ORIGINAL ARTICLE

EFFECT OF STANDARD INTERFERON AND RIBAVIRIN ON HAEMOGLOBIN LEVEL IN HEPATITIS-C PATIENTS

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Background: The standard treatment for HCV infection involves combination therapy with pegylated interferon and ribavirin. The study was conducted to determine the effect of standard interferon and ribavirin on the haemoglobin level in patients treated for hepatitis-C. **Methods:** PCR confirmed 58 patients of chronic hepatitis-C treated with standard interferon and ribavirin for six months were included in this case series study. The patients were followed up monthly. Haemoglobin was measured by Sysmex Haematology analyser at monthly interval to study change in its level. **Result:** The study found decrease in the mean haemoglobin levels during the six months treatment. when the mean of baseline haemoglobin was compared with the mean haemoglobin of six months treatment, a decrease of 2.05 gm/dl was observed and the result was statistically significant (p=0.000). **Conclusion:** Six months treatment of chronic hepatitis-C with standard interferon and ribavirin decreases haemoglobin to a significant level causing anaemia in susceptible patients.

Keywords: interferon, ribavirin, haemoglobin, hepatitis-C

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INTRODUCTION

Around 2–3% of the World population is infected with hepatitis C virus (HCV), and death occurs in over 350000 patients due to HCV induced cirrhosis and hepatic cancer.[1] Over 70% of HCV infections become chronic and if untreated may lead to cirrhosis and hepatocellular carcinoma, necessitating liver transplantation.[2,3] The standard treatment for HCV infection involves combination therapy with pegylated interferon and ribavirin.[4] The interferons (IFNs) can directly suppress bone marrow erythropoiesis,[5] whereas Ribavirin, is associated with side-effect, like haemolytic anaemia, which often renders therapy intolerable,[6] or may need modification of the dose.[7]

Phosphorylated Ribavirin is concentrated in the cytoplasm of erythrocytes,[8] where its level increases many folds.[9] The increasing concentration of ribavirin in the erythrocytes interferes with energy producing metabolic reaction responsible for membrane protection, resulting in oxidative membrane damage. The reticulo-endothelial cells break down damaged erythrocytes resulting in extensive hemolysis.[10] The severity of haemolysis greatly varies amongst individuals and may have genetic influence. The haemolytic process is related to the malfunctioning of enzyme inosine triphosphate pyrophosphatase functioning as intracellular purine cleaner.[8] Anaemia produced by interferon has different mechanisms. It directly effects the erythropoiesis[5], not requiring other mediators.[11] This is the reason that anaemia produced by interferon may be corrected by giving erythropoietin.[12] The conventional method of managing anaemia during hepatitis-C combination therapy, is to reduce the dose of ribavirin for haemoglobin levels of <10 g/dL and obtaining the complete blood counts at two weekly interval. In all patients, ribavirin should be discontinued altogether, if the haemoglobin falls below 8.5 g/dl.[13]

The completion of recommended dose of ribavirin and interferon alpha, i.e., 3 Mu of interferon alpha subcutaneously thrice weekly and ribavirin three times daily according to weight for six months is crucial for chronic hepatitis c treatment. The effectiveness of therapy is mandatory for sustained viral response.

Depending upon the severity; dose reduction or termination of treatment is required If the patient develops anaemia during the treatment. In a large population based study patients treated with combination therapy PEG-IFN α-2a and ribavirin, about 20% of patients required dose reduction of ribavirin as a result of anemia.[14] The quantity of dose reduced proportionately hampers the effectiveness of treatment, therefore adherence to full dose scheduling is mandatory (definitive cut-off at a critical ribavirin dose of 10.6 mg/kg)[14,15] and ultimately crucial to the sustained viral response. The use of erythropoietin has therefore, been studied to correct the inadequate haemopoiesis and improve the anaemia in patients treated with ribavirin and interferon. A recent trial demonstrated that Epoetin α given at 40000–60000 IU s/c weekly had significant improvement in haemoglobin levels.[16] The purpose of this study was to find out the decrease in haemoglobin of our patients during six months of treatment with standard interferon and ribavirin.

MATERIAL AND METHODS

The patients presented to the outdoor department of Ayub Teaching Hospital and Oursh General Hospital for the treatment of chronic hepatitis-C were included in this case series study. The patients included in the study

were HCV RNA PCR positive whether by qualitative or quantitative assay. Those who had decompensated liver disease, any other co morbidity with reduced life expectancy or extreme of ages were excluded from the study. Informed consent was obtained from every patient before starting the treatment. The selected patients were started on treatment with standard interferon 3 M units thrice weekly subcutaneously and ribavirin 400 mg three time daily with slight modification in accordance with the body weight. The patients were followed up weekly for 4 weeks and then monthly for six months. During follow up period at each successive visit, laboratory investigations done were periodic measurement of complete blood counts to look for change in haemoglobin level, neutropenia and thrombocytopenia. ALT levels measured to see variation during treatment. At the completion of treatment after six months the HCV RNA PCR was done to detect its level in the blood. Those patients who were able to clear the virus from their blood were responders, and those who could not clear the virus from their blood were non responders

RESULTS

Mean age of the patients was 41.24±10.183 years. Majority (46.6%) of the patients were in the age group 31–40 years. Male patients were 33 (56.9%), and 25 (43.1%) were females. Baseline mean haemoglobin of the patients was 12.62±1.682 gm/dl. Among these patients 33 (56.9%) had normal liver on ultrasonography. Fatty liver, chronic liver disease and cirrhosis was present in 9 (15.5%), 11 (19%) and 5 (8.6%) respectively. Six months of treatment with standard interferon and ribavirin was given to all patients. After six months of treatment, the response was assessed by performing PCR. PCR was negative in 42 patients making the response rate of 72.4%. The response to the treatment was higher among female patients (76%) than males (69.7%). However, the difference was not statistically significant (p=0.595).

The study results revealed that there was decrease in the mean haemoglobin levels during the six months treatment, and it was statistically significant (Table-1). When the mean of baseline Haemoglobin was compared with the average mean Haemoglobin over six months treatment period, a mean decrease of 2.05gm/dl was observed and the result was statistically significant (p=0.000). The temporal comparison of haemoglobin levels between successive months showed significant decrease during first three months and last month (Table-2). The decrease in haemoglobin levels did not have statistically significant relationship with age (p=0.457). Similarly no significant relationship was found in decrease in haemoglobin between male and female patients at the end of treatment (p=0.830). The fall in haemoglobin level was consistent in all the three morphological hepatic groups except cirrhosis (Table-3).

Table-1: Comparison of Hb levels during six months of treatment

Haemoglobin at different time intervals	Paired Differences					T	Df	*p*-value
	Mean	SD	SEM	95% CI Lower	95% CI Upper			
Baseline Hb - Hb at 1 month	0.914	1.050	.138	.638	1.190	6.630	57	.000
Baseline Hb - Hb at 2 months	1.748	1.436	.189	1.371	2.126	9.269	57	.000
Baseline Hb - Hb at 3 months	2.193	1.584	.208	1.777	2.610	10.542	57	.000
Baseline Hb - Hb at 4 months	2.431	1.817	.239	1.953	2.909	10.187	57	.000
Baseline Hb - Hb at 5 months	2.355	1.543	.203	1.950	2.761	11.626	57	.000
Baseline Hb - Hb at 6 months	2.655	1.678	.220	2.214	3.096	12.054	57	.000

Table-2: Temporal comparison of Hb during treatment period

Haemoglobin at different time intervals	Paired Differences					T	df	*p*-value
	Mean	SD	SEM	95% CI Lower	95% CI Upper			
Baseline Hb - Hb at 1 month	0.914	1.050	.138	.638	1.190	6.630	57	.000
Hb at 1 month - Hb at 2 months	0.834	1.042	.137	.560	1.109	6.098	57	.000
Hb at 2 months - Hb at 3 months	0.445	.898	.118	.209	.681	3.772	57	.000
Hb at 3 months - Hb at 4 months	0.238	1.136	.149	-.061	.537	1.595	57	.116
Hb at 4 months - Hb at 5 months	-.076	1.101	.145	-.365	.214	-.525	57	.602
Hb at 5 months - Hb at 6 months	.300	1.095	.144	.012	.588	2.086	57	.041

Table-3: Comparison of decrease in Hb levels in different liver morphological groups

Hepatic morphological patterns on ultrasound		*p*-value
Normal	Fatty Liver	0.427
	Chronic Liver Disease	0.779
	Cirrhosis	0.035*
Fatty liver	Chronic Liver Disease	0.490
	Cirrhosis	0.013*
Chronic liver disease	Cirrhosis	0.008*

*The mean difference is significant at the 0.05 level.

DISCUSSION

Hepatitis-C treatment consists of ribavirin and interferon, given over six months. The effectiveness of therapy depends on, the optimum dose over six months duration. The efficacy of therapy decreases when due to some reason there is compulsion to reduce the dose of either, ribavirin or interferon. Second reason may be inability to complete therapy over six months for genotype-2 & 3 and 48 weeks for genotype-1. One of the major side effect of hepatitis-C treatment is anaemia. Interferon directly inhibits erythropoiesis and ribavirin causehaemolysis.[6,17] The extent of anaemia vary between individuals, some patients may experience marked haemolysis to become symptomatic. These patients may need erythropoietin to increase the haemoglobin level or modification of ribavirin dose.[18] Various previous studies revealed, that during treatment of hepatitis-C with interferon and ribavirin, maximum haemoglobin reduction was observed during the first month of treatment, with mean maximum decrease of 3g/dl.[19,20] In this study we compared the mean of the baseline and average mean of the six months the drop in the haemoglobin was 2.05g/dl. When the decrease in haemoglobin was analysed temporally over six month period, the maximum decrease in haemoglobin was during the first month of treatment (table-2). Previously some studies indicated that other factors like female gender and old age may adversely affect the haemoglobin level during treatment with interferon and ribavirin.[9,10] In contrast in this study no significant relationship was found in decrease in haemoglobin between male and female patients at the end of treatment (p=0.830). Similarly no relationship was observed with increasing age and reduction in haemoglobin. Another important fact came into light that the reduction in haemoglobin was more significant in those patients who had cirrhosis when compared with other morphological groups on abdominal ultrasound (normal, fatty change and chronic liver disease).

CONCLUSION

Six months treatment of chronic hepatitis-C with standard interferon and ribavirin decreases haemoglobin to a significant level causing anaemia in susceptible patients.

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