

Prevalence and Risk Factor of Anemia during Interferon Alpha and Ribavirin Combination Therapy in Chronic Hepatitis C Patients

Femmy Nurul Akbar*, Zuljasri Albar**, Abdul Muthalib***,
LA Lesmana****, Nurul Akbar*****

* Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital

** Division of Rheumatology, Department of Internal Medicine,
Faculty of Medicine University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital

*** Division of Hematology and Medical Oncology, Department of Internal Medicine,
Faculty of Medicine University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital

**** Division of Hepatology, Department of Internal Medicine, Faculty of Medicine
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital

ABSTRACT

Background: Interferon alfa and ribavirin combination therapy is one of effective standard therapy for chronic hepatitis C (CHC.) However, anemia is a common side effect of this therapy that patients have to reduce or discontinue ribavirin therapy. But ribavirin dose reduction or discontinuation can reduce the effectivity of the therapy. Hence, it is important to know the prevalence of anemia and to determine the factors associated with anemia.

Objective: To know the prevalence of anemia and some risk factors associated with anemia caused by the combination therapy in chronic hepatitis C.

Method: Sixty one of CHC patients who received combination therapy were included in this study. The study used cross sectional design and data were obtained by measured complete blood count on 8th week of therapy.

Result: Subjects 47 (77%) were males, 14 (23%) were females with mean age 38.9 years. Subjects had genotype 1 and 4 were 23 (71.9%) and 44 (72.1%) subjects received 1,000 mg ribavirin. Prevalence of anemia was found to be 52.5%. On multivariate analysis, only pretreatment hemoglobin concentration < 14 g/dl was found to be the risk factor of anemia.

Conclusion: Prevalence of anemia was 52.5%. Pretreatment hemoglobin concentration < 14 g/dl was only found to be the risk factors of anemia. Although age $\geq$ 50 years or female were not found to be the risk factor of anemia but patient with these risk factors should be carefully monitored. Intervention to prevent anemia should be considered to these patients. Eight subjects from 32 anemia patients had ribavirin dose reduction, and no patient had discontinuation treatment on 8th week of therapy.

Keywords: chronic hepatitis C, IFN-alfa- RIB combination therapy, risk factors of anemia

INTRODUCTION

Chronic hepatitis C (CHC) is one of common chronic liver infections. Hepatitis C is caused by RNA virus which has 6 genotypes and 50 subtypes.¹⁻³ Prevalence of hepatitis C in Indonesia is 3-4 %. About 60-90% of CHC patients become chronic, 30-50% of patients have liver cirrhosis and 4-15% of patients become hepatocellular carcinoma. Therefore, hepatitis C is one of crucial health problem in

Indonesia.³

One of CHC standard therapy is combination of interferon alpha (IFN) and ribavirin (RBV) given in 24-48 weeks. The sustained viral response are 31-51%.^{2,4-8} However, this combination therapy may cause some adverse effects, that one of adverse effect is anemia. The etiologies of anemia are hemolytic, inhibition of erythroid progenitor cells or mixed.^{5-10,11,12} RBV cause erythrocyte oxidative

membrane damage and also impair antioxidant defense mechanisms which lead to extravascular hemolysis by the reticuloendothelial system.⁸⁻¹⁰

Many clinical trials reported that the prevalence of anemia (Hb < 10 g/dL) is 8 - 20.5%.^{2,5-7,13} Standard dose of ribavirin is 800-1,200 mg daily. Anemia depends on dose of RBV therefore the dose should be decreased to 600 mg if hemoglobin (Hb) level less than 10 g/dL and temporarily discontinued if the hemoglobin level less than 8.5 g/dL. Reduction or discontinuation RBV therapy before 20th week of therapy are often associated with poor treatment response (decrease SVR 12-15%) and cause relapse in patients with genotype 1.^{4,5} Anemia occurs between 2nd to 12th week of therapy but usually happened on the 8th week of therapy. Anemia will continue during therapy and generally return to normal level within 4-8 weeks of therapy cessation.^{7,12,13} Previous studies indicated that hemoglobin level decreases between 2-4 g/dL or 25% reduction from baseline.^{7,12-14}

Many studies reported that age more than 55 years old, female gender and ribavirin dose more than 800 mg were found to be the risk factor of anemia during combination therapy.¹³ Elderly people have higher risk of anemia because they have lack of reverse capacity of erythroid progenitor cell and also have erythrocyte membrane anomaly associated with hemolysis.¹⁰ Women has a higher risk of anemia may be because their pretreatment hemoglobin level is significantly lower than men.¹³

There is no study about prevalence and risk factor of anemia caused by IFN alpha and RBV combination therapy in patient with CHC has published in Indonesia. By knowing risk factor of anemia such as age, sex, genotype, ribavirin dose and pretreatment hemoglobin level, we may provide a better monitoring for patients with such factors. Intervention to prevent anemia such as exogenous erythropoietin for patients with hemoglobin level < 12 g/dL should be also considered, because if the hemoglobin level further decreases, intervention with erythropoietin may not succeed.¹² As a result, ribavirin dose may not be sustained and therapeutic success will decrease. Vitamin C and E or ribavirin alternative therapy such as virimidine are kind to manage anemia.^{15,16,17}

The objective of this study is to determine the prevalence of anemia in patient who receives combination therapy, to determine the risk factor of anemia such as certain age, sex, genotype, ribavirin dose, and pretreatment hemoglobin level in CHC patient.

This study can provide data to evaluate anemia in patient with certain risk factor. So that intervention for anemia may be considered, then patients have higher quality of life and drug compliance.

METHODS

This study was a cross-sectional design conducted from September – December 2005. The population was CHC patients who received combination therapy of IFN and RBV therapy. Sixty one subjects had found with consecutive sampling technique. Analyzed variable were age, sex, ribavirin dose, genotype and pretreatment hemoglobin level that associated with anemia (based on WHO criteria; Hb ≤ 13 g/dL for men and Hb ≤ 12 g/dL for women).

Inclusion criteria are CHC patients on 8th week of combination therapy IFN 3 MIU, 3 times a week plus RBV 800-1,200 mg based on body weight, with age 20-65 years, and pretreatment Hb level was ≥ 12 g/dL in women or ≥ 13 g/dL in men, and also willing to participate in this study. Exclusion criteria are patient with contraindication with combination therapy, i.e. patient who received immunosuppressive therapy or other antiviral therapy, patient with liver cirrhosis or hepatoma, co-infection with hepatitis B or HIV, cardiovascular disease, diabetes mellitus, chronic renal failure, and pulmonary TB, history of malignancy, pregnancy and lactation, malnutrition, history of bleeding or other blood disorder, history of drug consumption that may decrease Hb level.

Data was collected through interview process using study questionnaire, complete physical examination and laboratory examination. Bivariate analysis was evaluated by Chi-square test with 5% significance level and 95% confidence interval. If there is expected value less than 5, more than 20% cells, then absolute Fisher test was performed. Variable with $p < 0.25$ was included in multivariate analysis by using analysis of logistic regression with significance level < 0.05 and 95% confidence interval.

RESULTS

Subject characteristics

Characteristic of 61 subjects is represented in table 1. The age range of subject is between 20 and 65 years.

This data indicated that most of subject were male, less than 50 years old, had genotype 1 & 4, and most of them received 1,000 mg dose of ribavirin. The mean of overall pretreatment Hb level was 14.7 ± 1.4 g/dL. The mean of pretreatment Hb level was 15.2 ± 1.2 g/dL in male and 13.1 ± 0.5 g/dL in female.

Table 1. Demographic characteristic (n = 61)

Characteristic	Total	%
Sex		
Male	47	77
Female	14	23
Age group		
< 50 years	42	68.9
≥ 50 years	19	31.1

Table 2. Medical characteristics (n = 61)

Characteristics	Total	%
Genotype*		
1 & 4	23	71.9
2 & 3	9	28.1
Ribavirin dose		
800 mg	8	13.1
1,000 mg	44	72.1
1,200 mg	9	14.8
Pretreatment Hemoglobin level		
< 14 g/dL	19	36.1
= 14 g/dL	42	63.9

*: genotype n = 32

The mean of pretreatment Hb level in female was significantly lower than male.

Prevalence of Anemia in IFN and RIB Combination Therapy

Table 3. Prevalence of anemia in combination therapy (n = 61)

Anemia	Total	%
Yes	32	52.5
No	29	47.5

Table 4. Characteristics of anemia patient

	Received Ribavirin Dose Reduction	Not Received Ribavirin Dose Reduction
Total patients	8	24
Age = 50 years	6 (75%)	9 (37.5%)
Pretreatment Hb level < 14 g/dL	6 (75%)	11 (45.8%)
Female	5 (62.5%)	6 (25%)

In this study, the prevalence of anemia was 52.5%. From 32 subjects who had anemia, only 8 subjects (25%) had ribavirin dose reduction on the 8th week of therapy and no subject had ribavirin discontinuation.

Table 5. Risk factor and anemia (n = 61)

Factors	Anemia				OR 95% CI
	Yes		No		
	N	%	N	%	
Age					
= 50 years	15	78.9	4	21.1	5.51*
< 50 years	17	40.5	25	59.5	(1.56-19.5)
Gender					
Female	11	78.6	3	21.4	4.54*
Male	21	44.7	26	55.3	(1.12-18.41)
Genotype ‡					
2 & 3	5	55.6	4	44.4	1.36
1 & 4	11	47.8	12	55.2	(0.29-6.41)
Ribavirin dose					
< 1,000 mg	27	50.9	26	49.1	0.62
= 1,000 mg	5	62.5	3	37.5	(0.14-2.88)
Pretreatment Hb level					
< 14 g/dL	17	89.5	2	10.5	15.30*
= 14 g/dL	15	35.7	27	64.3	(3.10-75.43)

Explanation: ‡: genotype n = 32, *: significant

Risk Factor of Anemia

From bivariate analysis age 50 years or more, female and lower pretreatment Hb level was found to be significant factor associated with anemia.

From multivariate analysis using logistic regression analysis, only pretreatment Hb level less than 14 g/dL was a significant factor associated with anemia.

DISCUSSION

This study reported that prevalence of anemia was 52.5%. This study use WHO criteria (Hb < 13 g/dL for male and < 12 g/dL in female), in order to have early anticipation before adjusting ribavirin dose (Hb < 10 g/dL).^{6,7}

Prevalence of anemia in this study was lower than prevalence in Van Vlierbergh et al study i.e. 67% which also use similar hemoglobin level.^{13,18} In this study, prevalence of anemia with hemoglobin level less than 10 g/dL was 13.1%. Generally, there was a significant mean value of hemoglobin level on the 8th week of therapy, i.e. 2.1 ± 1.4 g/dL with the lowest hemoglobin level is 9.1 g/dL.

This study reported that anemia occurred easily in age 50 years or more. Risk of anemia in age group ≥ 50 years was five and half time higher than age < 50 years on the 8th week of combination therapy.

This result was not different from previous studies, which indicate that age group more than 50 years was associated with anemia.^{13,19,20} Nomura study found that incidence of anemia may achieve 30% in age more than 50 years.¹³ While Takaki study found significant reduction of ribavirin dose in the age group more than 55 years.¹⁹ This study found that the all subjects who have ribavirin dose reduction were more than 50 years old.

There was significant decreased hemoglobin on the 8th week of therapy in the age ≥ 50 years compared to the subject with the age less than 50 years in this study with mean value of 2.64 g/dL.

It is certainly unknown why the older patient is more likely had anemia or ribavirin dose reduction. Based on literature, we found that in elder people have erythrocyte membrane anomaly associated with hemolysis and they have a lack reverse capacity of erythroid progenitor cell.¹⁰

This study found that females subject is only one per third compared to males subjects. But females subjects tend to have risk of anemia four times greater

than males. Previous studies also found that female is one of risk factor of anemia in IFN alpha and RBV combination therapy.^{13,19,20} One of possibility that anemia occurred easily in female because they had a significant lower pretreatment hemoglobin level than male ($p = 0.000$).

Sulkowski's study reported that incidence of anemia in females subjects was five times greater than male. But the decreased hemoglobin level more or equal to 3 g/dL of pretreatment Hb level occurred easily in male.²⁰ While in this study, there was lowest decreased of hemoglobin level on 8th week therapy i.e. 6.4 g/dL in male and only 4.9 g/dL in female subject. But the mean value of decreased hemoglobin in the 8th week of therapy is similar, i.e. 2.12 ± 1.4 g/dL in male and 2.0 ± 1.3 g/dL in female.

Female is one of predictors of successful chronic hepatitis C therapy. Therefore, we should conduct a more careful monitoring in female patient in order to achieve successful therapy.^{21,22}

In accordance with characteristic of CHC patient in Indonesia, the most common genotype in this study is genotype 1 & 4 (71.9%). From this study, it was found that genotype 2 & 3 tend to have more anemia, although it is not statistically significant, may be because the small sample size.¹⁸ Sample size is small because genotype examination is too expensive. Takaki et al study also did not find any correlation between genotype and anemia.¹⁹

The limit value of pretreatment hemoglobin level as a risk factor of anemia was hemoglobin level of < 14 or ≥ 14 g/dL because the mean value of decreased hemoglobin level in this study was 2 g/dL. Consequently, when the hemoglobin level on the 8th week of therapy decreases 2 g/dL or become 12 g/dL, it is the appropriate time to perform anemia intervention. Moreover, the mean value of pretreatment hemoglobin level in this study was 14.7 g/dL.

This study found that subjects with pretreatment hemoglobin level < 14 g/dL tend to have risk of anemia fifteen times greater than subjects with hemoglobin level of 14 g/dL or more. Multivariate analysis revealed that only pretreatment Hb level < 14 g/dL had significant association with anemia. This may occur because anemia happened more easily in the lower pretreatment Hb level compared to the high pretreatment Hb level. The mean value of pretreatment Hb level of anemia patients were also significantly lower than pretreatment Hb level of non anemia patient. ($p = 0.00$; OR = 1.52; 95% CI = 0.92-2.12).

Takaki et al study also found that subjects with pretreatment hemoglobin level less than 14g/dL had significant correlation with ribavirin dose reduction (Hb < 10).¹⁹ Sulkowski et al reported that high

pretreatment Hb level correlated to greater decreased of hemoglobin level.²⁰ While Nomura study, found that pretreatment Hb level is not correlated to anemia, although the hemoglobin level of patient with anemia will rapidly decreased after ribavirin is given.

The most common ribavirin dose is 1,000 mg (72%). In this study, subject was classified into two groups, i.e. a group of ribavirin dose $< 1,000$ mg and a group of ribavirin dose of $\geq 1,000$ mg. From meta analysis, Chang found that ribavirin dose 1,000 mg or more has a higher risk of anemia (OR = 0.09; 95% CI = 0.04-0.13), although there are different IFN alpha and RBV doses in each study.²³

But there is no correlation between ribavirin dose and anemia in this study. Among previous studies only Nomura et al found that anemia correlated to ribavirin dose more than 12 mg/kg BW/day, while other studies indicated no correlation. Takaki and Nomura mutually use a high interferon alpha dose, i.e. 6 million units daily and a low ribavirin dose, i.e. 600-800 mg.^{13,18-20}

From this study, reported that there were 32 subjects who experience anemia till the 8th week of therapy, but there were only 8 subjects (25%) who had ribavirin dose reduction, and no subject had ribavirin discontinuation. Consequently, there was no intervention of anemia in this study.

Subjects with ribavirin dose reduction consist of 5 female and 3 male. Six subjects with ribavirin dose reduction were ≥ 50 years old, who received 1,000 mg ribavirin and had pretreatment hemoglobin level less than 14 g/dL. Therefore, it is clear that age ≥ 50 years and a low initial hemoglobin level were the risk factor of anemia.

The result in this study is similar to study by Takaki et al, which ribavirin dose reduction correlated to age over 55 years, female, and pretreatment hemoglobin level < 14 g/dL.

In the standard management of chronic hepatitis C therapy, anemia should be evaluated every 2 weeks in the first month and it is continued with once a month during therapy. But, if there is any suspicion of anemia, anemia should be evaluated every 2 weeks at least until the first 3 months of therapy.

CONCLUSION

Prevalence of anemia in CHC patient who received combination therapy was 52.5%. Pretreatment hemoglobin level of < 14 g/dL was only found to be the risk factor of anemia. Although age 50 years or more and female were not found to be the risk factor of anemia, careful monitoring and intervention to prevent anemia should be considered. Ribavirin dose reduction on 8th week of therapy is found in 8 subjects (25%) of 32 anemia subjects, and no subject had ribavirin discontinuation.

SUGGESTION

Patient with the age ≥ 50 years, female and pretreatment hemoglobin level < 14 g/dL require special monitoring by examination of hemoglobin level every 2 weeks at least in the first 3 months of therapy. Intervention to prevent anemia should be conducted in appropriate time in order to have a better and successful management of CHC. Further study with larger sample size is needed to determine other risk factor of anemia and the type of anemia.

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