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ORIGINAL ARTICLE

FREQUENCY OF ANEMIA AND ITS ASSOCIATION WITH OUTCOME (SUSTAINED VIROLOGICAL RESPONSE) IN PATIENTS OF CHRONIC HEPATITIS C GENO 3, TREATED WITH STANDARD INTERFERON ALPHA 2a AND RIBAVIRIN

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ABSTRACT:

Chronic Hepatitis C is one of the leading cause of chronic liver disease globally. The past two decades have seen many advances in Hepatitis C treatment. Despite these advances side effects of treatment are common. Hematological complications of treatments can result in treatment cessation and suboptimal results

We observed the development of haematological side effects chiefly anaemia and its effect on SVR in a cohort of 240 patients. The mean Haemoglobin at baseline was 13.2 gm, range 10.9-16, SD=0.8. At 6 months the mean Haemoglobin was 10.6 gm (7-11gm) SD=0.7. Clinically significant anaemia defined as haemoglobin of less than 10 gm/dl occurred in 56 % (n=134) of patients. Out of these 36% (n=48) were males and 64% (n=86) were females. More than 69 % of the total cohort (n=165 pts) experienced a drop of Hb of ≥ 3 gm/dl. Hemoglobin decreased by 2.8 gm at week 4 in 44% of patients and by 3.5 gm in 25% of patients at 3 months. A decrement in Hb of upto 2.9% was seen at the end of 6 months of treatment.The P value is < 0.05, this difference is considered to be statistically significant.

Overall SVR was 71%. SVR rates in those who developed anaemia was 76% and in those who did not develop anaemia was 68%. The P value equals 0.5, this difference is considered to be not statistically significant.

Anaemia is a frequent complication of interferon and ribavirin treatment for chronic hepatitis C and needs management with dose reduction and erythropoietin to optimize SVR. Erythropoietic agents are effective in treating anemia, preventing ribavirin dose reduction and improving patient's quality of life.

Keywords: Chronic Hepatitis C, Anaemia, Ribavirin.

INTRODUCTION

Chronic Hepatitis C is a leading cause of death and morbidity globally. The past two decades have seen many advances in Hepatitis C treatment (Fried 2002) and (Manns 2001). Despite these advances the burden of liver disease continues to grow. In part this is due to an ever increasing pool of treatment failures (Shepard 2005).

Efforts to improve the effectiveness of treatment have centered on identifying host and viral predictors of response. In addition adherence to treatment and delivery of adequate drug dosages have been shown to be

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one of the important reasons leading to success or failure of treatment regimens (McHutchison, 2009). It has been confirmed that treatment have to ensure delivery of 80% or more of scheduled doses of interferon and ribavirin and together with the duration of treatment the 80,80,80 rule has been established, high-lighting the primary importance of ensuring adequate dose delivery for achieving optimal SVRs (McHutchison, 2009).

Hematological complications of treatment can result in treatment cessation or dosage reduction and sub optimal results. Anemia, neutropenia and thrombocytopenia frequently occur during anti HCV treatment, necessitating reduction in drug dosages and at time stoppage of treatments. These factors highlight the importance of maintaining optimal or near optimal doses of interferon and ribavirin for as long as possible. This study was conducted to identify the incidence of anemia and its response to erythropoietic growth factors in patients treated with standard interferon and ribavirin and to see the effect of anemia on likelihood of achieving SVR, since there are suggestions that patients who develop anemia during treatment with interferon and ribavirin are more likely to achieve a SVR (Sievert 2011 and Sulkowski 2010).

MATERIALS AND METHODS

This observational study was carried out at the Department of Medicine KRL General Hospital, Islamabad from November 2009 till December 2011. All patients provided written informed consent.

Inclusion criteria

Previously untreated adults who had HCV RNA detectable in serum by PCR with genotype 3a; who had undergone liver biopsy within one year before entry that was consistent with chronic hepatitis, and who had ALT values from normal (> 30 IU/L for men and 19 IU/L for women) to four times the normal, with the hematological and bio-chemical values of hemoglobin; white blood count, platelet counts, bilirubin, albumin, prothrombin time and creatinine within normal limits.

Exclusion criteria

Patients with decompensated cirrhosis, other causes of liver disease, seizure disorders, cardiovascular disease, hemoglobinopathies, thyroid disease, hemophilia, poorly controlled Diabetes, autoimmune disease, previous organ transplant or if they were unable to use contraception.

Study Plan

All the patients fulfilling the inclusion criteria were treated with interferon 2b alpha 3 MIU sub-cutaneously on alternate days, plus ribavarin 1000-1200 mg/day. The dose of ribavarin was adjusted according to the body weight (1000 mg for weight below 75 kg and 1200 mg for weight 75 kg or more). Treatments were administered for 24 weeks with a subsequent 24-week follow-up period. During treatment patients were assessed as outpatients at weeks 2, 4, 8, 12, 16, 20 and at 24 , and then at 24 weeks after the end of the therapy. Qualitative PCR for HCV RNA was done at weeks 0, 4, 24 and 48. At each visit, blood cell counts and ALT were measured and recorded. Side effects were also monitored at each visit and were graded as mild, moderate, severe and life threatening. A sustained virological response (SVR) was defined as undetectable HCV RNA by a qualitative PCR test 6 months after stopping treatment in patients who had achieved end of treatment responses. An EOTCR i.e. end of treatment complete response was defined as undetectable HCV RNA by qualitative PCR at 24 weeks of the treatment. Non-response was defined as a positive qualitative PCR at any time before or at 24 weeks of the treatment. All PCR tests were done by a Cobas Amplicor with a lower cut off value of 100 copies/ml. The variables studied were age, gender, weight, positive family history, Hb levels, total white cell counts, platelet counts, ALT and liver histology.

Table 1
Baseline characteristics

Parameter	Mean ± SD	Median	Range
Age	39.79±8.13	40	20-65
Weight (Kg)	66± 9.5	68	45-96
ALT (IU/L)	98±68.8	80	14-496
Hb (gm/dl)	13.3±1.89	13.6	9-17
Platelets	199677±59.068	198000	48000-331000

The RBV dose was reduced by 200 mg in patients receiving 1000 mg (by 400 mg in those receiving 1,200 mg) when hemoglobin decreased <12 g/dL, and by another 200 mg when it was below <10 g/dL. Interferon dose was reduced by one-half when the leukocyte count decreased <1,500/mm^3, neutrophil count <750/ mm^3, or platelet count <80 x 10^3/mm3; IFN was withdrawn when they decreased <1,000/mm^3, 500/ mm^3, or 50 x 10^3/mm^3, respectively.

The distribution of individual characteristics was evaluated by simple descriptive statistics. To compare the overall distribution of response, end of treatment complete response, non-responder, relapse, sustained response status, the electronic database organized in SPSS for windows version 15 was used. Quantitative data i.e. age, height, weight and ALT was presented as mean ± SD. P-value less than 0.05 was considered significant. Sample size was calculated by using WHO sample size calculator (sample size determination in health studies, a practical manual, software version by KC Lun and Peter Chiam, National University of Singapore) taking confidence level of 95%, anticipated population proportion 77.5% (proportion of patients who achieved SVR) and relative precision 8%.

RESULTS AND DISCUSSION

Anemia is a common side effect of treatment for chronic hepatitis C virus infection and is due to red blood destruction (hemolytic anemia) caused by ribavirin, and bone marrow suppression by interferon (Nomura 2004). It is known that the triphosphate metabolite of ribavirin accumulates in red blood cell and causes oxidative injury to red blood cells membranes, thereby resulting in hemolysis. Patients who develop anemia on ribavirin therapy have a responsive reticulocytosis. However the compensatory reticulocytosis seen in patients treated with combination therapy is much less then that seen in patients treated with ribavirin alone showing that interferon induced bone marrow suppression prevent an adequate reticulocytosis. Erythropoietin alpha over-comes this effect of inadequate reticulo-cytosis and improves the anemia in patients treated with combination therapy (Tod 2005). Patients receiving erythropoietin were able to maintain their initial dose of ribavirin. However erythropoietin alpha use did not effect SVR or treatment discontinuation rates among patients who developed anemia.

Most patients treated with complications of interferon/ribavirin, experience anemia of mild to moderate severity. Conventional management of anemia is to reduce ribavirin dose for hemoglobin <10g/dl and obtain blood counts every two weeks or more frequently if indicated. Patient with cardiac function abnormalities may require discontinuation of ribavirin if they become anemic. Ribavirin dosing is recommended to be discontinued if hemoglobin falls <8g/dl, but both dose reduction and discontinuation increases the risk of post treatrment relapse, thereby decreasing the likelihood of achieving SVR. Practically erythropoietin stimulating agents (Mac Nicholas 2010) which increase RBC production are added when Hb falls to less than 10 gm/dl.

This results in significant improvement in quality of life, energy and activity levels. It is hoped that this will translate into improved adherence.

In our study 240 patients fulfilling the inclusion/exclusion criteria were enrolled in between November 2010 till Dec. 2011. There were 49% males and 51% females.The mean age of pts was 39.79 yrs ± 8.13 yrs and mean weight was 66± 9.5 kg. The mean value of Alanine aminotransferase was 98±68.8 Iu/l with a range of 14-496.The base-line characretistics are given in the Table 1.

We observed the development of haematological side effects chiefly anaemia and its effect on SVR in this cohort. The mean Hb at baseline was 13.2 gm, range 10.9-16, SD=0.8 and decreased to 10.6 gm (7-11gm) SD 0.7 at six months (Figure 1).

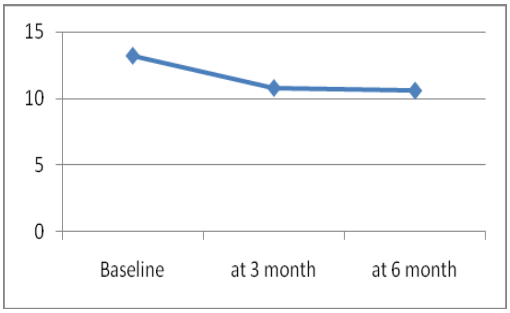

Figure 1: decrease in Hb level during therapy

Clinically significant anaemia defined as serum haemoglobin of less than 10 gm/dl was seen in 56 % (n=134) of patients , out of these, 36% (n=48) were males and 64% (n=86) were females,Table 2 and Figure 2.

Table 2
Haemoglobin of less than 10gm/dl (n=134) in males and females

Sex	Number	%
Male	48	36%
Females	86	64%

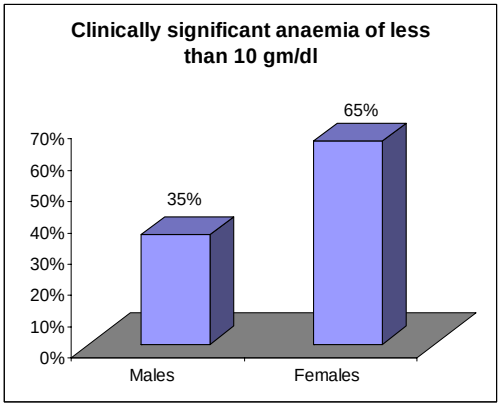

Figure 2: percentage of anaemia in males and females

More than 69% of the total cohort (n=165 pts) experienced a drop of Hb of ≥3 gm/dl. Hb decreased by 2.8 gm at week 4 in 44% of patients and further decreased by 3.5gm from baseline in 25% of patients at 3 months. A decrement in Hb of upto 2.9% was seen at the end of 6 months of treatment (Figure 3).

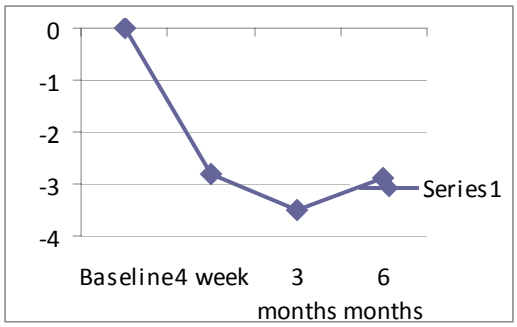

Figure 3: decrease in haemoglobin level of more than 2.5 gm/dl from baseline.

Ribavarin dose reduction was done in all patiens who developed a haemoglobin below 10 gm and erythropoietin stimulating agents were used in patients who failed to msaintain their hb above 8.5gm/dl.

Overall SVR was 71%. SVR rates in those who developed anaemia was 76% and in those who did not develop anaemia were 68% (Table 3).

Table 3
SVR rates in patients with anaemia and in those without anaemia

Overall SVR	71%	P=0.5
SVR rates in patients with anaemia	76%	
SVR in patients without anaemia	68%	

More than 69 % of the total cohort (n=165 pts) experienced a drop of Hb of ≥ 3 gm/dl from the baseline. This is similar to and slightly more than that shown in recent studies which have shown a prevalence of anaemia in upto 44% of subjects (Suzuki 2011). This increased incidence of anaemia may reflect an initial lower Hb value in our cohort and a increased genetic tendency to develop ribavirin induced anaemia, compounded by an overdue emphasis on diet restriction in Pakistani patients with liver disease due to cultural practices and food norms. In Pakistani studies (Saeed 2006) anaemia prevalence in similar cohorts have been shown to be around 10 %.

In the Chariot study (Sievert 2011) anemia was seen in 76% of patients overall. Reduction of Hb to less than 10 gl/dl which is a cutoff point for antiviral dose reduction and if that fails initiation of erythropoietin alpha was seen in upto 56% (n=134) of patients in our cohort in our cohort which is in accordance with published results. The Hb decrease following initiation of therapy can be seen as early as 2 weeks. A decrease of upto 1.63gm/dl ±0.92 can be seen at 2 weeks and can progress to upto 2.9 gm decrement by the end of treatment. Greater falls in Hb are usually seen in females in 64% (n=86) and in those with age more than 50 yrs in our study.

CONCLUSION

Clinically significant anaemia occurs in a majority of patients of chronic hepatitis C treated with interferon and ribavarin and results in dose modifications of drugs and use of eryhthropoietin stimulating agents. Early detection and appropriate management of anaemia is very important to attain a favorable outcome in response to therapy. The number of patients achieving SVR was more in those who developed anaemia as compared to those who did not develop anaemia but the difference was not statistically significant.

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