Original Article

Severity of Anemia during Interferon and Ribavirin Therapy in Patients with Chronic Active Hepatitis C Genotype-3 and its Association with Risk Factors

Aftab Ahmed Sheikh, Mona Humaira, Madiha Zaki, Mohammad Adnan Bawani, Sadik Memon

ABSTRACT

Hepatitis C is a major public health problem globally. It is one of the commonest cause of chronic liver disease in Pakistan. The prevalent genotype is "3" in our country. The standard of care treatment is combination of interferon and ribavirin. This combination has important adverse effects especially hemolytic anemia.

AIMS & OBJECTIVES: This study has been conducted to determine the frequency of anemia (< 10gm/dl) at 4, 12 and 24 weeks of interferon and ribavirin treatment CAH-C Genotype-3patients along with assessment of associated risk factors.

PLACE AND DURATION: This study was conducted in department of Gastroenterology & Hepatology, Isra University Hospital, Hyderabad, Sindh from April 2009 to October 2010.

STUDY DESIGN: Prospective & case series study

MATERIALS AND METHODS: All patients who fulfilled the inclusion and exclusion criteria were enrolled. The proforma was filled after patients verbal consent, by asking questions .Their BMI was recorded and other demographic characteristics were also noted .Patients were followed at 4,8,12,16,20 and 24 week. Their Blood CP was checked and if Hb fall within the range of 10.1 - 11.9 mg/dL then the dose of ribavirin was reduced (200 mg/day reduction) and if Hb was <8.5 g/dL then both drugs were stopped altogether.

RESULTS: A total of 140 patients were remained for final analysis. Male were 73(52%, n = 140). Only 18(13%, n = 140) patients developed anemia at week 4 of treatment. Compared to baseline mean Hb% SD 13.31±1.18 (12 to 17 gm/dl), week 4 post treatment mean Hb ±SD (Range) was 11.2 ± 1.15(gm/dl. Almost 76.4% (107) of patients dropped hemoglobin more than two grams at week 4 from baseline. The mean Hb% level at week 12 of treatment was 11.2 gm/dl. There were 31 (22%) patients developed anemia Hb<10.0 gm/dL .It was significantly seen in females. One hundred and seven (76.4%) patients dropped Hb more than 2 gm at week 12.

Total of 30 (18%) patients developed anemia (Hb<10.0 gm/dL) at week 24. Mean hemoglobin level at week 24 was 11.1 gm/dl. Anemia at week 4 & 12 were the two strong predicators of anemia at week 24. Other significant factors associated with anemia at week 24, were female sex and body weight less than 60kg at baseline.

CONCLUSION: Anemia is a frequent complication of Anti HCV therapy.

KEYWORDS: Anemia, interferon and ribavirin, chronic hepatitis C.

INTRODUCTION

Chronic hepatitis C virus (HCV) affects at least 170 million people globally and cause significant morbidity and mortality[1].There are 6 different genotypes of this virus with different geographical distribution. In our country Genotype 3 is prevalent. Other countries where this genotype is prevalent are India, Thailand, Australia, and Scotland .Genotype 1a is found in 50-60% of patients while Genotype 1b occurs in 15-20 % of patients in the United States, later type is also most prevalent in Europe, Turkey, and Japan.[2]

The recommended treatment for chronic HCV is combination of interferon and ribavirin (RBV)[1]. In a randomized controlled clinical trial researchers found that in genotype 3 HCV patients 24 weeks therapy with 40 KD pegylated interferon α-2a and 800 -1200 mg ribavirin was equally good as 48week of treatment, indicating that therapy with 24 weeks and a low dose of ribavirin is required to eliminate this virus in a high proportion of those who are infected.[3] Genotype 3patients respond well to therapy with successful treatment rates of 80%.[4]

Although therapy has good result but it also has got some important adverse effects and RBV-induced haemolytic anaemia, is one of them because it may be so troublesome to require dose modification in up to 15% of patients.[1] Because of dose reductions efficacy may be compromised. In the 2 phase 3 registration trials of pegylated interferon alfa (pegIFN-) and RBV, dose modification for anemia was required in 9% to 22% of patients.[3,4].Haemolytic anemia produced by ribavirin is caused by the extensive RBV accumulation in erythrocytes.[5] Concentration of phosphorylated ribavirin exceed 50 -100 fold from that of plasma.[6] This lead to an inhibition of intracellular energy metabolism and oxidative membrane damage, resulting in an accelerated extravascular hemolysis by the reticulo-endothelial system.[5]

There are several clinical risk factors associated with severity of ribavirin induced anemia. These include impaired renal function, old age, high dose per body weight and female gender [5,6]. Baseline platelet level, baseline hemoglobin (Hb) level plasma concentration of ribavirin, and haptoglobin phenotype all are found to be important predictors.[6]. The extent of anemia caused by ribavirin varies greatly among individuals, suggesting a genetic influence. Recently, using a genome-wide association technique, Fellay et al reported that functional variants in inosinetriphosphatepyrophosphatase (ITPA), including one coding and one intronic variant, were associated with treatment-induced anemia in HCV-infected patients[1]. There are a good number of patients whose stopped due to adverse effects of interferon and ribavirin. Treatment induces anemia in almost all patients but it is the severity of anemia due to which ribavirin either stops or discontinued. As most of the studies carried out on the patients of genotype 1 we conducted this study in genotype3 patients of chronic HCV which is prevalent type in our country. This study was designed to assess the severe anemia in HCV Genotype 3 patients on PEG Interferon and Ribavirin treatment and quantify those patients who required dose reduction of ribavirin. We also tried to detect the factors which predispose these patients for development of anemia. Elaborating associated risk factors would help in modifying them if possible for better treatment. These findings would be beneficial for proper treatment of patients as dose reduction of ribavirin has bad effect on SVR[7]We prospectively evaluated in this study the frequency and risk factors which are associated with treatment induced anemia in Genotype-3, chronically HCV patients treated for six months with ribavirin and conventional interferon α-2b.

MATERIALS &METHODS

This study was carried out to know the frequency of anemia (< 10gm/dl) at 4, 12 and 24 weeks of interferon and ribavirin treatment in patients with CAH-C Genotype-3 and to detect risk factors associated with anemia at 4, 12, 24 weeks.

This was a prospective case series study conducted at Department of Gastroenterology & Hepatology, Isra University Hospital, Hyderabad, Pakistan.

Study drug was purchased by patients themself, they were advised to return the used syringes so that the compliance was make sure .

Intensity of anemia would be graded as mild, moderate, severe and life-threatening withHb% less than 12gm but more than 10gm/dl,less than 10 gm but > 8.5 gm/dl, less than 8.5, >7gm/dl and less than 7gm/dl respectively. Our cut off value for anemia was less than 10 gram/deciliter

Inclusion Criteria;

Adults of either sex aged ≥18 years with chronic genotype 3 HCV infection as evidenced by HCV antibody and RNAby PCR positivity with genotyping.

Patients CBC values Platelet count ≥ 150,000 cells/ mm^3, Neutrophil count > 1500 cells/mm^3,baseline Hb% > 12 gm/dl in both sexes.

Exclusion Criteria;

Along with all usual contraindication for the therapy , Co-infection with HIV/HBV, previously treated patients,use of colony stimulating factors e.g.G-CSF), erythropoietin or other therapeutic agents prior to starting treatmentDiabetic patients were also excluded.

Statistical Analysis

The data were evaluated in statistical program SPSS version 16.0.Qualitative data included descriptive statistics (frequency and percentage of categorical parameters are presented as n(%) and Fisher`s exact and Pearson`s test of chi-square were applied with 95% confidence interval. Continuous variables are expressed as Mean+/- Standard Deviation and Student`s test (2 tailed) was used to compare the means among the patients with anemia (Hb% less than 10.0 gm/dl) and non-anemic groups. The P-value <0.05 was considered as statistically significant for all comparisons.

RESULTS

There were one hundred fifty five (155) patients included in the study initially. But only 140 patients completed the therapy for 6 month. Fifteen patients were dropped out from the study due to following reasons.

Patients drop out

1. Five Patients did not tolerate the interferon due to exacerbation of cardiac & pulmonary diseases.

2. Four patients were lost to follow-up
3. One Patient died due to road traffic accident during study period.
4. Five Patients refused to comply with protocol of the investigators.

A total of 140 patients were remained for final analysis.

Mean age of the participants was 40.46 years, male were 73 (52%) . Other baseline characteristics of participants are listed in table.1

The frequency of anemia found in our study was 13%,22% and 21% at 4,12 and 24 weeks respectively.

Anemia at week 4 of treatment

Only 18(13%) patients developed anemia (Hb% <10 gm/dl at week 4 of treatment. Compared to baseline mean Hb %(13.31 gm/dl), week 4 post treatment mean Hb was 11.2 gm/dl. Almost *76.4% (107)* of patients dropped hemoglobin more than two grams at week 4 from baseline..Factors associated with week 4 anemia (Hb% less than 10.0 gm/dl) are shown in Table no. 2.

No statistically significant risk factors were found for anemia (Hb<10 gm/dl) at week 4 of combination therapy. Shown in the table no.2, that appreciable anemia was prevalent in patients, age more than 35 years, belongs to rural community, female sex, BMI more than 25 and low level of education.

Table no. 3 also added that baseline mean Hb% less than 12.7 gm/dl is the predictor of week 4 anemia.

Anemia at week 12 (Hb<10gm/dl)

The mean Hb level at week 12 of treatment was 11.2 gm/dl. There were 31 (22%) patients who developed anemia according to our cut off line that is <10.0 gm/dL. Anemia (Hb<10gm) at week 12 was significantly seen in female sex, patients having week 4 Hb% less than 10 gm/dl, mean age 41 years, patient having mean baseline ALT 61 IU/L and patients having mean base line platlets count 235. One hundred and seven (76.4%) patients dropped Hb more than 2 gm at week 12. The above results are well depicted in table 4.

Anemia at week 24

Although all the patients, who developed anemia at week 4 or 12 were treated accordingly, (this includes ribavirin dose reduction, addition of folic acid and or addition of erythropoietin-α) a total of 30 (21%) patients developed anemia (Hb<10.0 gm/dL) at week 24. Mean hemoglobin level at week 24 was 11.1 gm/dl. Anemia at week 4 & 12 were the two strong predicators of anemia at week 24 as shown in table no. 5. Other significant factors associated with anemia at week 24, were female sex and body weight less than 60kg at baseline.

TABLE I: BASELINE CHARACTERISTICS

Characteristics	n=140
Male	73
Female	67
Mean Age	40.46
Mean Hb% at baseline	13.13 gm/dl
Mean body weight at baseline	63 kg
Mean BMI at baseline	26.6
Rural population	108(77%)
Patients having education level >5 years	51(36.4%)
Patients belongs to lower class	37(26.4%)
Field workers	116(83%)
Sindhi speaking	89(63%)
Mean ALT at baseline	80 IU/ml
Mean platelets at baseline	240

TABLE II: FACTORS ASSOCIATED WITH WEEK 4 ANEMIA (Hb% < 10.0 gm/dl)

Factors	Anemia at 4 week		P-value
	Yes	No	
Age			
Less than 35	6(33%)	40(32%)	0.9
More than 35	12(67%)	82(67%)	
Sex			
Male	7(39%)	54(54%)	0.23
Female	11(61%)	56(46%)	
Weight			
<60	8(44.4%)	50(41%)	0.78
>60	10(55.6%)	72(59%)	
BMI			
<25	5(10.6%)	42(89.4%)	0.57
>25	13(14%)	80(86%)	
Baseline platelets			
<200	3(7.1%)	39(92.9%)	0.18
>200	15(15.3)	83(84.7%)	
Ethnicity			
Sindhi	10(55.6%)	79(64%)	0.45
Non-Sindhi	8(44.4%)	43(35.2%)	
Level of education			
< 5 years	11(61%)	78(64%)	0.81
> 5 years	7(39%)	44(36%)	
Type of residence			
Urban	3(16.7%)	29(24%)	0.5
Rural	15(83.3%)	93(76%)	
Type of occupation			
Field work	17(14.7%)	99(85.3%)	0.16
Bench work	1(4.2%)	23(95.8%)	
Socioeconomic class			
Lower class	4(22.2%)	23(27%)	0.6
Upper class	14(77.8%)	89(73%)	
Hypertension			
Yes	5(27%)	48(37%)	0.34
No	13(72%)	74(60.7%)	
ALT at baseline			
<33 IU/L	3(16.7%)	16(13.1%)	0.68
>33 IU/L	15(83.3%)	106(86.9%)	
HCV RNA			
Detected	9(50%)	56(46%)	0.7
Not Detected	9(50%)	66(54%)	

TABLE III: INDEPENDENT T TEST FOR ANEMIA AT 4 WEEKS, 12 WEEKS AND 24 WEEKS

Characteristics	Hb< 10gm	Hb> 10gm	P-value
Anemia at 4 weeks			
Mean dose of Ribavirin(mg/day)	1036	1022	0.64
Mean Age (years)	40.72	38.6	0.53
Baseline Mean ALT (IU/L)	65	82	0.4
Mean Hb% at baseline (mg/dL)	12.7	13.4	0.3
Mean platelets at baseline (10^9/ml)	238	260	0.6
Anemia at week 12			
Mean dose of ribavirin(mg/day)	1038	1019	0.45
Mean age (years)	41	38	0.003
Mean ALT at baseline (IU/L)	61	85	0.01
Mean Hb% at baseline	12.64	13.5	0.25
Mean platelets at baseline(10^9/ml)	231	274	0.035
Anemia at week 24			
Mean age (years)	38.0	41.0	0.75
Mean weight (kg)	57	64	0.8
Mean dose of Ribavirin	920	1065	0.4
Mean ALT level	73	81	0.58
Mean platelets count	244	240	0.14

TABLE IV: ANEMIA AT 12 WEEKS

Characteristics	<10gm	>10gm	p-value
Age			0.936
<35	10(21.7%)	36(78.3%)	
>35	21(22.3%)	73(77.7%)	
Sex			0.001
Male	8(11%)	65(89%)	
Female	23(34.3%)		
Ethnicity			0.58
Sindhi	21(23.6%)	68(76.4%)	
Non Sindhi	10(19.6%)	41(80.47%)	
Residence			0.967
Urban	7(22%)	25(78%)	
Rural	24(22.2%)	84(77.8%)	
Occupation			0.07
Field work	29(25%)	87(75%)	
Bench work	02(8.3%)	22(91.7%)	
Socioeconomic status			0.6
Lower class	7(19%)	30(81%)	
Middle class	24(23%)	79(77%)	
Weight			0.63
<60	14(24%)	44(76%)	
>60	17(20.7%)	65(79.3%)	
BMI			
<25	13(27.7%)	34(72.3%)	0.264
>25	18(19.4%)	75(80.6%)	
HTN			
Yes	12(22.6%)	41(77.4%)	0.91
No	19(21.8%)	68(78.2%)	
EVR			0.5
Detected	16(24.6%)	49(75.4%)	
Not detected	15(20%)	60(80%)	

TABLE V: ANEMIA AT 24 WEEK

Characteristics	Hb% at 24 week		P-value
	<10gm	>10gm	
Hb% at week 4			0.01
<10gm	8(44.4%)	10(55%)	
>10gm	22(18%)	82(82%)	
Age			0.16
<35	13(28.3%)	33(71.7%)	
>35	17(18%)	77982%)	
Sex			0.02
Male	10(13.7%)	63(86.3%)	
Female	20(30%)	47(70%)	
Ethnicity			0.40
Sindhi	21(23.6%)	68(76.4%)	
Non Sindhi	9(17.6%)	42(82.4%)	
Level of education			0.64
<5 years	18(20.2%0	71(79.8%)	
>5 years	12(23.5%)	39(76.5%)	
Residence			0.16
Urban	4(12.5%)	28(87.5%)	
Rural	26(24%)	82(76%)	
Type of occupation			0.53
Field work	26(22.4%)	90(77.6%)	
Bench work	4(16.7%)	20(83.3%)	
Socioeconomic			0.07
status	4(10.8%)	33(89.2%)	
Lower class	26(25.2%)	77(74.8%)	
Upper class			<0.001
Body weight	21(36.2%)	37(63.8%)	
<60	9(11%)	73(89%)	
>60			0.97
BMI	10(21.3%)	37(78.7%)	
<25	20(21.5%)	73(78.5%)	
>25			
Hypertension	11(20.8%)	000	
Yes	000	000	
No			
ALT			0.519
<33	3(15.8%)	16(84.2%)	
>33	27(22.3%)	94(77.7%)	
Hb level week 12			<0.001
<10 gm	15(48.4%)	16(51.6%)	
>10 gm	15(13.8%)	94(86.2%)	
HCV RNA at week 24			0.24
Detected	3(12.5%)	21(87.5%)	
Not detected	27(23.3%)	89(76.7%)	
Platelets count			0.65
<200	10(24%)	32(76%)	
>200	20(20%)		

DISCUSSION

Hepatitis C is a global health problem. According to World Health Organization" approximately 3.3 per cent of the world's population (200 million people) have been infected with the hepatitis C virus." Hepatitis C is one of the commonest causes of chronic liver disease in Pakistan and stands second in prevalence of hepatitis C in the globe after Egypt.[8] It is proved from many studies that genotype 3a is the most prevalent HCV genotype in Pakistan.[9]

The standard of care treatment is combination of interferon & ribavirin with response rate greater than 75% in genotype 3[10]. Nevertheless there are a few side-effects of this therapy, most troublesome include, ribavirin therapy induced hemolytic anemia; a reduction in hemoglobin of up to 2–3 g or in hematocrit of 5–10% can occurred. Some patients experience marked hemolysis, resulting in symptomatic anemia, requiring ribavirin dose reductions or addition of erythropoietin.[10]

In this study 76.4% (107) patients dropped hemoglobin more than two grams at week 4 from baseline. Out of them 56% developed significant anemia i.e. Hb<10g/dl. 13%, 22% & 21% of patients dropped Hb<10g/dl at week 4,12 & 24 respectively. Other studies are also in favor of this Jacques Fellay et al found that severe anemia occurred in up to 15% of patients taken treatment of HCV.[1]

Chao-Hung Hung study suggest anemia is major side effect of combination antiviral therapy which is specially more severe among the Asian population.[11]

The mechanism behind ribavirin induced hemolytic anemia is it's peculiarity to accumulate inside RBCs in the phosphorylated form, which leads to the oxidative damage and finally extra vascular hemolysis. According to a research "RBC lifespan decreased from 10+/- 22 days in HCV patients not exposed to ribavirin to 39+/-13 days in HCV patients taken treatment." [12]

There are some factors associated with the reduction in Hb. Genetic link also detected in the causation of anemia. Studies shows that several single nucleotide polymorphisms {SNPs} on chromosome 20 (20p13 region) were found to be strongly associated with treatment-induced reduction in Hb at week 4.[1].

There are different Independent factors associated with reduction in hemoglobin. It has been observed that reduction in hemoglobin of>1.5 gm/dL at week 2 strongly predicts >2.5 gm/dL reduction at week 4.[12] other factor is baseline creatinine clearance. In our study we could not find out any definite (statistically significant) risk factors for anemia (Hb<10 gm/dl) at week 4 of combination therapy. Although it was more in patients aged greater than 35 years, belongs to rural community, female, BMI more than 25 and low level of education.

The problem with, ribavirin induced hemolytic anemia is that it frequently leads to ribavirin dose reductions. This is not a new discovery it was came into notice during trials of peginterferon alfa-2a plus ribavirin that patients had reduction in hemoglobin of 3.7 g/dL, and a large no of patients{ 22%} required dose reduction of ribavirin.[8] In another study more than 50% of patients experienced a decrease in hemoglobin of ≥3.0 g/dL, [11]and, in another study, by 24 weeks of treatment ribavirin dose reduction was required in 27.6% of patients, with a mean maximal decrease in hemoglobin of 4.0 g/dL[13].

Approximately 25% to 35% of patients treated with standard interferon alfa and ribavirin suffered from reduction in hemoglobin to below 11 g/dL In these trials, the mean maximal decline in hemoglobin concentration (from a baseline above 12.0 g/dL in women and 13.0 g/dL in men) ranged from 2.0 to 3.1 g/dL while 8% to 13% of patients had hemoglobin levels below 10 g/dL[14]

In this study the mean Hb level at week 12 of treatment was 11.2 gm/dl. There were 31 (22%) patients who developed anemia at week 12 , according to our cut off line that is <10.0 gm/dL. Anemia (Hb<10gm) was significantly seen in female sex, patients having week 4 Hb% less than 10 gm/dl, mean age 41 years, patient having mean baseline ALT 61 IU/L and patients having mean base line platelets count 235$10^9$/l

Chao-Hung Hung et al also found in their study high rates (39%) of severe anemia ,patients suffered during antiviral therapy and noticed that occurrence of severe anemia before 12 weeks was associated positively with achieving EVR. Other associated factors which were significantly correlated for decrease in hemoglobin were old age (≥50 years), female sex ,low body weight (<65 kg) and reduced platelet counts.[11]

In our study at week 24 a total of 30 (21%) patients developed anemia (Hb<10.0 gm/dL) .. Mean hemoglobin level at week 24 was 11.1 gm/dl. Anemia at week 4 & 12 were the two strong predicators of anemia at week 24 as shown in table no. 7. Although all these patients were treated accordingly, (this includes ribavirin dose reduction, addition of folic acid and or addition of erythropoietin-α) .Other significant factors associated with anemia at week 24, were female sex and body weight less than 60kg at baseline.

These associations were also noticed by other researcher . Several factors including old age, female gender, amount of the drugs, pretreatment platelet counts, and haptoglobin phenotype were found to be associated with development of anemia during antiviral therapy.[5.6.] In one study authors found that, old age and baseline hemoglobin level were associated with decreases in hemoglobin.[11]

So it is obvious from the discussion so far that anemia

is a frequently occurring(10%-30%)complication of hepatitis C antiviral therapy resulting in hemoglobin (Hb) declines of 2to 3 g/dL. However reduction in ribavirin>20% of actual dose to combat anemia may reduce SVR,

Preliminary data indicates that recombinant erythropoietic growth factors may overcome treatment-related anemia, maintain higher ribavirin doses and increase patient quality of life.[7]

CONCLUSION

Anemia is a frequently encountered complication of interferon plus ribavirin therapy in chronic HCV patients. Important associated risk factors were female sex ,body weight less than 60kg at baseline and Hb<10 gm/dl) at week 4 and 12.

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AUTHOR AFFILIATION:

Dr. Aftab Ahmed Sheikh
Assistant Professor, Department of Pharmacology
Isra University Hospital, Hyderabad, Sindh-Pakistan.

Dr. Mona Humaira *(Corresponding Author)*
Assistant Professor, Department of Medicine
Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Sindh-Pakistan.
Email: monaahmed2810@gmail.com

Dr. Madiha Zaki
Medical Officer
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Mohammad Adnan Bawani
Assistant Professor, Department of Medicine
Isra University Hospital Hyderabad, Sindh-Pakistan.

Dr. Sadik Memon
Professor, Department of Medicine
Isra University Hospital Hyderabad, Sindh-Pakistan.