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### Evaluation of treatment complications with Ribavirin and Interferon alpha 2b in HCV patient's 1b genotype

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#### KEYWORDS

Hepatitis C,  
Ribavirin,  
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#### A B S T R A C T

Chronic infection with hepatitis C virus is a global health problem that can lead to cirrhosis, liver disease and liver cancer. One of the standard treatments for hepatitis C genotype 1 is using Peginterferon and Ribavirin for 48 weeks which is associated with different complications. The aim of this study was to determine the side effects and complications due to combination therapy of interferon alpha 2b + Ribavirin in patients with Chronic Hepatitis C. In a descriptive study at the infectious diseases department at the University of Medical Sciences on patients with Chronic hepatitis C treated with Interferon-alpha 2b And Ribavirin, side effects and complications in the combination therapy of interferon alpha 2b + Ribavirin in patients with chronic hepatitis were studied. In this study, 92 patients with hepatitis c Genotype 1b were selected and studied in terms of the rate of side effects and complications of combination therapy with interferon alpha 2b + Ribavirin. 45 cases (48.9%) were male and 47 cases (51.1%) were female. The mean age of patients was  $11.10 \pm 38.01$  years. The mean ALT in patients before and 8 weeks after treatment, was dropped by  $69.58 \pm 54.03$  and  $38.48 \pm 39.92$ , respectively and the mean AST in patients before and 8 weeks after treatment,  $49.88 \pm 33.84$  and  $34.17 \pm 30.22$  respectively. The mean number of WBC in patients before and 8 weeks after treatment was  $6.37 \pm 2.34$  And  $4.00 \pm 1.59$  respectively. The mean number of RBC in patients before and 8 weeks after treatment was  $4.63 \pm 0.70$  and  $3.74 \pm 0.48$  respectively. The mean number of platelets in patients before and 8 weeks after treatment was  $237.01 \pm 89.86$  and  $198.14 \pm 96.63$  thousand respectively. Post-treatment complications in patients under study included lethargy, Myalgia, bone pain and fever, cough and fever, loss of appetite, sleep disorders, depression and anxiety. There was a significant decrease in the levels of ALT, AST, number of WBC, RBC and platelets after treatment ( $P < 0.001$ ), however, there were no significant changes during the follow-up to 48 weeks ( $P < 0.001$ ).

## **Introduction**

HCV is one of the causes of cirrhosis and liver transplantation, which will turn into a major health economy issue within the next 10-20 years. Fortunately, significant advances have been made in the course of therapy of this disease in recent years (1-3). Interferon-alpha 2b/Ribavirin therapy has proven efficacy in the treatment of viral infections (1-3). However, the important point in such therapy is adverse drug reactions (ADRs). Several ADRs have been reported during the course of this combination therapy. Many of these ADRs are mild and reversible, but some are extremely severe and even life-threatening. Overall, 15% complete cessation of the therapy as well as 25% reduction in therapeutic doses during the course of this combination therapy has been reported. The intake of optimum dosage of drugs used to treat chronic HCV, which involve the Interferon-alpha 2b/Ribavirin combination, is highly critical in the first 12 weeks of the therapy. These first twelve weeks during the course of the therapy is the period in which ADRs are mostly detected (1-3). However, the capacity to tolerate such ADRs can be increased by taking educational measures for patients; accordingly, frequent examinations and proper treatments of ADRs occurred during the course of therapy, as well as reduced changes in doses of received drugs lead to enhanced efficiency of the therapy. In contrast, the physician's lack of experience in proper managing of ADRs and also, improper training of patients results in high cases of cessation of the therapy or reduced dose of drug consumption, which ultimately leads to decreased therapeutic efficacy (1-3).

In a study conducted in 2005 in the United States, 82% of patients receiving the Interferon-alpha 2b/Ribavirin therapy were observed to have MDD disorder, the major

part of which was basically emerged in the first week of the therapy and the rest until the 8th week of the treatment. Moreover, 30% of the patients were reported to become cognitively impaired. Such cognitive impairment is even possible to continue to exist in 50% of patients after cessation of the therapy. Also, about 30% of patients with C\_HCV, despite having detectable HCV-RNA level, contain normal levels of liver aminotransferase. Initiation of therapy with interferon triggers liver aminotransferase levels and results in its increase. Drug therapy does not appear to greater influence patients with high level of liver aminotransferase than those with normal basic level of liver aminotransferase. During the total 48 week Interferon-alpha 2b/Ribavirin therapy, SVR in 52% of patients is associated with normal levels of liver aminotransferase and thus, decision to initiate HCV therapy must not be influenced by normal levels of liver aminotransferase (1-4).

The above mentioned side effects of the HCV therapy urged us to conduct a study to both investigate these ADRs on recipients of the Interferon-alpha 2b/Ribavirin therapy (MSD Co.) and evaluate and measure tolerability of patients against such ADRs and therefore, propose some approaches to physicians who initiate such therapies for their patients so that they avoid cessation of therapies and/or reduction of dose of drugs in cases where it is not really required to do so and can reach their main goal which is SVR in these patients.

## **Methods and Materials**

In a descriptive study conducted at the infectious diseases department of the Tabriz University of Medical Sciences on C-HCV patients treated with oral Interferon-alpha 2b/Ribavirin, we investigated the degree of

ADRs occurred during the course of the combination therapy.

This study was conducted on 92 C-HCV patients with the indication for therapy who underwent the Interferon-alpha 2b/Ribavirin-based oral combination therapy. The patients were monitored and examined up to 48 weeks after the therapy regarding post-treatment complications.

All the patients with the indication to receive Interferon-alpha 2b/Ribavirin for C-HCV therapy were included in the study and the following ADRs were examined in them according to a timeline.

### **Inclusion criteria**

Patients with the indication to receive the Interferon-alpha 2b/Ribavirin combination therapy.

### **Exclusion criteria**

Patients, who demonstrated thyroid disorders, prior to the therapy of mood disorders, patients with PMN<750 and Hb<8g/dl pre-therapy and PLT<500000, patients with decompensate cirrhosis and pregnant women.

### **Ethical Considerations**

All the measures taken to monitor ADRs are among the processes that should be carried out for each patient during the course of the Interferon-alpha 2b/Ribavirin combination therapy within a 48-week period. Therefore, consent form about the cooperation of such patients during the period of receiving this combination therapy must be taken, and the patients are responsible to pay for the cost of the study, as performing such processes is essential during the therapy.

### **Statistical Analysis**

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean  $\pm$  SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value  $\leq 0.05$  was considered statistically significant.

### **Results and Discussion**

In this study, 92 patients with HCV genotype 1b were chosen and examined regarding the degree of ADRs occurred during the course of the Interferon-alpha 2b/Ribavirin combination therapy and the following results were obtained:

The males were 45 (48.9%) and females were 47 (51.1%). The mean age of the patient was  $38.01 \pm 11.10$  years with the median of 35.50 (16-63) years.

Consumption of opium was observed in one case (1.1%), alcohol in 7 cases (7.8%) and cigarettes in 20 cases (22.2%).

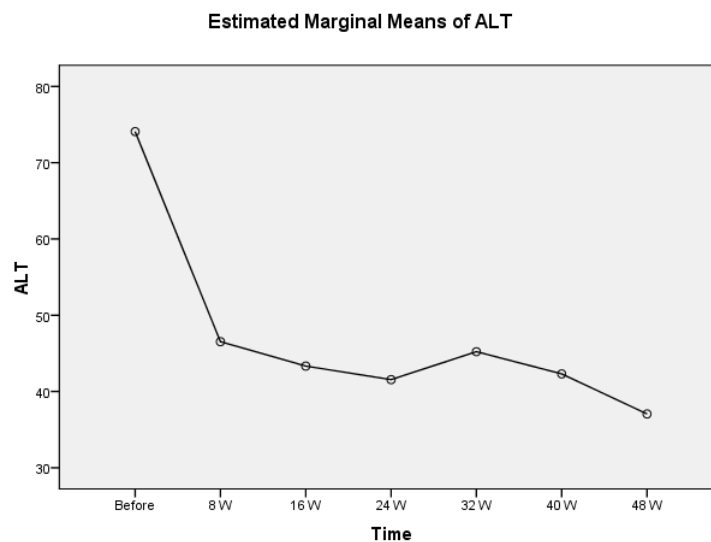
The mean ALT in the patients was  $69.58 \pm 54.03$  pre-treatment, which was reduced to  $38.48 \pm 39.92$  within the eight weeks post-treatment ( $P < 0.001$ ). The mean AST in the patients was  $49.88 \pm 33.84$  pre-treatment, which declined to  $34.17 \pm 30.22$  within the eight weeks post-treatment ( $P < 0.001$ ). However, no significant changes were observed in AST and ALT levels during the follow-up to the 48th week.

**Table.1** Laboratory finding of patients

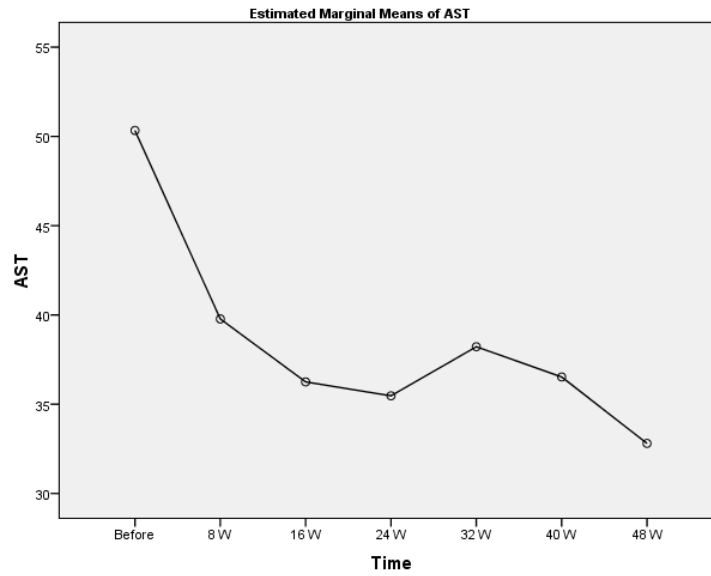
	Before	8 week late	16 week late	Fallow up time			
				24 week late	32 week late	40 week late	48 week late
ALT	69.58±54.03	38.48±39.92	38.40±41.89	35.67±42.79	35.90±42.39	35.29±46.94	36.13±41.88
AST	49.88±33.84	34.17±30.22	33.55±28.32	32.50±29.78	33.22±34.36	31.48±32.91	32.05±29.07
Zn	88.83±18.86	85.01±16.23	82.31±18.83	83.48±16.22	85.10±13.89	84.38±16.17	87.70±13.08
Haptoglobolin	0.77±0.42	0.69±0.48	0.64±0.45	0.59±0.48	0.58±0.43	0.55±0.45	0.56±0.51
BS	102.51±31.66	103.51±27.20	104.82±26.13	104.68±34.72	109.15±44.95	96.49±17.88	102.89±35.82
WBC	6.37±2.34	4.00±1.59	3.81±2.60	3.79±2.76	3.47±1.37	3.63±2.95	3.22±1.38
RBC	4.63±0.70	3.74±0.48	3.51±0.57	3.51±0.73	3.41±0.56	3.34±0.53	3.38±0.57
PLT	237.01±89.86	198.14±96.63	194.58±93.10	181.48±68.34	178.35±62.30	175.90±65.87	179.11±83.33

**Table.2** Side effects of treatment in patients

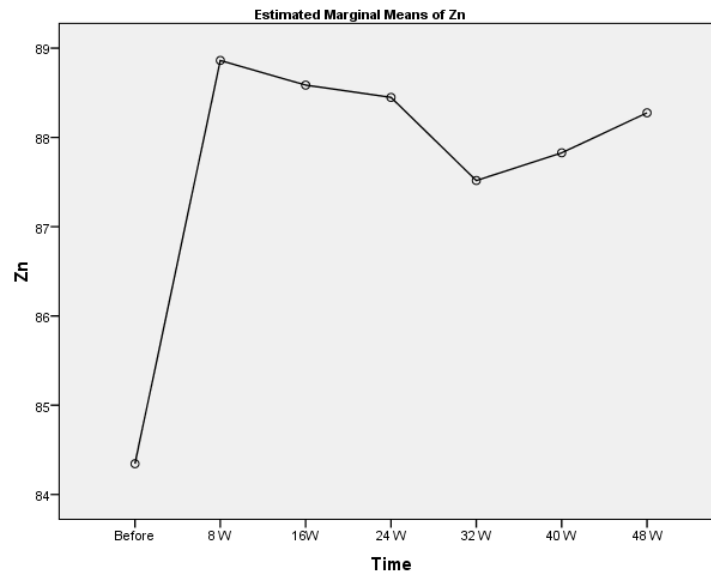
	Before	8 week late	16 week late	Fallow up time			
				24 week late	32 week late	40 week late	48 week late
Myalgia	37	66	70	62	57	42	26
Itching	21	26	49	43	40	30	18
Fever	14	62	61	44	41	32	21
Weakness	42	75	77	61	64	52	32
Cough	13	33	42	37	36	21	11
Tachycardia	22	40	42	41	35	28	17
Loss of appetite	14	47	46	34	30	23	16
Abnormal thyroid test	20	10	10	9	8	6	3
Sleep Disorder	23	38	43	38	32	23	15
Depression	26	38	42	43	44	31	16
Anxiety	30	42	47	45	43	31	17



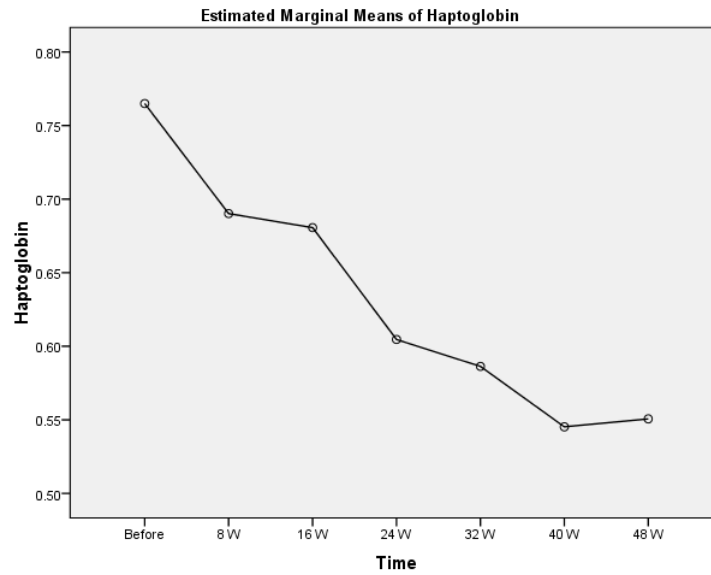
**Figure.1** Distribution of ALT in patients at the fallow up time



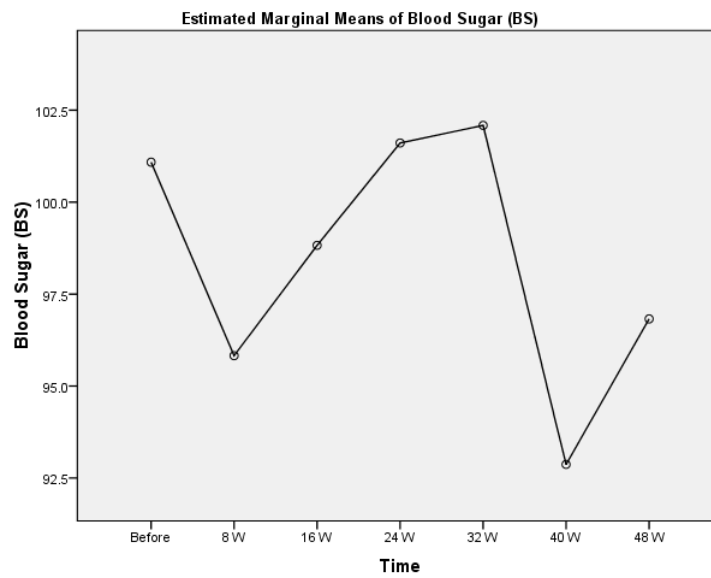
**Figure.2** Distribution of AST in patients at the follow up time



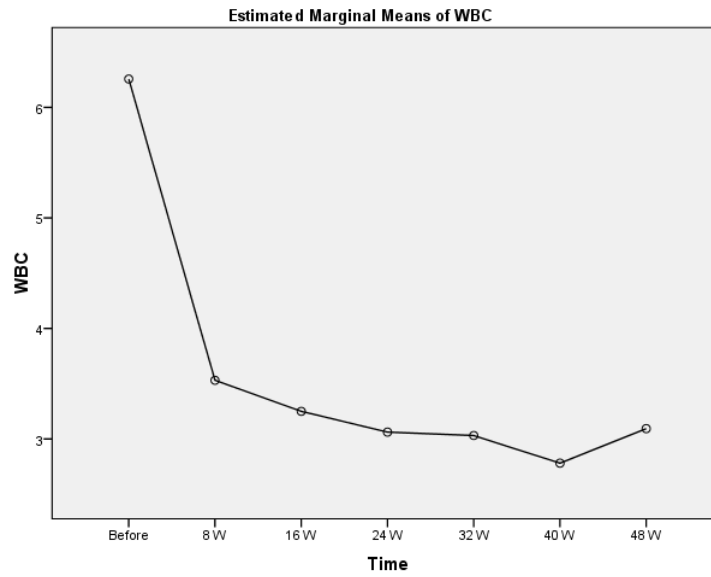
**Figure.3** Distribution of Zn level in patients at the follow up time



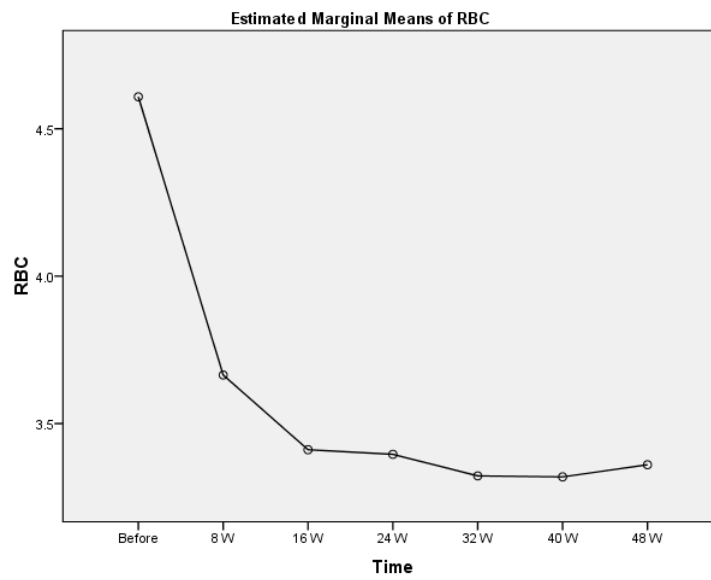
**Figure.4** Distribution of Haptoglobin level in patients at the fallow up time



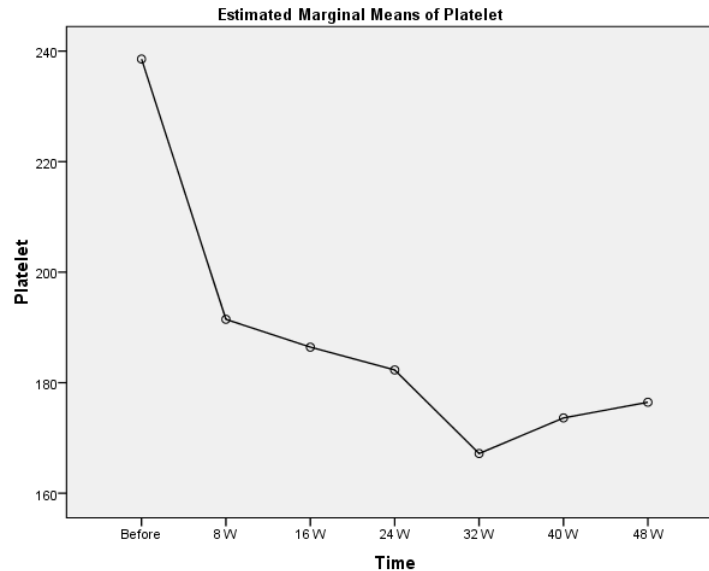
**Figure.5** Distribution of Blood sugar level in patients at the fallow up time



**Figure.6** Distribution of WBC in patients at the fallow up time



**Figure.7** Distribution of RBC in patients at the fallow up time



**Figure.8** Distribution of Platelet count in patients at the follow up time

Hepatitis C infection is a major cause of chronic liver disease worldwide. The long-term effects of viral infection are very different and are defined from minor liver changes to extensive fibrosis, cirrhosis and hepatocellular carcinoma. The number of people with hepatitis C has been estimated as about 160 million worldwide, who are often unaware of their infection. Viral infections are transmitted by medical interventions, sexual intercourse, and needle/syringe sharing in injecting drug users and from mother to fetus. Until 1990, the main reason for transmission of viral infections was transfusion as well as unsafe injection methods. Today, with screening blood products for hepatitis C because of unsafe medical intervention in other developed countries is infection with the virus (5). However, today, with screening blood products for hepatitis C virus in developed countries, unsafe medical interventions are no longer the reason for hepatitis C virus infection (5).

The primary goal of the treatment of hepatitis C is to improve infection. A SVR is

determined by the week 12 or 24 after completion of the therapy through an undetectable HCV RNA. Infection is improved in more than 99% of patients receiving SVR. SVR in patients without cirrhosis is generally associated with improved liver disease. However, cirrhosis patients are at risk of life-threatening complications. However, SVR may lead to regressed liver fibrosis and decreased risk of complications such as liver failure and portal hypertension (9-10).

Prior to initiation of therapy, other causes of chronic liver disease or factors affecting the progression of liver disease should be assessed and all patients should be examined for other hepatotropic viruses, particularly hepatitis B and immunodeficiency viruses. Moreover, alcohol consumption should be assessed and patients should be recommended to stop any use of alcohol. Possible co morbidities including autoimmune disease, genetic or metabolic liver disease or drug hepatotoxic also need to be evaluated (11).



Prior to initiation of therapy, assessing the severity of liver disease in terms of advanced cirrhosis or fibrosis is also important. Evaluation of fibrosis in patients with clinical evidence of cirrhosis is not necessary, but these patients need to be evaluated in terms of hepatocellular carcinoma. Liver biopsy for years has been the acceptable method for determining the stage of histologic development and disease activity (12-13).

In our study, extensive clinical and laboratory evaluation was conducted on patients under the therapy.

Peginterferon alfa and Ribavirin blood side effects include neutropenia, anemia, anemia, thrombocytopenia, and lymphopenia. These parameters shall be checked at the weeks 1, 2 and 4 of therapy and then every 4-8 weeks to be checked (11).

In our study, the mean number of WBC in the patients was  $6.37 \pm 2.34$  and  $4.00 \pm 1.59$  pre-therapy and 8 weeks post-therapy, respectively. Also, the mean number of RBC in the patients was  $4.63 \pm 0.70$  and  $3.74 \pm 0.48$  pre-therapy and 8 weeks post-therapy, respectively. The mean number of platelets in the patients was  $237.01 \pm 89.86$  and  $198.14 \pm 96.63$ , pre-therapy and 8 weeks post-therapy, respectively; yet a significant reduction was observed in the number of WBC, RBC and platelets post-therapy ( $P < 0.001$ ), but no significant changes were observed during the follow-up to the 48th week ( $P < 0.001$ ).

HCV-induced liver cirrhosis is among most common indications for liver transplantation and also, the major contributing factor in the increased prevalence of hepatocellular carcinoma. About 130-150 million people worldwide are chronically infected by this disease and annually, 300-500 thousand

people die due to HCV (14-15). Successful treatment of HCV is associated with achieving SVR (16-17).

One of the standard therapies for genotype 1 HCV is through Interferon-alpha 2b/Ribavirin combination therapy, in which 41-48% of the patients received SVR which seem to be long lasting and associated with long-term benefits (18-19). It has been shown that the Interferon-alpha 2b/Ribavirin combination causes the response to improve up to 54%. Moreover, the retrospective study reveals the response of 61% when Peginterferon and Ribavirin doses are assessed based on the patients' weights. The -2b $\alpha$  interferon or peg Interferon-alpha 2b/Ribavirin combination therapy requires a balanced therapeutic regimen of subcutaneous injection, oral administration of twice daily and frequent visits along with blood tests to assess the health and ADRs in almost all patients (20).

A-HCV leads to myalgia, nausea, pain in the upper right quadrant of the abdomen, dark urine and jaundice. HCV RNA can be detected in the blood a few days after exposure to the virus, and serum levels of ALT and AST are then gradually increased and bilirubin occurs in some cases.

In our study, body pain existed in 66 patients during 8 weeks post-treatment, which increased to 70 cases at 16 weeks post-treatment, whereas declined to 26 people at 48 weeks post-treatment. Moreover, muscle and bone pain existed in 44 patients during 16 weeks post-treatment, which was reduced to 15 people at 48 weeks post-treatment.

The incubation period of 6 to 112 days is expected from the time of entry of the virus until occurrence of clinical symptoms or laboratory abnormalities. Fifty percent to

85% of these people go toward a permanent viral infection. C-HCV often causes myalgia and fatigue.

Similar to above studies, in our study, weakness and lethargy were observed in 42 cases, body aches in 37 cases and fever in 14 patients prior to initiation of the therapy.

The quality of life drops even without cirrhosis, which improves with successful treatment. Extrahepatic manifestations such as cryoglobulinemia, protracted porphyria and membranoproliferative glomerulonephritis can occur. In hepatic manifestations, serum levels of ALT often fluctuate unrelated to symptoms. Although HCVRNA serum levels remain constant, the degree of inflammation that is characterized by liver biopsy may also vary. Fibrosis occurs in some patients, which can lead to the destruction of liver structure and ultimately, cirrhosis. In this case, decompensate cirrhosis occurs in 10% to 20% of these patients within 5 years, which is revealed with esophageal varices, ascites, coagulopathy, encephalopathy and hepatocellular carcinoma (7).

In our study, the mean ALT in the patients was  $69.58 \pm 54.03$  pre-treatment, which was reduced to  $38.48 \pm 39.92$  within the eight weeks post-treatment ( $P < 0.001$ ). Also, the mean AST in the patients was  $49.88 \pm 33.84$  pre-treatment, which declined to  $34.17 \pm 30.22$  within the eight weeks post-treatment ( $P < 0.001$ ). Results in this study also revealed significant changes in AST and ALT levels post-treatment, but not during the follow-up to the 48th week ( $P < 0.001$ ).

### **Conclusion**

In this study, 92 patients with HCV genotype 1b were chosen and examined

regarding the degree of ADRs occurred during the course of the Interferon-alpha 2b/Ribavirin combination therapy.

The males were 45 (48.9%) and females were 47 (51.1%), and the mean age of the patient was  $38.01 \pm 11.10$  years. The mean ALT in the patients was  $69.58 \pm 54.03$  pre-treatment, which was reduced to  $38.48 \pm 39.92$  within the eight weeks post-treatment. Also, the mean AST in the patients was  $49.88 \pm 33.84$  pre-treatment, which declined to  $34.17 \pm 30.22$  within the eight weeks post-treatment. The mean number of RBC in the patients was  $4.63 \pm 0.70$  and  $3.74 \pm 0.48$  pre-therapy and 8 weeks post-therapy, respectively. The mean number of platelets in the patients was  $237.01 \pm 89.86$  and  $198.14 \pm 96.63$ , pre-therapy and 8 weeks post-therapy, respectively.

The mean number of RBC patients before and 8 weeks after treatment was  $3.74 \pm 0.48$  and  $4.63 \pm 0.70$ , respectively. The mean number of platelets in patients before and 8 weeks after treatment respectively was  $237.01 \pm 89.86$  and  $198.14 \pm 96.63$  thousand. Post-therapy complications in the studied patients included lethargy, myalgia, bone pain and fever, cough and fever, loss of appetite, sleep disorder, depression and anxiety. A significant reduction in levels of ALT, AST, as well as in number of WBC, RBC and platelets was observed post-therapy ( $P < 0.001$ ), but no significant changes were detected during the follow-up to the 48th week.

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