Journal of
Antivirals & Antiretrovirals
ISSN: 1948-5964

Singh et al., J Antivir Antiretrovir 2013, 5:7
DOI: 10.4172/jaa.1000084

Research Article Open Access

Anemia in Patients with Chronic Hepatitis C Infection during Triple Therapy with Telaprevir or Boceprevir - A Controlled Study

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Abstract

Introduction: Triple therapy with protease inhibitors, telaprevir and boceprevir, is the new standard of treatment for hepatitis C virus (HCV) genotype 1 infection. In this study, we investigated the natural history of anemia in patients treated with triple therapy compared to those treated with pegylated-interferon and ribavirin (PEG/RBV) in the real-life setting.

Methods: Anemia was monitored in 72 consecutive patients treated with telaprevir- (46) or boceprevir-based triple therapy (26) for 16 weeks. These patients were statistically matched to 72 controls with respect to age, sex, race, and fibrosis that were treated previously with PEG/RBV. Anemia was treated by dose RBV dose reduction, red blood cell (RBC) transfusions, or epoetin alfa injections (EPO).

Results: The mean age for the study population was 52.1 years, 58.3% were male, 41.4% were treatment naïve, and 30.3% were cirrhotic. The control group was similar in terms of age, sex, race, and fibrosis. The mean baseline hemoglobin was 14.8 ± 1.3 g/dL. Incidence of grade 2-4 anemia (hemoglobin<10g/dL) in patients was 50% for those treated with telaprevir, 50% for those treated with boceprevir, and 27.5% treated with PEG/RBV ($p<0.005$). Lowest mean hemoglobin was 10.3 ± 1.8 g/dL, 10.4 ± 1.8 g/dL, and 11.0 ± 1.8 g/dL for telaprevir, boceprevir, and controls respectively ($p<0.061$). Hemoglobin nadir was reached between treatment weeks 6-10 in all treatment arms. Anemia required RBV dose reduction in 60% of those on telaprevir, 57.1% of those on boceprevir and 17.9% of the controls ($p<0.001$). PEG dose reduction, use of EPO, and/or RBC transfusion was not significantly different between the three groups. None of the patients had to discontinue HCV therapy due to anemia.

Conclusion: Using protease inhibitors such as telaprevir or boceprevir to treat patients with hepatitis C results in more significant anemia when compared to treatment with PEG/RBV alone. Ribavirin dose reduction was used more frequently in patients treated with protease inhibitors compared to controls; however, the need for RBC transfusions, EPO injections, and PEG dose reduction was similar in both groups.

Keywords: Hepatitis C; Anemia; Protease Inhibitors; Telaprevir; Boceprevir; Ribavirin; Interferon

Introduction

Chronic hepatitis C virus (HCV) infection affects 180 million people worldwide [1], and the growing complication of hepatocellular carcinoma has been contributing to increased number of deaths [2]. The sustained virologic response (SVR) for patients with HCV genotype 1 infection was approximately 40% with this previous standard of therapy of pegylated interferon (PEG) and ribavirin (RBV) [3]. In 2011, protease inhibitors, telaprevir and boceprevir, were brought out of phase III clinical trials into the real life setting and have since played a revolutionary role in the treatment for hepatitis C virus genotype 1 infection [4]. Higher SVR rates of 68-79% were achieved in hepatitis C treatment naive patients who received combination therapy of boceprevir or telaprevir along with RBV and PEG during these trials [5,6]. However, the use of these medications as part of triple therapy resulted in increased adverse events and drug-drug interactions. Anemia has emerged as the most significant adverse event associated with both protease inhibitors.

Recent phase III trials have shown that triple therapy with telaprevir and boceprevir can cause additional drops in hemoglobin levels when compared to treatment with PEG and RBV alone [5-8]. The SPRINT-2 trial and RESPOND-2 trial used boceprevir in treatment naïve and treatment experienced HCV patients, respectively, and had a significant anemia event rate of 49% in SPRINT-2 and 43-46% in RESPOND- 2 [6,7]. The ADVANCE trial and REALIZE trial used telaprevir in treatment naïve and treatment experienced HCV patients respectively, and had a significant anemia event rate of 36% in ADVANCE and 30% in REALIZE [5,8]. The control groups for the boceprevir trials had anemia event rates of 20-29% and the telaprevir trials had anemia event rates of 15-19% [6,7]. During the clinical trials with telaprevir, anemia was treated by dose-reducing RBV, whereas in the boceprevir trials, anemia was treated by RBV dose reduction and the use of epoetin alfa injections (EPO).

It is clear that significant anemia was more common in patients treated with protease inhibitors, but this has only been exhibited in the clinical trials. In this study, we investigated the development, natural history, and management of anemia in patients who were treated with telaprevir or boceprevir in the real life setting outside of clinical trials.

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Received October 24, 2013; **Accepted** December 06, 2013; **Published** December 08, 2013

Citation: Singh G, Issa D, Sedki E, Hanouneh I, Lopez R, et al. (2013) Anemia in Patients with Chronic Hepatitis C Infection during Triple Therapy with Telaprevir or Boceprevir - A Controlled Study. J Antivir Antiretrovir 5: 173-177. doi:10.4172/jaa.1000084

Methods

Study population

The study was approved by the Cleveland Clinic Institutional Review Board. Patients started on treatment with triple therapy followed protocol based care with respect to lab work and routine follow-up. Laboratory results including hemoglobin, white blood cell count, platelets, absolute neutrophil count, alanine aminotransferase, aspartate aminotransferase, serum creatinine, and hepatitis C RNA were recorded at baseline and then throughout treatment at specified time intervals according to the approved treatment protocols. Retrospective analysis of this prospectively obtained data was completed.

Our patient population comprised of 46 patients on telaprevir-based triple therapy, and 26 patients on boceprevir-based triple therapy. Treatment choice for using protease inhibitors was discussed with each patient and they chose a modality of treatment based on treatment protocol, duration of treatment, and adverse effects associated with the different types of treatment. Treatment was not based on pre-selected patient data.

Patients were treated with weight based dosing of RBV with all patients starting out at greater than 1,000 mg/day, and peg-interferon alfa-2a was the most frequently interferon used. Those on boceprevir were treated with a 4 week lead-in phase of RBV and PEG before instituting boceprevir treatment.

The total of 72 patients on protease inhibitor treatment were matched 1:1 with historic controls on basis of age, sex, race, and fibrosis stage from a database of patients who had completed treatment with PEG and RBV at our institution from 2001 to 2008.

Anemia definition and management

Guidelines from the National Cancer Institute (NCI) toxicity criteria was used to define the severity of anemia: Grade 0 (normal): 12.0-16.0 g/dL for women and 14.0-18.0 g/dL for men, Grade 1 (mild): 10.0-normal g/dL, Grade 2 (moderate): 8.0-9.9 g/dL, Grade 3 (serious/severe): 6.5-7.9 g/dL, and Grade 4 (life threatening):<6.5 g/dL [9]. Symptomatic anemia was defined as any drop in hemoglobin from baseline, which resulted in symptoms including shortness of breath (on exertion or at rest), chest pain, lethargy, and/or fatigue.

Patients, who had a drop in hemoglobin levels to less than 10 g/dL, were initially treated with RBV dose reduction by 400-600 mg. If anemia persisted, and hemoglobin levels dropped below 8.5 g/dL, PEG dose reduction, EPO, or red blood cell (RBC) transfusions were used at the clinician's discretion.

Statistical analysis

We used univariable analysis to compare the three treatment regimens: Treatment group 1 consisted of patients treated with telaprevir-based triple therapy, treatment group 2 consisted of patients treated with boceprevir-based triple therapy, and control group consisted of patients who had been treated with PEG and RBV. Analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test were used to assess differences in continuous variables and Pearson's chi-square tests were used for categorical factors; ad-hoc pair-wise comparisons were done using a significance criterion of 0.017 (0.05/3) as the Bonferroni correction in order to account for multiple comparisons.

In addition, a multivariable logistic regression analysis was performed assess the association between treatment and occurrence of anemia and/or need of anemia treatment (EPO or blood transfusion). An automated stepwise variable selection method performed on 1000 bootstrap samples was used to choose the final multivariable model. Treatment was forced into the model and all demographics and baseline variables were considered for inclusion; variables with inclusion rates of at least 20% were included in the final models. A $P<0.05$ was considered statistically significant. All analyses were performed using SAS (version 9.2 software, The SAS Institute, Cary, NC) and R (version 2.15.1, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics, medical history, and baseline characteristics

The main demographic and clinical data are summarized in Table 1. The mean age of patients treated with telaprevir and boceprevir was 52.1 years, 58.3% were male, 41.4% were treatment naive, and 30.3% were cirrhotic. In the control group, the mean age was 50.3 ± 7.3 (standard deviation), 65.3% were male, 92.5% were treatment naïve, and 18.6% were cirrhotic. When comparing the baseline demographic factors (including age, sex, race, body mass index, and medical co-morbidities), we found that there were no significant differences between the three groups.

Factor	Telaprevir (n=46)	Boceprevir (n=26)	PEG/RBV (n=72)	*P*
Age (years)	51.2 (10.3)	53.5 (9.4)	50.3 (7.3)	0.28
Sex, n (%)				0.38
Female	17 (37.0)	13 (50.0)	52(34.7)	
Male	29 (63.0)	13 (50.0)	47 (65.3)	
Race, n (%)				0.17
Caucasian	26 (68.4)	12 (60.0)	38 (54.3)	
African-American	6 (15.8)	7 (35.0)	24(34.3)	
Hispanic	0 (0.0)	0 (0.0)	3 (4.3)	
Other	6 (15.8)	1 (5.0)	5 (7.1)	
Baseline BMI, kg/m^2, mean (SD)	29.7 (5.6)	29.2 (4.2)	29.0 (6.6)	0.84
Baseline weight, kg, mean (SD)	88.4 (19.7)	87.8 (16.6)	94.4 (26.3)	0.89
Diabetes, n (SD)	2(4.4)	0(0.0)	1(1.4)	0.38
Hypertension, n (SD)	8 (17.8)	3 (11.5)	4 (5.6)	0.11

Values presented as Mean (Standard Deviation with Analysis of variance)
Abbreviations: n=number of patients, SD=standard deviation

Table 1: Demographics and Patient Characteristics.

Pre-treatment labs and hepatitis C history between the 3 groups is summarized in Table 2. Subjects who received PEG/RBV were more likely to be treatment naïve and have lower HCV RNA at baseline (p<0.001).

Anemia during HCV treatment

The mean baseline hemoglobin was 14.8 ± 1.4, 14.9 ± 1.2, 14.9 ± 1.2 (p<0.93) for telaprevir, boceprevir, and controls respectively. Incidence of grade 2-4 anemia (hemoglobin<10 g/dL) in patients was 50% for those treated with telaprevir, 50% for those treated with boceprevir, and 27.5% treated with PEG/RBV (p=0.015). Lowest mean hemoglobin on HCV therapy was 10.3 ± 1.8 g/dL 10.4 ± 1.8 g/dL, and 11.0 ± 1.8 g/dL for telaprevir, boceprevir, and controls respectively (p<0.061). Hemoglobin nadir was reached between treatment weeks 8-10 in all treatment arms (Figure 1).

Anemia management: RBV dose reduction, epoetin alfa and/or blood transfusion

Anemia with patients on telaprevir required RBV dose reduction in 60% of patients, PEG dose reduction in 16.7%, EPO in 15.2%, and blood transfusion in 11.5% of patients. Anemia with patients on boceprevir required RBV dose reduction in 57.1% of patients, PEG dose reduction in 14.3%, EPO in 30.7%, and blood transfusion in 11.5%. Anemia in the control group required RBV dose reduction in 17.9% of patients, PEG dose reduction in 20.9%, EPO injection in 33.3%, and blood transfusion in 2.8%. RBV dose reduction was significantly different between the use of both protease inhibitors compared to controls (p<0.001). There was no significant difference in using EPO and/or blood transfusions between these three treatment groups (p=0.4) (Table 3).

In multivariable logistic regression analysis, there was no difference in the development of severe anemia when comparing the telaprevir group to the control group (p=0.44), or when comparing the boceprevir group to the control group (p=0.99). Female gender (odds ratio [OR] of 6.7, p<0.001) and hypertension (OR of 3.8, p=0.04) were associated with the development of grade 3-4 anemia (Hg<8) or the need to use EPO/ RBC transfusion (Table 4). A significant inverse association with BMI was noted indicating that obesity might be protective from severe anemia on HCV therapy. Increased age (by 5 years) displayed a trend towards developing severe grade 3-4 anemia (p=0.059).

Discussion

The principal findings of this study relate to the following: 1) there is indeed significantly increased severity of anemia in patients treated with protease inhibitor-based triple therapy for chronic HCV genotype 1 infection in the real life setting when compared to matched patients who were treated with PEG/RBV; 2) RBV dose reduction was required more frequently when protease inhibitors were used; however, this was a successful management strategy with no increase in the need for PEG dose reduction, use of EPO injections, or RBC transfusions for the anemia experienced by those treated with protease inhibitors compared to those treated with PEG/RBV; and 3) Female gender, hypertension, and lower BMI but not the use of PIs were associated with severe anemia.

Factor	Telaprevir (n=46)	Boceprevir (n=26)	PEG/RBV (n=72)	*P*
HCV Mode of Transmission, n (%)				
IVDU	13 (33.3)	8 (40.0)	25 (54.3)	0.14
Blood transfusion	13 (33.3)	9 (45.0)	22 (47.8)	0.38
Tattoo	5 (12.8)	3 (15.0)	9 (19.6)	0.69
Cocaine	2 (5.1)	4 (20.0)	7 (15.2)	0.19
Health-care associated	1 (2.6)	1 (5.0)	4 (8.7)	0.47
Vertical Transmission	3 (7.7)	1 (5.0)	0 (0.0)	0.17
Fibrosis stage				0.15
0	3 (7.3)	6 (24.0)	8 (11.4)	
1	5 (12.2)	4 (16.0)	12 (17.1)	
2	8 (19.5)	3 (12.0)	21 (30.0)	
3	12 (29.3)	5 (20.0)	16 (22.9)	
4	13 (31.7)	7 (28.0)	13 (18.6)	
Previous therapy with PEG/RBV, n (%)				***<0.001***
Treatment naïve	15 (36.6)	11 (50.0)	62 (92.5)	
Relapser	16 (39.0)	2 (9.1)	2 (3.0)	
Partial responder	6 (14.6)	3 (13.6)	2 (3.0)	
Null responder	4 (9.8)	6 (27.3)	1 (1.5)	
Baseline ALT, U/L, mean (CI)	68.0 (41.0, 100.0)	71.0 (37.0, 99.0)	66.0 (42.0, 94.0)	0.96
Baseline AST, U/L, mean (CI)	54.0 (35.0, 79.0)	52.0 (41.0,87.0)	56.0 (41.5,99.5)	0.52
Baseline HCV RNA (×10^5), IU/mL, mean (CI)	24.0 (8.1, 64.6)	23.0 (9.4, 42.9)	8.0 (3.6, 15.4)	***<0.001***
Baseline Serum Creatinine, mg/dL, mean (SD)	0.82 (0.20)	0.81(0.25)	0.92 (0.36)	0.25
Baseline Hemoglobin, g/dL, mean (SD)	14.8 (1.4)	14.9 (1.2)	14.9 (1.2)	0.93
Interferon dose, n, (%)				***0.031***
peg-interferon alfa-2a	41(91.1)*	21(80.8)	48 (70.6)*	
peg-interferon alfa-2b	4 (8.9)	5 (19.2)	20 (29.4)	

Values presented as Mean (Standard Deviation with Analysis of variance)
*Use of peg-interferon alfa-2a was significantly higher in Telaprevir arm as compared to PEG/RBV arm
Abbreviations: n=number of patients, CI=confidence interval, IVDU=Intravenous drug use, PEG=peg-interferon, RBV=ribavirin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, HCV=hepatitis C virus, U/L=units/Liter, IU/mL=International Units/milliliter, mg=milligram

Table 2: Baseline clinical and histologic data.

The mechanism of anemia with the use of protease inhibitors is multifactorial, but is not completely understood. There is likely contribution of all three medications to the anemia that we notice. Interferon is thought to cause bone marrow suppression [10], and RBV has been implicated in causing membrane damage to RBC via phosphorylation, which results in an extravascular hemolysis from the reticuloendothelial system [11]. The enzyme inosine triphosphate pyrophosphatase (ITPA) plays a large role in this ribavirin-induced hemolysis and is of interest because there are polymorphisms that can confer protection from ribavirin anemia. Studies have shown that polymorphisms of the ITPA gene cause a deficiency of this enzyme resulting in decreased incidence of anemia during treatment of HCV with RBV and decreased need for RBV dose reduction [12]. A study by Suzuki et al. [13] looked at how the ITPA polymorphism impacted hemoglobin levels on triple therapy with telaprevir in Japanese patients, and found that there was a protective effect of the ITPA polymorphisms from patients with RBV induced hemolysis. In our study, we did not have the appropriate resources to test for the ITPA polymorphism and therefore were not able to account for this confounding effect. The additive effect on the anemia by using protease inhibitors may also lead to an increased effect of bone marrow suppression. The cumulative affect of all these factors explains why the anemia is even more significant in patients on protease inhibitors.

Factor	Telaprevir (N=46)	Boceprevir (N=26)	PEG/RBV (N=72)	*P*
RBV dose adjustment, n (%)	27(60.0)**	12(57.1)*	12(17.9)*,**	***<0.001***
PEG dose adjustment, n (%)	7(16.7)	3(14.3)	14(20.9)	0.74
Lowest Hemoglobin, mean (SD)	10.3(1.8)	10.4(1.8)	11.0(1.8)	0.061
Anemia grade, n (%)				***0.019***
No anemia	1(2.2)**	2(7.7)	6(8.7)**	
Grade 1	22(47.8)	9(34.6)	44(63.8)	
Grade 2	19(41.3)	12(46.1)	16(23.2)	
Grade 3 and 4	4(8.7)	1(3.8)	3(4.3)	
Grade 2-4 Anemia	23 (50.0)**	13 (50.0)*	19 (27.5)*,**	***0.015***
EPO use	9(19.6)	8(30.7)	24(33.3)	0.27
Packed red blood cell transfusion	7(15.2)**	3(11.5)	2(2.8)**	***0.031***
Anemia, EPO use and/or blood transfusion, n (%)	24 (52.2)	13 (50.0)	29 (40.3)	0.4

*: Boceprevir arm was significantly different from PEG/RBV arm
**: Telaprevir arm was significantly different from PEG/RBV arm
Abbreviations: n=number of patients, RBV=ribavirin, PEG=peg-interferon, SD=standard deviation, EPO=erythropoietin alfa

Table 3: Anemia during treatment.

Factor	Odds Ratio (CI)	*P*
Boceprevir vs. PEG/RBV	1.00 (0.36, 2.8)	0.99
Telaprevir vs. PEG/RBV	1.4 (0.59, 3.3)	0.44
Female	6.7 (2.9, 15.1)	***<0.001***
BMI (1 kg/m^2 increase)	0.93 (0.87, 0.99)	***0.027***
Hypertension	3.8 (1.07, 13.7)	***0.04***
Age (5 year increase)	1.2 (0.99, 1.5)	*0.059*

Abbreviations: CI=confidence interval, BMI=Body mass index, kg=kilogram, m=meter CI: 95% confidence interval

Table 4: Multivariable Logistic Regression Analysis: Development of Severe Anemia requiring use of EPO and/or blood transfusion when comparing treatment arms to control arm and adjusting for sex, BMI, baseline hypertension, and age.

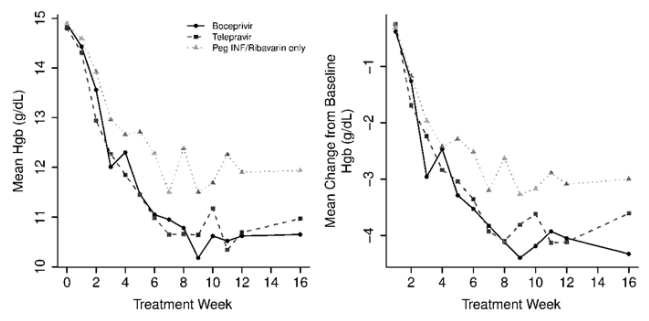

Figure 1: Hemoglobin levels during treatment of hepatitis C: Hemoglobin nadir was reached between treatment weeks 8-12 in all treatment arms during the first 16 weeks of treatment.

In the telaprevir trials, the use of erythropoietin was not permitted to treat anemia, and the anemia was treated strictly by RBV dose reduction or blood transfusions. Also, telaprevir dose reductions were prohibited, and if RBV or interferon was to be discontinued due to side effects, there was complete halt of treatment. The boceprevir trials did allow the use of EPO to treat anemia in their patients, and EPO was used in 43% of their patients [6,7]. There is little data on the use of protease inhibitors in clinical practice outside of clinical trials. Patients in these trials are selectively gathered, have strict inclusion/exclusion criteria, and have very close follow-up. Our study was not targeted to a specific population, and was rather a retrospective study of all patients on treatment at our HCV clinic.

In our cohort, it was shown that although patients with anemia due to protease inhibitors needed RBV dose reductions more frequently compared to the PEG/RBV group, the need for PEG dose reduction, EPO and/or RBC transfusion was not significantly different. If differentiating between the interventions, there was no significant difference between patients in all three cohorts that required EPO, and the telaprevir group did require a significantly more RBC transfusions. This could be due to persistent anemia, or the fact the patients did not respond to EPO as effectively.

Further study on this population up till the end of treatment to evaluate SVR rates would be more informative and help us determine associations including how dose reductions of the RBV and PEG played out on the actual SVR rates and if the use of EPO impacted SVR rates. In the PEG/RBV era, RBV dose reduction increased the relapse rate of patients on treatment of HCV from 11% to 60% [14]. The IDEAL study found that SVR rates were significantly different: 36.7% for those who had RBV dose reduction secondary to anemia vs. 48.8% who did not have anemia or RBV dose reduction [15]. A retrospective post-hoc analysis on boceprevir patients in the SPRINT-2 trial showed patients who did not have incident anemia during treatment had an SVR rate of 58%, compared to an SVR rate of 72% in those who developed anemia and were treated by RBV dose reduction, EPO alone, both or neither [16].

The multivariable analysis performed gives us a good idea at what risk factors are associated with a severe anemia (Table 4). We found that being female, and having underlying hypertension were both significant risk factors. Increased age did have a trend associated to developing severe anemia, and BMI had an inverse association, making obesity protective against severe anemia. The type of HCV therapy was not associated with a severe anemia when compared to the PEG/RBV patients.

The anemia that initiated from triple therapy started abruptly with a steep decline in hemoglobin levels that eventually hit their lowest point between weeks 8-12 and then continued through treatment (Figure 1). Patients who had symptoms including shortness of breath (on exertion or at rest), chest pain, lethargy, and/or fatigue were considered to have anemia. At times the symptoms would precede any blood tests indicating anemia, and if any patients did present with such symptoms, a complete blood count was obtained, and treated accordingly.

Remaining vigilant about blood work by obtaining frequent complete blood counts is important in the first several weeks of treatment for this reason. Once treatment has gone beyond 10 weeks, the hemoglobin levels stabilized.

In conclusion, in the real life setting of HCV therapy with protease inhibitors, anemia is just as significant a factor as it was in the clinical trials with regards to incidence and severity. The use of RBV dose reduction appears to be an effective strategy to treat the anemia. In fact, the use of EPO and RBC transfusions was not different with protease inhibitors when compared to the previous standard of therapy. As clinicians, it is important to remain cognizant of the significant factors that are associated with the development of severe anemia such as the female gender, presence of hypertension, decreased BMI, and the trend with age.

Authorship Statement

GS and NA performed the research, GS, DI, ES, RL, IH collected and analyzed the data, GS, NZ, NA designed the research study and wrote the paper, and GS, NA contributed to the design of the study.

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Citation: Singh G, Issa D, Sedki E, Hanouneh I, Lopez R, et al. (2013) Anemia in Patients with Chronic Hepatitis C Infection during Triple Therapy with Telaprevir or Boceprevir - A Controlled Study. J Antivir Antiretrovir 5: 173-177. doi:10.4172/jaa.1000084