ORIGINAL RESEARCH

Is there a relationship between ribavirin-induced anemia and viral response rates during HCV therapy?

Ribavirine bağlı anemi yüksek viral yanıtlarla ilişkili midir?

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Background and Aims: *Pegylated interferon and ribavirin combination is the standard therapy for hepatitis C; sustained viral response rates are reported as 42-52% for genotype 1. Hemolytic anemia due to ribavirin is an important side effect. Ribavirin dose reduction leads to reduction in the response to antiviral therapy. We planned a retrospective study to investigate whether anemia due to ribavirin affects the virologic outcomes.* ***Materials and Methods:*** *164 patients infected with chronic hepatitis C genotype 1 and given pegylated interferon and ribavirin for a 48-week period were included. Drug-induced hemoglobin decrease was defined as >3 g/dl below the pretreatment value. 8.5-10 g/dl was defined as mild and <8.5 g/dl as severe anemia. Ribavirin dose was reduced by 200 mg/day if hemoglobin <10 g/dl or was ceased for two weeks if hemoglobin was <8.5. Later, if hemoglobin increased to above 8.5 g/dl in this period, ribavirin was restarted. We investigated the relationship between the presence of the above-mentioned status (during the first 12 weeks and weeks 13-48) and the response rates.* ***Results:*** *The mean age was 53 years. In the first 12 weeks, anemia was observed in 55 patients (33.5%). There were no differences between this group (n=55, 33.5%) and the group without anemia (n=109, 66.5%) in virologic responses (p=0.1, 0.385, 0.456, 0.730, for rapid, early, end of treatment, and sustained viral responses, respectively). There were also no statistically significant differences regarding virologic responses between the groups in relation to the severity of anemia. Erythropoietin was never used; rather, the ribavirin dose was reduced or stopped.* ***Conclusions:*** *We are encouraged by our results suggesting that if ribavirin can be completed without dose reduction (with additional erythropoietin therapy), it may lead to even higher virologic responses.*

Key words: Ribavirin, anemia, viral responses

Giriş ve Amaç: *Pegile interferon ve ribavirin kombinasyonu hepatit C için standart tedavidir; kalıcı viral yanıt oranları genotip 1 için 42-52% olarak bildirilmiştir. Ribavirin nedeniyle hemolitik anemi önemli bir yan etkisidir. Ribavirin dozunun azaltılması antiviral tedaviye yanıtın azalmasına yol açar. Ribavirin kaynaklı aneminin virolojik sonuçları etkileyip etkilemediğini araştırmak için retrospektif bir çalışma planladık.* ***Gereç ve Yöntem:*** *Kronik hepatit C genotip 1 ile enfekte olan ve 48 hafta süreyle pegile interferon ve ribavirin verilen 164 hasta çalışmaya dahil edildi. İlaç kaynaklı hemoglobin düşüşü tedavi öncesi değerden >3 gr/dl düşüş olarak tanımlandı. 8,5-10 gr/dl hafif anemi, <8,5 gr/dl şiddetli anemi olarak tanımlandı. Tedavi sırasında hemoglobin <10 gr/dl düzeyine düşerse ribavirin dozu 200 mg/gün azaltıldı, <8,5 gr/dl düzeyine düşerse iki hafta durduruldu. Yanıt oranları (ilk 12 hafta ve 13-48 haftalar sırasında) ile yukarıda belirtilen durumların varlığı arasındaki ilişki araştırıldı.* ***Bulgular:*** *Hastaların yaş ortalaması 53 yıl idi. İlk 12 haftada anemi 55 hastada (% 33.5) gözlendi. Bu grupla anemi olmayan diğer grup arasında viral yanıtlar açısından anlamlı bir farklılık (n = 55, %33,5) saptanmadı (sırasıyla p=0.1, 0,385, 0,456, 0,730). Aneminin şiddetine göre de gruplar arasında viral yanıtlar açısından istatistiksel olarak anlamlı bir fark saptanmadı. Eritropoietin hiç kullanılmadı, yerine ribavirin dozu azaltıldı veya kesildi.* ***Sonuç:*** *Yukarıdaki bulgular, ribavirin dozu azaltılmadan (ek eritropoietin tedavisi ile) tedavinin tamamlanması halinde daha yüksek virolojik yanıtlara ulaşılabileceği konusunda uyarıcıdır.*

Anahtar kelimeler: Ribavirin, anemi, viral yanıtlar

INTRODUCTION

An estimated 180 million people worldwide are currently infected with hepatitis C, rendering hepatitis C a major public health care concern (1,2). Standard therapy for chronic hepatitis C (CHC) consists of a combination of pegylated interferon (PEGIN) and ribavirin. Of patients with genotype 1 infections, 42-52% have sustained viral response (SVR), whereas patients with genotype 3 or 4 have response rates of 66-74% and 76-80%, respectively. Ribavirin has been used as a complementary drug in hepatitis C virus (HCV) therapy since it was approved for clinical use in 1998. However, ribavirin-induced hemolytic anemia is an important problem during therapy.

The concentration of ribavirin is 60 times higher in erythrocytes than in serum (3,4). Ribavirin causes adenosine triphosphate (ATP) deficiency via triphosphatase activation. Erythrocytes have no ribavirin triphosphate hydrolyzing enzymes; therefore, ribavirin accumulates in the

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red blood cells (RBC). In the meantime, ATP deficiency disrupts anti-oxidant defenses and oxidative membrane damage occurs. Erythrocytes then break down in the reticuloendothelial system. During the first four weeks of combination therapy, hemoglobin (Hb) levels usually decrease 2.5-3 g/dl (5,6).

Most patients present with ribavirin-induced hemolytic anemia, and dose reduction or discontinuation may be required in 15% of them. Risk factors for ribavirin-induced hemolytic anemia include female gender, age over 50, platelet count lower than 150000/mm3 before treatment, increased serum creatinine levels, and a decrease in Hb levels of more than 2 g/dl within the first two weeks of therapy (7). Asian populations seem to have increased risk of hemolytic anemia (8-10). Reduced doses of ribavirin have lower SVR rates. In lieu of reducing ribavirin dosages, a number of institutions additionally administer growth factors, such as erythropoietin and darbepoetin. Some studies have also reported that hemolytic anemia has a predictive value for SVR (11,12).

The present study investigates decreases in Hb that require ribavirin dose reduction, the timing of decreases in Hb levels and the association with viral response in patients previously treated with a combination of PEGIN and ribavirin.

MATERIALS AND METHODS

Chronic hepatitis C (CHC) patients treated with PEGIN-ribavirin combination for 48 weeks by the Department of Gastroenterology at Mersin University Hospital were recruited. Inclusion criteria were as follows: age over 18, previously untreated, CHC genotype 1b, and viral load over 400.000 IU/L. A total of 164 patients were included. Therapy was initiated given an absolute neutrophil count of 1500 or above and a platelet count of 80.000/mm^3 or above.

Complete blood count (CBC) was performed after two weeks and four weeks of treatment, and then every four weeks thereafter through the 48^{th} week. HCV RNA levels were assessed before treatment and after 4, 12, 24, and 48 weeks of treatment. Patient groups were administered 180 mcg/week of pegylated interferon alpha-2a or 1,5 mcg/kg/week of pegylated interferon alpha-2b. Ribavirin doses were adjusted to 1200 mg/day for patients that weighed more than 75 kg. Patients that weighed less than 75 kg were administered 1000 mg/day. The dosage of ribavirin was reduced to 200 mg/day for patients with Hb levels between 8.5-10 g/dl. If hemoglobin (Hb) levels fell below 8.5 g/dl, treatment was stopped for two weeks. Therapy was restarted if levels increased to 10 g/dl or above; otherwise, Hb levels were monitored at two-week intervals.

All patients experienced a drop in Hb levels of approximately 2.7 g/dl. Therefore, we considered a ribavirin-induced decrease in Hb (drug-induced hemolytic anemia [DIHA]) of 3 g/dl or above as a significant decrease in Hb (SDH). Decreases in Hb levels required dose adjustment given the following conditions: a) mild anemia defined by Hb levels of 8.5 g/dl-10 g/dl and b) severe anemia defined by Hb levels ≤8.5 g/dl. We also investigated the association between DIHA and anemia that occurs within 12 weeks or within 13-48 weeks and the association with fast, early and sustained viral response rates, as well as viral response rates at the end of the treatment.

Mean values were used as descriptive statistics for the age parameter. Number and percent values were used for categorical parameters in the groups as descriptive statistics. Z test was used to evaluate the rate differences between the two groups. Statistical significance was accepted at values of $p<0.05$. The Statistical Package for the Social Sciences (SPSS) 11.5 and MedCalc 11.0.1 programs were used.

RESULTS

Of the patients, 91 were female (55,5%) and 73 were male (44,5%). The mean age was 53.0 years (females: 53.7 years; males: 52.1 years).

During the first 12 weeks of treatment, 55 patients (33,5%) experienced a decrease in Hb levels of more than 3 g/dl, whereas 109 patients (66,5%) had no SDH. The rapid viral responses (RVR), early viral responses (EVR), end of treatment viral responses (ETR), and sustained viral responses (SVR) were not significantly different between these two groups (Table 1). Eleven patients (6,7%) developed severe anemia within the first 12 weeks. No differences in RVR, EVR, ETR, and SVR were observed between patient groups with and without severe anemia (Table 2). Statistically comparable results were also found between patients with mild anemia (37 patients, 22,6%) and patients without mild anemia (127 patients, 77,4%; (Table 3), as well as between patients with DIHA (78 patients, 47,6%) and without DIHA (86 patients, 52,4%; Table 4). Severe anemia was observed in 13 patients (7,9%) between 13 and 48 weeks. During this time period, RVR, EVR, ETR, and SVR were comparable between patients with and without severe anemia (13 patients, 7,9%; 151 patients, 92,1%, respectively; Table 5), as well as between patients with and without mild anemia (74 patients, 45,1% and 90 patients, 54,9%, respectively; Table 6).

DISCUSSION

No association was demonstrated between viral response and onset of anemia during PEGIN and ribavirin combination therapy. SVRs were also not related to either SDH or the severity of anemia. Authors commonly define a threshold based on Hb levels requiring dose reduction (8.5-10 g/dl) and/or levels requiring treatment interruption (<8.5 g/dl). The major problem with studies of drug-induced anemia is a lack of consensus as to a threshold level. Therefore, a third definition has been proposed: DIHA. DIHA is determined by defining a baseline decrease in Hb levels for the entire patient population and then using that baseline to estimate a threshold. In our study, the baseline was 2.7 g/dl, and we estimated a threshold of 3 g/dl. Each institution may estimate its own cut-off level.

Table 1. Viral responses in patients with and without DIHA within 12 weeks

		First 12 weeks		
Hb decrease		**(< 3 g/dl (n=109) (n-%)**	**(3 g/dl (n=55) (n-%)**	**p**
RVR	Absent	59 (72,8)	22 (27,2)	0,1
	Present	50 (60,2)	33 (39,8)	
EVR	Absent	40 (71,8)	16 (28,6)	0,385
	Present	69 (63,9)	39 (36,1)	
ETR	Absent	30 (71,4)	12 (28,6)	0,456
	Present	79 (64,8)	43 (35,2)	
SVR	Absent	40 (69,0)	18 (31,0)	0,73
	Present	69 (65,1)	37 (34,9)	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response. DIHA: Drug induced hemolytic anemia

Table 2. Viral responses in patients with and without severe anemia within 12 weeks

		First 12 weeks		
Hb levels		**(≤8,5 g/dl (n=11) (n-%)**	**(>8,5 g/dl (n=153) (n-%)**	**p**
RVR	Absent	5-6,2	76-93,8	0,517
	Present	6-7,2	77-92,8	
EVR	Absent	4-7,1	52-92,9	0,554
	Present	7-6,5	101-93,5	
ETR	Absent	3-7,1	39-92,9	0,569
	Present	8-6,6	114-91,4	
SVR	Absent	5-8,6	53-91,4	0,521
	Present	6-5,7	100-94,3	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response.

Table 3. Viral responses in patients with and without mild anemia within 12 weeks

		First 12 weeks		
Hb levels		**(8,5-10 g/dl (n=37) (n-%)**	**(>10 g/dl (n=127) (n-%)**	**p**
RVR	Absent	15-18,5	66-81,5	0,264
	Present	22-26,5	61-73,5	
EVR	Absent	11-19,6	45-80,4	0,561
	Present	26-24,1	82-75,9	
ETR	Absent	6-14,3	36-85,7	0,198
	Present	31-25,4	91-74,6	
SVR	Absent	11-19,0	47-81,0	0,443
	Present	26-24,5	80-75,5	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response.

Interestingly, neither reduction nor interruption of ribavirin therapy changed the partial virologic response (PVR) rates. This may be due to prolonged deleterious effects of ribavirin on erythrocytes. Accumulated ribavirin in RBCs may increase the extracellular concentration of the drug after injury and may prolong the drug exposure of hepatocytes (7).

PEGIN and ribavirin combination, generally administered with antiviral drugs, is the standard therapy for CHC. To improve anemia, the dosage of ribavirin is commonly reduced; however, dose reduction may cause decreased SVR rates, and therefore, some institutions prefer erythropoietin (11-17). A study by Sulkowski et al. (17) comparing these two interventions reported an association between erythropoietin therapy and higher SVR rates.

Table 4. Viral responses in patients with and without DIHA between 13 and 48 weeks

		13-48 weeks		
Hb decrease		**<3 g/dl (n=109) (n-%)**	**3 g/dl (n=55) (n-%)**	**p**
RVR	Absent	40-49,4	41-50,6	0,532
	Present	46-55,4	37-44,6	
EVR	Absent	28-50,0	28-50,0	0,742
	Present	58-53,7	50-46,3	
ETR	Absent	23-54,8	19-45,2	0,858
	Present	63-51,6	59-48,4	
SVR	Absent	31-53,4	27-46,6	0,489
	Present	55-51,9	51-48,1	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response. DIHA: Drug induced hemolytic anemia

Table 5. Viral responses in patients with and without severe anemia between 13 and 48 weeks

		13-48 weeks		
Hb levels		**≤8,5 g/dl (n-11) (n-%)**	**>8.5 g/dl (n-153) (n-%)**	**p**
RVR	Absent	7-8,6	74-91,4	0,481
	Present	6-7,2	77-92,8	
EVR	Absent	4-7,1	52-92,9	0,526
	Present	9-8,3	99-91,7	
ETR	Absent	3-7,1	39-92,9	0,563
	Present	10-8,2	112-91,8	
SVR	Absent	5-8,6	53-91,4	0,513
	Present	8-7,5	98-92,5	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response.

Table 6. Viral responses in patients with and without mild anemia within 13-48 weeks

		13-48 weeks		
Hb levels		**8.5-10 g/dl (n=37) (n-%)**	**> 10 g/dl (n=127) (n-%)**	**p**
RVR	Absent	36-44,4	45-55,6	0,494
	Present	38-45,8	45-54,2	
EVR	Absent	24-42,9	32-57,1	0,400
	Present	50-46,3	58-53,7	
ETR	Absent	15-35,7	27-64,3	0,107
	Present	59-48,4	63-51,6	
SVR	Absent	27-46,6	31-53,4	0,456
	Present	47-44,3	59-55,7	

RVR: Rapid viral response. EVR: Early viral response. ETR: End of treatment viral response. SVR: Sustained viral response.

In our study, we used dose reduction and interruption. No statistically significant differences between the SVR rates of anemic and non-anemic patients were observed. Our results may indicate that maintaining the dosage of ribavirin using erythropoietin or transfusion can accomplish higher SVR rates. Further clinical studies are needed.

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