Original Article

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Effect of Glucose-6-Phosphate Dehydrogenase Deficiency in Patients with Chronic Hepatitis C Who Were Treated with Pegylated Interferon and Ribavirin

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells. It is uncertain whether ribavirin (RBV) is associated with more severe anemia in patients with this disorder. The aim of this study was to evaluate the severity of anemia in patients with GPD deficiency treated at Siriraj hospital during pegylated interferon and ribavirin therapy for chronic hepatitis C (CHC).

Method: CHC patients treated with pegylated interferon/ribavirin and followed at Siriraj hospital were enrolled. All patients were tested for G6PD level. Their medical records were reviewed, data including baseline clinical characteristics, complete blood count (CBC) at week 0, 4, 8 12, 24, 48 and 12 after treatment. Index cases with G6PD deficiency were matched 1:3 with normal G6PD controls with regard to age, sex, HCV genotype and treatment with pegylated interferon alfa2a or 2b plus ribavirin.

Results: Of 186 CHC patients tested, there were 12 with G6PD deficiency (6 male and 6 female) and 36 controls. All baseline characteristic were similar in both groups except baseline Hb level in patients with G6PD deficiency which was lower than in controls (13.3±1.5 gm/dL vs 14.2±1.2, p=0.046). Six patients with G6PD deficiency (50%) and 16 patients without G6PD deficiency (44.4%) received erythropoietin during the course of treatment. There was no difference in the average doses of ribavirin in patients with or without erythropoietin. There was no difference in sustained virological response (SVR). We have observed that controls who did not received erythropoietin had statistical significant declined in Hb level at week 8, 12, 24 after treatment when compared with patients with G6PD deficiency.

Conclusion: CHC with G6PD deficiency can be treated successfully with pegylated interferon/ribavirin without an increased risk of ribavirin-induced anemia.

Key words : Glucose-6-phosphate dehydrogenase deficiency, chronic hepatitis C, pegylated interferon

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INTRODUCTION

It is estimated that about 170 million people are infected with hepatitis C virus worldwide[1]. Since as many as 55-85% will develop chronic infection which over the next two decades will become a major public health problem with increasing morbidity and mortality from chronic liver disease and hepatocellular carcinoma[2,3]. The risk of developing liver cirrhosis ranges from 5-25% over 25 to 30 years[6,7]. Persons with HCV-related cirrhosis are at risk for development of hepatic decompensation (30% over 10 years) and hepatocellular carcinoma (1-3% per year)[8]. The major goal of therapy is to eradicate the virus to prevent disease complications and death from HCV infection. Currently, recommended treatment of CHC is the combination of a pegylated interferon alfa and ribavirin[9-12]. Almost all patients treated with peginterferon/ribavirin experience one or more adverse events during the course of therapy. Such adverse events account for dose reduction, impaired quality of life, early discontinuation and most importantly treatment failure including relapse or non-response. Anemia is a frequent side effect observed in approximately one-third of patients, reaching nadir in 6 to 8 weeks. The major mechanism of anemia is hemolysis from ribavirin and less importantly bone marrow suppression from interferon. Dose modification of ribavirin due to anemia (hemoglobin level <10 g/dL) was required in 9-15% in the two phase-III registration trials. Growth factors such as erythropoietin and darbepoietin have been used to alleviate anemia associated with peginterferon/ribavirin. Although growth factor improves a patient's sense of well-being and reduces the need for ribavirin dose reduction, its use has not been shown to improve SVR rates[12-13]. In one analysis, the use of a hematological growth factor nearly doubled the cost of treatment for chronic hepatitis[14]. Another approach is ribavirin dose reduction which however, may increase the relapse rate and lower the SVR. G6PD deficiency is an x-linked hemolytic anemia found in nearly 10% of Thai population. These patients are hemolysis prone, especially when exposed to strong oxidant agents. Little is known about the safety of RBV treatment in patients with concomitant G6PD deficiency. The objective of this study was to evaluate the severity of anemia during pegylated interferon/RBV therapy in CHC.

MATERIAL AND METHOD

The study design was a retrospective cross sectional study. Chronic hepatitis C patients who had completed treatment with pegylated interferon/RBV for at least 24 weeks between 1997 and 2010 and who were followed up at Siriraj hospital, Mahidol University, Bangkok, all patients were older than 18 years old, HCV RNA positive, liver biopsy compatible with chronic hepatitis C. All patients were compensated liver disease (total serum bilirubin <1.5 g/dL, INR <1.5, serum albumin > 3.4 gm/dL, platelet count >75,000 mm^3) with acceptable hematological indices (hemoglobin >13 g/dL for men and >12 g/dL for women, neutrophil count >1500 /mm^3) and serum creatinine <1.5 mg/dL. The patients was selected if he had good compliance to the treatment and regularly followed. Exclusion criteria included decompensated liver cirrhosis, hepatitis C (HCV) and/or human immunodeficiency virus (HIV) co-infection, concomitant chronic liver disease (such as Wilson's disease, autoimmune hepatitis, or alcoholic liver disease), patients in whom interferon treatment was contraindicated, patients with previous interferon treatment in duding conventional interferon, and patients on immunosuppressive therapy. Treatment for CHC consisted of pegylated interferon alfa-2a or alfa- 2b subcutaneously once weekly (180 μg or 1.5 μg/kg respectively) and RBV orally daily 800 to 1,200 mg according to body weight (BW) and genotype (1000 mg if BW < 75 kg, 1200 mg if BW ≥ 75 kg for genotype 1, and 800 mg flat dose for genotype 3). Treatment duration was 48 weeks for genotype 1 and 24 weeks for genotype 3. After giving an informed consent, patients were tested for G6PD enzyme using the MR test method. Patients with G6PD deficiency were matched with normal controls at 1:3 in terms of sex, age, HCV genotype and treatment with pegylated alfa 2a or 2b plus ribavirin. Baseline data and hemoglobin level were reviewed and recorded at 0, 2, 4, 8, 12, 24, 48 weeks during treatment and at 12 weeks after treatment completion. Ribavirin dose reduction and use of erythropoietin during the course of treatment, if any, were recorded.

Statistical analysis

Demographic data were expressed as descriptive analysis. For numerical variables, the results were expressed as a mean ± standard deviation. Qualitative

variables were shown in percentages. The comparison of numerical variables between groups was accomplished by using the Student's *t*-test or the Mann-Whitney test, as appropriate. For comparison of percentages, we used the chi-square test or the Fisher's exact test. The *p* value of <0.05 was considered significant. The SPSS 18.0 for windows was used for the statistical analysis.

Results

From February 2010 to February 2011, 186 CHC patients who had been completed treatment with pegylated interferon alfa-2a or alfa-2b plus ribavirin were tested for G6PD level with the MR test method. Twelve of 186 patients had G6PD deficiency and were enrolled and matched with 36 control patients without G6PD deficiency, with regard to sex, age, HCV genotype, treatment with pegylated interferon alfa 2a or 2b plus ribavirin. Of the 12 G6PD deficient patients, 6 were male with a mean age of 55, 6 were of genotype 1, and 8 had cirrhosis before treatment, as shown in Table 1. Of the 36 controls, 21 were male, with a mean age of 52, 21 were of genotype 1, and 18 had cirrhosis. The baseline characteristics of the two groups were similar, except a lower mean Hb level (13.3±1.5 gm/dL) in G6PD deficient patients especially female compared to controls (p=0.046).

During the course of treatment, 6 patients (50%) in the G6PD deficiency group and 16 controls (44.4%) received erythropoietin (EPO). In patients who were treated with EPO, there was no significantly different fall of hemoglobin between the two groups at every time-point during treatment. By contrast, without EPO treatment, there was a more profound drop of hemoglobin in the control group at weeks 8, 12, and 24. However, there was no statistical difference regarding the total dose of ribavirin and the SVR in both groups, regardless of the use of EPO (Table 2).

Table 1. Baseline characteristics according to G6PD status.

Baseline Characteristic	Patients with G6PD deficiency (n=12)	Patients without G6PD deficiency (n=36)	*p*-value
male (n, %)	6 (50)	21 (58)	0.87
age (yrs.)	54.8 ± 7.6	51.6 ± 4.6	0.19
HCV genotype (n)			0.87
1	6	21	
3	6	15	
median viral load (IU/mL)	328,500	1,360,000	0.29
histology			0.44
not done	8	17	
F0	0	2	
F1	0	2	
F2	1	3	
F3	1	10	
F4	2	2	
cirrhosis (n)	8	18	0.50
Cr (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.64
baseline Hb (gm/dL)	13.3 ± 1.5	14.2 ± 1.2	0.046*
body weight (kg)	64.1 ± 11.0	65.9 ± 10.6	0.63
AST (U/L)	96.6 ± 59.7	84.6 ± 52.6	0.54
ALT (U/L)	111.2 ± 67.7	94.4 ± 50.6	0.40
treatment			1.00
PEG alfa 2a + RBV	5	14	
PEG alfa 2b + RBV	7	22	

Table 2. Treatment parameters according to G6PD status and EPO status.

Parameter	Patients with G6PD deficiency (n=12)	Patients without G6PD deficiency (n=36)	*p*-value
No. of patients receiving EPO (n, %)	6 (50)	16 (44)	1.00
mean Hb change in patients without EPO treatment (g/dL)			
week 2	0.3 ± 0.6	0.9 ± 0.8	0.13
week 4	1.9 ± 1.7	1.9 ± 1.3	0.82
week 8	1.7 ± 1.6	2.9 ± 1.2	0.049*
week 12	1.8 ± 2.1	3.4 ± 1.3	0.039*
week 24	1.0 ± 0.6	3.4 ± 1.1	0.004*
week 48	1.5 ± 0.2	3.3 ± 2.5	0.059
mean Hb change in patients with EPO treatment (g/dL)			
week 2	0.7 ± 1.1	1.0 ± 1.2	0.60
week 4	1.8 ± 1.2	2.4 ± 1.3	0.52
week 8	1.6 ± 1.3	2.8 ± 1.5	0.12
week 12	1.9 ± 1.8	3.2 ± 1.6	0.12
week 24	2.1 ± 1.2	2.5 ± 1.6	0.50
week 48	2.7 ± 0.3	2.7 ± 1.6	0.78
Hb at 12 week post-treatment	13.2 ± 2.1	13.8 ± 1.5	
time to first EPO (n, %)			1.00
week 1-4	1 (16.7)	4 (25)	
week 5-8	2 (33.3)	5 (31.3)	
week 9-12	2 (33.3)	6 (37.5)	
week 12-48	1 (16.7)	1 (6.3)	
average RBV dose (mg/kg)			
patients with EPO	13.2 ± 3.2	12.0 ± 2.5	0.54
patients without EPO	11.7 ± 2.6	13.5 ± 1.8	0.08
SVR (n, %)			
patients with EPO	6 (100)	12 (75)	0.54
patients without EPO	5 (83)	14 (70)	1.00

DISCUSSION

A very common side effect of RBV in the standard treatment for chronic hepatitis C combination therapy with pegylated interferon/RBV is hemolytic anemia. On the other hand, G6PD deficiency is the most common enzymatic disorder of RBC. Data on the risk of RBV therapy for chronic hepatitis C patients with G6PD deficiency are conflicting, however. Balestrieri et al[15]. did not observe hemolytic anemia in 26 patients with G6PD deficiency in Italy. Another study in 26 Sardinian patients with G6PD deficiency patients also reported the safety of RBV administration in a Mediterranean variety of G6PD deficiency[16]. Bini et al., on the contrary, observed the occurrence of important anemia in 30 G6PD deficient patients of various ethnic groups, especially African-Americans[17].

Our retrospective study was aimed at evaluating the severity of anemia in G6PD deficient patients during treatment with pegylated interferon and ribavirin, and to determine whether the varieties of G6PD deficiency would be more susceptible to the hemolytic effect of ribavirin. Our result showed that at baseline, patients with G6PD deficiency had a lower Hb level when compared with patients without G6PD deficiency. During treatment, up to 50% of patients with G6PD deficiency and 44.4% of patients without G6PD defi-

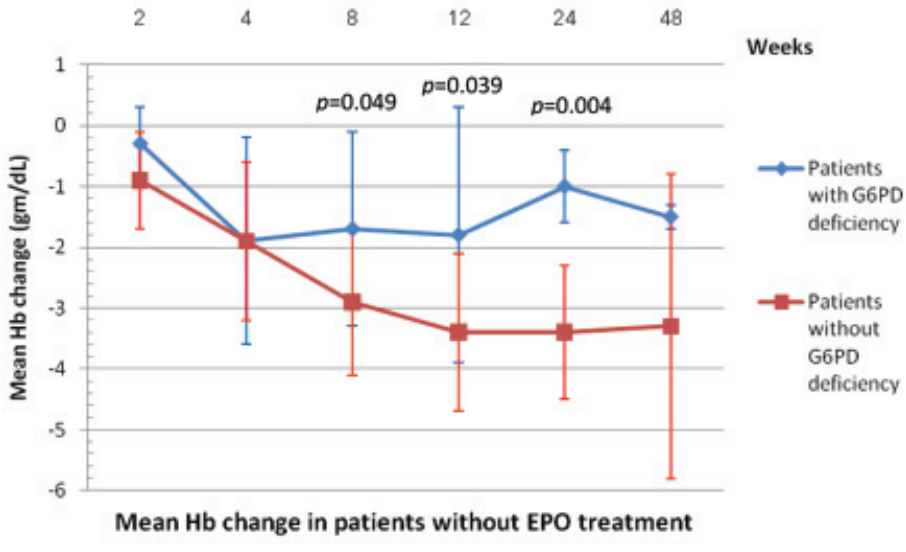

Figure 1. Mean Hb change at week 2, 4, 8, 12, 24, 48 in patients without EPO treatment.

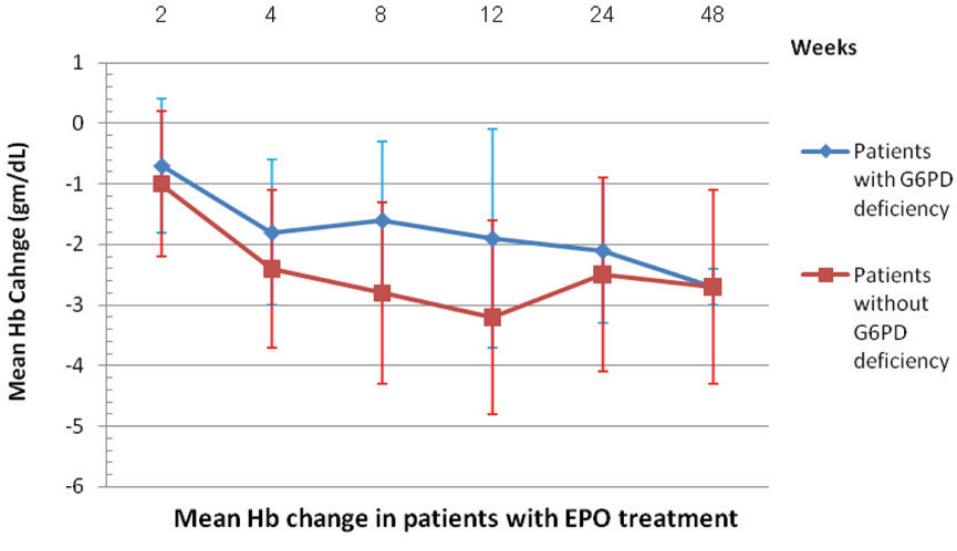

Figure 2. Mean Hb change at week 2, 4, 8, 12, 24, 48 in patients with EPO treatment.

ciency received EPO which were not statistically different. The use of EPO could have obscured the effects of RBV induced hemolytic anemia in both groups. In order to detect the effect of ribavirin induced hemolysis, we decided to separate patients with and without EPO in both the G6PD deficiency group and the control group. This analysis revealed that, in patients treated with EPO there was no significant drop of Hb in both groups. However, without EPO treatment, Hb dropped more profoundly in controls at weeks 8, 12, and 24. This observation was not noted in previous studies using EPO. There was limitation in our retrospective study with a small sample size. However, patients in this study were matched with controls in term of sex and age.

Conclusion

The presence of G6PD deficiency did not influence the total dose of ribavirin and the SVR, no matter whether EPO was used or not. The use of erythropoietin might improve patients' sense of well-being, but our study was not designed to elaborate such observation.

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