver disease, psychological disorders, thyroid dysfunction, autoimmune diseases, diabetic patient and patients that discontinued the treatment due to side effects.
2. Liver diseases other than hepatitis C including hepatitis B, autoimmune hepatitis, alcoholic liver diseases, drug induced liver disease, hepatocellular carcinoma and Wilson disease.
3. Patients with conditions or diseases that may affect serum iron level such as patients receiving oral or parental iron therapy, hemolytic anemias, hemochromatosis, iron depletion therapy and hemoglobinopathies.

Ethics and human rights

Informed written consent was obtained from all the patients and the study was approved by the ethical committee of Ain Shams University.

All the patients in this study were subjected to the following:

1. Full history taking and thorough clinical examination.
2. Laboratory investigations including: CBC, Liver Profile (ALT, AST, and T.bil.), viral markers (HBsAg and HCVAb), quantitative PCR for HCV RNA before starting treatment and at 4 and 12 weeks, genotype testing, thyroid function tests (TSH), autoimmune markers (ANA), and serum ferritin.
3. Fundus examination.
4. Abdominal U/S. Equipment used: Hitachi, EUB-5500.
5. Liver biopsy and histopathological examination according to histologic activity index (HAI) of Ishak scoring system (Shiha and Zalata, 2011) before starting treatment.

Laboratory assessment

Venous blood (8 ml) was withdrawn aseptically into a sterile disposable syringe from each patient, where 2 ml was placed in EDTA tube for performing complete blood count (CBC), and 4 ml was collected in 2 plain vacutainers and centrifuged (1500 g for 15 min at 4°C) for HCV RNA copy number analysis and measurement of biochemical markers including AST, ALT, total bilirubin, viral markers, TSH, ANA and serum ferritin. The laboratory work was conducted at Clinical Pathology Department. All tests were performed according to the manufacturer's instructions.

- CBC was done using Coulter counter (T660).
- AST, ALT and total bilirubin were measured on Synchron CX9 autoanalyzer (Beckman Instruments Inc.; Scientific Instruments Division, Fullerton, CA 92634,

3100).
- TSH was measured using TSH reagent kit.
- ANA was measured using Immunoscreen Fluro kit.
- HCV Ab was detected by HCV3.0 ELISA (third-generation) system with enhanced Sample Addition Verification (SAVe).
- HCV genotype was determined using Abbott Real Time HCV Genotype II assay.
- HBsAg was tested using HbsAg ELISA kitCat#4105 (Alpha Diagnostics).
- Serum HCV RNA was extracted automatically using Combas AmpliPrep, and viral loads were detected using Real-time PCR Cobas Taqman (Roche Diagnostics) that has a dynamic range between 10IU/ml and 2×10^8 IU/L.
- Measurement of serum ferritin was done by protemeter using "QuantImune Ferritin IRMA" kit, with reference range: 12-300 ng/mL in male and 12-150 ng/mL in female (Wang et al., 2010).

Liver biopsy and histopathological examination

Ultrasonography-guided liver biopsies were performed under conscious sedation using a 16-gauge Klatskin needle. The length of the histological specimens was no less than 2.5 cm.

All biopsy specimens were placed in 10% neutral buffered formalin solution for fixation and embedded in paraffin blocks. Serial sections (sectioned at 4-µm intervals) were concurrently stained with Hematoxylin-Eosin and Masson's trichrome. An experienced pathologist blinded to the clinical data scored the liver biopsies according to Ishak Modified HAI (Guido et al., 2011).

The Modified HAI Grading: Necroinflammatory scores are as follow: minimal (1-3); mild (4-8); moderate (9-12); and severe (13-18).

Follow up of cases was done by clinical examination and laboratory investigations including: CBC, Liver profile (ALT, AST and T.bil), ferritin levels and quantitative PCR for HCV RNA at weeks 4 and 12. A rapid virologic response, or RVR, is defined as an undetectable HCV RNA at week 4, while an early virologic response, or EVR, is defined as an undetectable serum HCV RNA or a 2 log 10 or greater drop in HCV RNA at week 12 of therapy.

The obtained results are shown in Tables 1 to 5.

Drugs, dose and route used

Patents under test were given the following: pegylated interferon alpha 2b (PEG Intron 1.5 µg/kg, MSD comp., 31qc40414) given by subcutaneous (SC) injection once/week combined with Ribavirin oral tablets (Rebetol 200 mg, Merck Sharp and Dome, a subsidary of Merck & Co., Inc., 4RCJA16A02) based on weight (1000 mg/day for weights <75 kg and 1200 mg/day for >75kg), given for 12 weeks.

Statistical analysis

IBM SPSS statistics (V. 20.0, IBM Corp., USA, 2011) was used for analysis of the obtained data. Data were expressed as Mean ± SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. The following statistical tests were done:

- Student *t - test* for comparison between two independent mean groups for parametric data.
- *Wilcoxon signed rank test(z)* for comparison between two independent groups for non-parametric data, repeated measures, or "before" and "after" measures.
- *Ranked Spearman correlation test(r)* used to study the possible association between each two variables among each group for non-parametric data.
- *Chi-square test (X^2)* to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error *<0.05* was considered significant. The 'ROC' was constructed to obtain the most sensitive and specific cutoff for each technique. To evaluate the most discriminating markers between the compared groups, 'AUC' was also calculated. The obtained results are shown in Tables 1 to 5.

RESULTS

This study was conducted on 96 naive patients with chronic HCV infection, genotype 4, receiving combined pegylated interferon α 2b and ribavirin therapy. A total of 54 patients (56.2%) achieved RVR, and 64 patients (66.6%) achieved EVR.

Demographic and laboratory characteristics of all patients in the study are shown in Table 1. Serum ferritin increased along the study period from 156.1±42.1 ng/ml in week 0 to 170.4±15.9 ng/ml in week 12 (Figure 1). Comparison between RVR and non RVR patients as regard different variables is shown in Table 2. The mean value of HCV RNA viral count at week 0 in RVR group was much lower than that in non-responders group with highly significant statistical difference. There was no statistical significant difference between the 2 groups as regards serum ferritin level in week 0 and week 4. The serum ferritin level increased in each group (at week 0 and week 4). Otherwise there was no statistical difference between the two groups. Multivariate analysis of variables associated with early virological response (EVR) versus non EVR showed that the mean values of ALT (40.4 IU/ml) and AST (39.3 IU/ml) at week 4 in EVR group were lower than that in-non responders group (61.96 IU/ml and 54.2 IU/ml) respectively with significant statistical difference. The mean values of ALT (32.32 IU/ml) and AST (36.6 IU/ml) at week 12 in EVR group were lower than that in non-responders group (48.2 IU/ml

Table 1. Demographic values (minimum, maximum and mean ± SD) of laboratory investigations of patients in the study (n = 96).

Test time/weeks post treatment	Item	Minimum	Maximum	Mean	SD
0	Age (years)	24.00	58.00	41.5729	9.78048
0	Weight (Kg)	65.00	117.00	82.3333	9.21060
0	BMI (kg/m^2	27.62	28.07	27.9	2.54
0		45.00	406.00	156.1771	42.16009
4	Ferritin (ng/mL)	98.00	560.10	171.4359	44.49871
12		104.00	201.00	170.4348	15.90515
0		268.00	8.50×10^7	1.4788×10^6	8.93033×10^6
4	PCR (IU/ml)	0.00	1.41×10^9	1.4735×10^7	1.44017×10^8
12		0.00	9.88×10^6	1.3474×10^6	1.01171×10^6
0		13.00	190.00	49.9355	30.56099
4	AST (IU/L)	12.00	244.00	44.1075	35.05197
12		15.00	199.00	42.0108	28.84422
0		12.00	390.00	62.5161	49.56717
4	ALT (IU/L)	10.00	313.00	47.3871	46.32542
12		10.00	154.00	37.4473	27.54213
0		0.3	1.6	0.7	0.20
4	Bilirubin (mg/dl)	0.4	2.1	1	0.39
12		0.30	2.2	0.89	0.36
0	TSH	0.4	3.1	1.3	0.66
0		11.90	17.30	14.7936	1.20392
4	HG (g/dl)	8.80	16.00	12.6819	1.40979
12		7.60	14.60	11.8989	1.26078
0		3.10	19.10	6.1447	2.31366
4	WBC (10^3/µL)	1.70	15.70	3.9798	1.67419
12		1.50	12.60	3.6266	1.68422
0		108.00	339.00	206.6064	49.06178
4	PLT (10^3/µL)	52.00	376.00	169.1596	58.64552
12		64.00	340.00	164.8085	52.70842
0	Fibrosis (biopsy)	.00	5.00	1.8021	1.16637
0	HAI (biopsy)	3.00	11.00	6.1042	2.12988

0: Pretreatment; 4: At week 4 of treatment; 12: At week 12 of treatment.

Table 2. Multivariate analysis of variables with rapid virological response (RVR) versus non RVR.

Test time/weeks post treatment	Variable	RVR (n=54) Mean±SD	Non RVR (n =42) Mean±SD	*P*	Sig
0	Age (years)	40.6±10.12	42.7±9.3	0.28	NS
0	Weight (Kg)	82.48±8.24	82.14±10.41	0.56	NS
0	BMI (kg/m^2)	27.81±2.54	28.05±2.51	0.84	NS

Table 2 Contd.

0	ALT (IU/L)	63.60±55.86	61.19±41.27	0.92	NS
4		39.35±26.26	57.14±61.61	0.12	NS
0	AST (IU/L)	47.09±28.95	53.38±32.42	0.5	NS
4		35.5±14.24	54.54±48.01	0.06	NS
0	BIL (mg/dl)	0.66±0.3	0.7±0.2	0.18	NS
4		0.89±0.5	1±0.5	0.31	NS
0	HG (g/dl)	14.87±1.12	14.68±1.29	0.44	NS
4		12.56±1.42	12.83±1.39	0.37	NS
0	WBC (10^3/µL)	5.76±166	6.61±2.87	0.16	NS
4		3.74±1.12	4.26±2.15	0.26	NS
0	PLT (10^3/µL)	201.46±41.41	212.97±57	0.24	NS
4		170.28±53.95	167.76±64.62	0.95	NS
	TSH (ulU/ml)	1.4±0.6	1.5±0.9	0.5	NS
0	Ferritin (ng/mL)	156.25±44.56	156±39.37	0.88	NS
4		176.9±54.84	163.65±21.34	0.15	NS
0	PCR0 (IU/ml)	208581.4±372673.33	$3.1120\times10^6\pm 1.34071\times10^7$	0.001	S

P: calculated probability; NS: none significant; S: significant.

Table 3. Multivariate analysis of variables associated with early virological response EVR versus non EVR.

Test time/weeks post treatment	Variable	EVR (n=64)	Non EVR (n=32)	*P*	Sig
		Mean±SD	Mean±SD		
0	Age (years)	40.98±9.90	42.75±9.56	0.36	NS
0	Weight (Kg)	81.79±8.56	83.40±10.44	0.72	NS
0	BMI (kg/m^2)	27.82±2.30	28.10±2.94	0.63	NS
0	ALT (IU/L)	58.58±35.58	70.76±70.59	0.6	NS
4		40.44±36.07	61.96±60.83	0.005	S
12		32.32±21.75	48.2±34.89	0.002	S
0	AST (IU/L)	46.01±24.61	58.16±39.55	0.16	NS
4		39.30±30.59	54.2±41.71	0.033	S
12		36.65±20.46	53.26±39.38	0.007	S
0	BIL (mg/dl)	0.79±0.26	0.86±0.29	0.61	NS
4		1±0.38	1±0.5	0.66	NS
12		0.89±0.36	1±0.44	0.53	NS
0	HG (g/dl)	14.83±1.2	14.71±1.2	0.65	NS
4		12.54±1.44	12.95±1.3	0.16	NS
12		11.77±1.3	12.15±1.1	0.23	NS
0	WBC (10^3/µL)	5.92±1.89	6.6±2.9	0.29	NS

Table 3 Contd.

4		3.81±1.18	4.30±2.36	0.49	NS
12		3.52±1.4	3.84±2.13	0.91	NS
0	PLT (10^3/µL)	208.82±48.55	202±50.5	0.61	NS
4		175.11±59.15	157±56.60	0.31	NS
12		172.17±53.7	149.83±47.84	0.05	NS
0	Ferritin (ng/mL)	147.98±30.43	172.56± 56.11	0.02	S
4		170.92±53.2	172.5±15.44	0.11	NS
12		169.46±15.25	172.73±17.26	0.5	NS
0	PCR (IU/ml)	1885153.797±10916213.73	666226.96±1097210.37	0.02	S
4		8878.156±35106.37	44187594.9±249435291.2	0.000	S

P: calculated probability; NS: none significant; S: significant.

Table 4. Spearman correlation between serum ferritin levels at week 0, week 4 and week 12 of treatment to different variables at different stages of treatment.

Test time/ weeks post treatment	Parameter	Week 0			Week 4			Week 12		
		R	***P***	**Sig.**	**R**	**P**	**Sig.**	***R***	***P***	**Sig.**
0	Age (years)	0.04	0.69	NS	-0.06	0.5	NS	-0.09	0.34	NS
0	Weight (Kg)	0.15	0.13	NS	0.10	0.31	NS	-0.04	0.69	NS
0	BMI (kg/m^2)	0.14	0.15	NS	0.13	0.18	NS	-0.16	0.11	NS
0	AST (IU/L)	-0.06	0.56	NS	0.004	0.96	NS	-0.05	0.60	NS
4		0.02	0.84	NS	0.008	0.9	NS	-0.05	0.58	NS
12		0.06	0.53	NS	0.007	0.94	NS	0.008	0.93	NS
0	ALT (IU/L)	0.00	0.99	NS	0.07	0.48	NS	0.078	0.470	NS
4		0.09	0.36	NS	0.03	0.71	NS	0.002	0.983	NS
12		0.05	0.57	NS	0.07	0.49	NS	0.029	0.787	NS
0	HB (g/dl)	0.19	0.5	NS	0.07	0.46	NS	0.002	0.982	NS
4		0.16	0.11	NS	0.04	0.70	NS	-0.146	0.170	NS
12		0.23	0.2	NS	0.14	0.16	NS	-0.025	0.815	NS
0	WBC (10^3/µL)	0.12	0.22	NS	-0.05	0.62	NS	-0.088	0.407	NS
4		0.10	0.33	NS	0.16	0.11	NS	-0.233-*	0.027	NS
12		0.09	0.37	NS	0.10	0.31	NS	-0.177	0.095	NS
0	PLT (10^3/µL)	0.052	0.61	NS	0.04	0.67	NS	0.094	0.380	NS
4		-0.05	0.6	NS	0.07	0.48	NS	0.030	0.776	NS
12		-0.15	0.13	NS	0.04	0.64	NS	0.046	0.669	NS
0	PCR (IU/ml)	0.006	0.95	NS	-0.02	0.80	NS	-0.07	0.48	NS
4		-0.17	0.09	NS	-0.02	0.84	NS	-0.009	0.92	NS
0	HAI Stage	0.042	0.73	NS	-0.08	0.507	NS	-0.452	0.065	NS
0	Fib	0.054	0.655	NS	0.056	0.643	NS	-0.187	0.121	NS

R: Spearman's correlation coefficient (Spearman rho); *P:* Calculated probability; NS: Non significant; S: significant.

Table 5. Ferritin levels changes in EVR and non EVR during the course of treatment using Wilcoxon signed rank test.

Ferritin changes	EVR			Non EVR		
	Z	***P***	**Sig**	***Z***	***P***	**Sig**
Ferritin 4-ferritin 0	-4.321-[a]	0.000	S	-1.698-[a]	0.09	NS
Ferritin 12-ferritin 0	-4.281-[a]	0.000	S	-1.080-[a]	0.28	NS

Z: Wilcoxon signed rank value; *P*: Calculated probability; NS: Non-significant; S: significant.

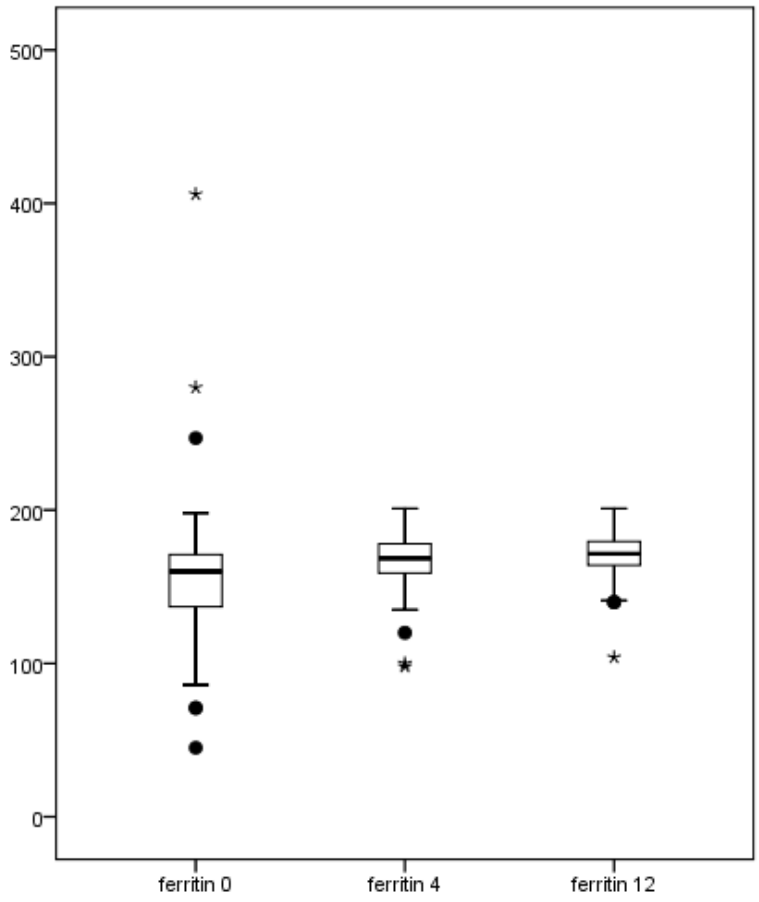

Figure 1. Comparison between serum ferritin at weeks 0, 4 and 12 in all patients of the study. Horizontal axis: Ferritin test time/weeks post treatment; Vertical axis: Serum ferritin level (ng/ml).

and 53.26 IU/ml) respectively with significant statistical difference. The mean value of pretreatment serum ferritin (147.98 ng/ml) in EVR group was lower than that in non-responders group (172.56 ng/ml) with significant statistical difference. Value of HCV RNA viral load at week 0, 4 in EVR group was much lower than that in non-responders group with highly significant statistical difference; otherwise, there was no statistical difference between the two groups (Table 3). There was no statistical significant correlations between serum ferritin levels during treatment and demographic and laboratory parameters at different stages of treatment. There was no correlation between serum ferritin level at different stages of the treatment and stage of fibrosis or the Histology Activity Index of the liver biopsy of the patient enrolled in the study (Table 4). Table 5 shows that the rise in SF level during treatment was found to be significantly higher in patients who achieved an EVR than in those without EVR with high statistical difference.

ROC curve analysis used to find the diagnostic

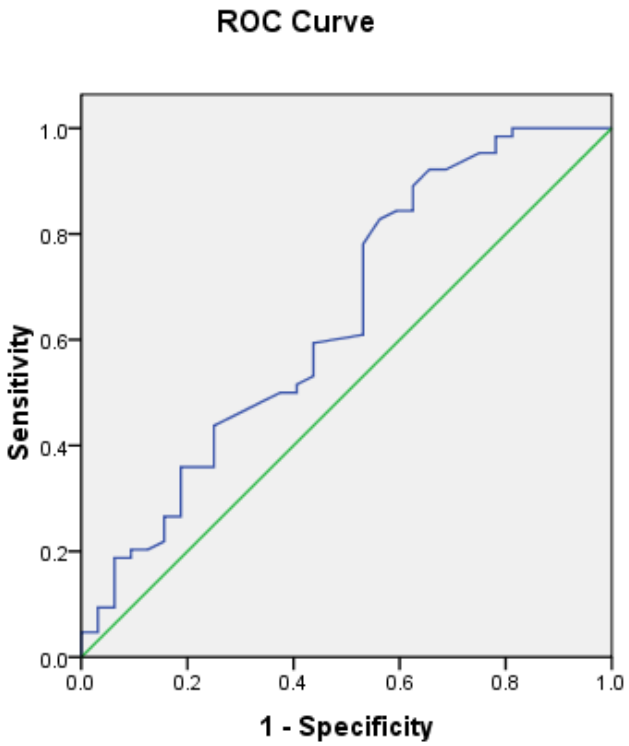

Figure 2. ROC curve analysis showing the diagnostic performance of value of pretreatment level of ferritin for discriminating EVR from non EVR. Diagonal segments are produced by ties.

performance of value of pretreatment level of ferritin for discriminating early virological responders from non-responders shows that serum ferritin level of 164 ng/ml is a cutoff value of pretreatment serum ferritin as predictor of EVR in CHC patients receiving PEG INF and ribavirin combination therapy, with a sensitivity of 60%, NPV: 53.6, PPV: 78.6 and AUC: 0.64 (Figure 2).

DISCUSSION

Chronic hepatitis C (CHC) is an important liver disease, which may progress to cirrhosis or hepatocellular carcinoma. The current treatment regimen for CHC includes pegylated interferon (PEG-IFN) combined with ribavirin (Barut et al., 2012).

Ferritin is the major iron storage protein and provides an indirect estimate of the body's iron stores. It is an acute phase reactant as well as an established marker for liver iron deposition and inflammatory processes. It has been suggested that serum iron and serum ferritin are predictors of therapeutic response to IFN therapy (Yada et al., 2010).

The current study showed that the level of pretreatment serum ferritin was significantly lower in patients with EVR than those who did not achieve EVR. This indicates that lower pretreatment serum ferritin is associated with better EVR. These results agree with the work of Barut et al. (2012) in which patients with lower baseline ferritin levels showed higher incidence of SVR in CHC patients.

It was suggested that elevated serum ferritin levels are independently associated with advanced liver fibrosis, hepatic steatosis, and poor response to interferon-based therapy in patients with CHC (Lange et al., 2012).

Iron inmesenchymal cells rather than total hepatic iron content were significantly related to fibrosis, and both mesenchymal iron deposits and high serum ferritin at baseline predicted a poor therapeutic response (Ferrara et al., 2009).

Different results were demonstrated by Yada et al. (2010) who found no significant statistical difference in serum ferritin levels before and during therapy between patients who achieved sustained viral response (SVR) and those who did not respond.

In this study, the recorded increased serum ferritin levels during treatment were significantly higher in patients who achieved EVR than those who did not. This could be explained by the activation of macrophage cells in response to the antiviral interferon therapy, which leads to release of ferritin from the macrophages independent on hemolysis. Also, the mechanism of hyperferritinemia is probably related to the immune stimulant and immune regulatory effects of IFN-α through

its attachment to cell surface receptors and activation of multiple interferon-stimulated genes, resulting in the induction of a Th-1 response that increases the synthesis and liberation of proinflammatory cytokines (that is, TNF-α, IL-1 and IL-6), which are known as up-regulators of the synthesis of ferritin (Ferrara et al., 2009). This is in agreement with Barut et al. (2012) who found that SF levels increased dramatically in both the SVR and non-SVR groups after starting the therapy, but remained high until the end of the treatment period, and returned to baseline levels after completion of treatment. However, the SF rise was found to be significantly higher in patients who achieved SVR than those who did not. In their study, SF increase at week 4 was considered as an independent factor predicting SVR, and that a 1 fold increase in SF at week 4 resulted in a 24% increase in the probability of SVR. It was concluded that SF increase during treatment was found to be correlated with favorable therapeutic outcome (Barut et al., 2012).

These results are similar to the work done by Ferrara et al. (2009) who stated that serum ferritin rise above 2.5 folds at week 12 during treatment, is considered as an independent predictor of favorable therapeutic response and was favorably associated with SVR (Wang et al., 2010). Distante et al. (2002) also found that increased serum ferritin levels during the antiviral therapy correspond with a favorable virological response. Ladero et al. (2009) have shown a significant increase in serum ferritin in a group of patients treated with high doses of interferon α after the surgical excision of a melanoma. However, Ladero et al. (2009) found that the median peak ferritin level reached during therapy of the enrolled patients was lower in the SVR group than in the non SVR group (Ferrara et al., 2009).

In the present study, there was no statistically significant correlation between serum ferritin levels and serum AST and ALT. These results were similar to the results of Yada et al. (2010) who found no significant correlation between serum ALT and ferritin levels at week 12 and 24 of therapy for each time point. Also Ferrara et al. (2009) reported that they found no associations between baseline serum ferritin and serum ALT; and that serum ferritin rise was not related to baseline serum ALT. Different results were observed by Ladero et al. (2009) who found that baseline serum ferritin correlated positively at a significant level with baseline serum ALT and serum AST also found that the highest serum ferritin level which reached between weeks 2 and 12 of therapy had a positive correlation at a significant level with serum ALT and serum AST at weeks 2, 6 and 12.

In the present study, there was no correlation between baseline serum ferritin and the stage of fibrosis and the grade of inflammation by the HAI score, where the cut off value for pretreatment serum ferritin for discriminating early virological response was 164 ng/ml with sensitivity of 60%, specificity of 59%, positive predictive value of 72% and negative predictive value of 53%.

Conclusion

This study pointed out that lower pretreatment serum ferritin levels and its increase during the course of treatment was associated with early virological response (EVR) in CHC patients receiving PEGINF and Ribavirin combination therapy.

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