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Anemia During Treatment With Peginterferon Alfa-2b/ Ribavirin and Boceprevir: Analysis From the Serine Protease Inhibitor Therapy 2 (SPRINT-2) Trial

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Boceprevir (BOC) added to peginterferon alfa-2b (PegIFN) and ribavirin (RBV) significantly increases sustained virologic response (SVR) rates over PegIFN/RBV alone in previously untreated adults with chronic hepatitis C genotype 1. We evaluate the relationship of incident anemia with triple therapy. A total of 1,097 patients received a 4-week lead-in of PegIFN/RBV followed by: (1) placebo plus PegIFN/RBV for 44 weeks (PR48); (2) BOC plus PegIFN/RBV using response-guided therapy (BOC/RGT); and (3) BOC plus PegIFN/RBV for 44 weeks (BOC/PR48). The management of anemia (hemoglobin [Hb] <10 g/dL) included RBV dose reduction and/or erythropoietin (EPO) use. A total of 1,080 patients had ≥1 Hb measurement during treatment. The incidence of anemia was 50% in the BOC arms combined (363/726) and 31% in the PR48 arm (108/354, $P < 0.001$). Among BOC recipients, lower baseline Hb and creatinine clearance were associated with incident anemia. In the BOC-containing arms, anemia was managed by the site investigators as follows: EPO without RBV dose reduction, 38%; RBV dose reduction without EPO, 8%; EPO with RBV dose reduction, 40%; and neither RBV dose reduction nor EPO, 14%. SVR rates were not significantly affected by management strategy (70%-74%), and overall patients with anemia had higher rates of SVR than those who did not develop anemia (58%). Serious and life-threatening adverse events (AEs) and discontinuations due to AEs among BOC-treated patients did not differ by EPO use. *Conclusion*: With BOC/PR therapy, SVR rates in patients with incident anemia were higher than nonanemic patients and did not vary significantly according to the investigator-selected approach for anemia management. Prospective studies are needed to confirm this observation. (HEPATOLOGY 2013;57:974-984)

Chronic hepatitis C virus (HCV) infects more than 170 million people worldwide, is a leading cause of cirrhosis, end-stage liver disease, and hepatocellular carcinoma, and is the most common indication for liver transplantation in Europe and the United States.[1] Since 2001, peginterferon alfa-2b

Abbreviations: AE, adverse event; BOC, boceprevir; EOT, end of treatment; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FDA, Food and Drug Administration; Hb, hemoglobin; HCV, hepatitis C virus; IQR, interquartile range; PegIFN, peginterferon alfa-2b; PI, protease inhibitor; PRCA, pure red blood cell aplasia; RBV, ribavirin; RGT, response-guided therapy; SVR, sustained virologic response.

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A complete list of SPRINT-2 Trial investigators is given in the Appendix.

(PegIFN) in combination with ribavirin (RBV) has been the standard treatment for HCV, leading to sustained virologic response (SVR) in approximately 40% of persons infected with HCV genotype-1.[2-5] However, as a result of RBV dose-dependent hemolytic anemia and PegIFN-induced suppression of hematopoiesis, this regimen causes significant reductions in hemoglobin (Hb) level in most treated patients, resulting in anemia, defined as an Hb level <10 g/dL, in approximately 30% of patients.[6-8] Interestingly, the development of PegIFN/RBV-related anemia has been strongly associated with greater likelihood of SVR.[9] In a large study involving 3,070 previously untreated HCV genotype 1 infected patients, patients who developed anemia had significantly higher rates of SVR (48.8%) compared with nonanemic patients (36.7%); in this analysis, RBV dose reduction to manage the anemia in these patients was not associated with a decrease in SVR, suggesting that anemia may be a pharmacodynamic marker of RBV exposure.[10] In addition, the effect of erythropoiesis-stimulating agents (ESAs), used for the management of PegIFN/RBV-related anemia,[10-13] varied by time to anemia; patients with early-onset anemia (≤8 weeks of treatment) had higher rates of SVR with ESA use, whereas no effect was observed in those with late-onset anemia.[10]

More recently, phase 2 and 3 studies have shown that the addition of boceprevir (BOC), an HCV NS3/4A protease inhibitor (PI), to PegIFN/RBV therapy resulted in both significantly higher rates of SVR and of incident anemia compared with PegIFN-RBV alone.[14-17] In these clinical trials, the management of anemia included RBV dose reduction and, at the discretion of the investigator, the use of erythropoietin (EPO). The relationship of incident anemia with triple therapy, the approach used for its management and clinical outcomes such as virologic response and safety has not been evaluated. The primary objective of this analysis was to determine the relationship between virologic response, adverse events (AEs) and treatment-associated anemia and its management, in previously untreated HCV genotype 1-infected patients enrolled in The Serine Protease Inhibitor Therapy 2 (SPRINT-2) Trial.[15]

Patients and Methods

Study Design. The SPRINT-2 Trial was a phase 3, international, randomized, placebo-controlled study comparing the safety and efficacy of therapy with PegIFN and RBV (PegIntron and Rebetol, respectively; Merck) to two treatment regimens that added BOC (Victrelis, Merck) after a lead-in treatment period with PegIFN/RBV alone. Enrolled patients were randomized in a 1:1:1 ratio to one of three treatment groups after stratification by baseline HCV RNA viral load (≤400,000 versus >400,000 IU/mL) and HCV genotype 1 subtype (1a versus 1b).

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Potential conflict of interest: Mark S. Sulkowski has received consultancy fees and has grants/grants pending from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Janssen, Merck, Novartis, Pfizer, and Vertex. Fred Poordad has received consultancy fees from Merck, Vertex, Abbott, Gilead, Achillion, Genentech, and Tibotec; has grants/grants pending from Merck; and has received payment for development of educational presentations and speaker fees from Merck, Genentech, Salix, and Gilead. Michael P. Manns has received consultancy fees from Achillion, Schering-Plough (now part of Merck), Roche, Bristol-Myers Squibb, Gilead, Boehringer-Ingelheim, Novartis, Idenix, Tibotec, Vertex, GlaxoSmithKline, and Merck; has grants/grants pending from Schering-Plough (now part of Merck), Roche, Gilead, Novartis, Boehringer-Ingelheim, and Bristol-Myers Squibb; and has received payment for development of educational presentations from Schering-Plough (now part of Merck), Roche, Bristol-Myers Squibb, GlaxoSmithKline, and Gilead. Jean-Pierre Bronowicki has received consultancy fees from Schering-Plough (now part of Merck), Roche, Gilead, Bristol-Myers Squibb, Janssen, Boehringer Ingelheim, Novartis, and Bayer; payment for lectures including service on speakers bureaus for Schering-Plough (now part of Merck), Roche, Bayer, and Bristol-Myers Squibb and travel/accommodations/meeting expenses unrelated to activities listed from Roche. K. Rajender Reddy has received consultancy fees from Roche, Merck, Salix, Vertex, Tibotec, and Human Genome Science; has grants/grants pending from Roche, Vertex, Tibotec, Bristol-Myers Squibb, and Gilead; and payment for development of educational presentations from ViralEd. Stephen A. Harrison has received grant support from Merck, is an advisory board member for Merck and Vertex; has grants/grants pending from Genentech and Bristol-Myers Squibb; and has received payment for lectures, including service on speakers bureaus for Merck. Nezam H. Afdhal has received grant support from Merck, Gilead, Vertex, GSK, Abbott, BMS, and Pharmasett. He has been a scientific advisor or consultant for Gilead, Vertex, Merck, Novartis, Tibotec, Johnson and Johnson, Medgenics, and Springbank. Heather L. Sings, Kenneth Koury, and Margaret H. Burroughs are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and hold stock and/or stock options. Vilma Sniukiene, Janice K. Albrecht, Clifford A. Brass and Lisa D Pedicone are former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and hold stock and/or stock options. Ira M. Jacobson has received consultancy fees from Bristol-Myers Squibb, Novartis, Gilead, Merck, Pfizer, Vertex, GlobeImmune, Boehringer-Ingelheim, Pharmasset, Tibotec, Abbott, Roche/Genentech, and Tibotec; Achillion, and GlaxoSmithKline; has grants/grants pending from Abbott, Merck, Tibotec, Roche/Genentech, Pharmasset, Boehringer Ingelheim, Novartis, Gilead, Vertex, GlobeImmune, Human Genome Sciences, Pfizer, and Bristol-Myers Squibb; payment for lectures including service on speakers bureaus from Merck, Vertex, Gilead, Bristol-Myers Squibb, Roche/Genentech, and Vertex; and payment for development of educational presentations from Bristol-Myers Squibb, Gilead, and Vertex.

Additional Supporting Information may be found in the online version of this article.

Patients. Previously untreated patients ≥18 years of age weighing 40-125 kg with chronic HCV genotype 1 and plasma HCV RNA level ≥10,000 IU/mL were eligible. Exclusion criteria included liver disease of other etiology; decompensated cirrhosis; renal insufficiency; human immunodeficiency virus or hepatitis B; pregnant/breastfeeding women; or active malignancy. Pretreatment liver biopsies were assigned METAVIR fibrosis and steatosis scores by a single pathologist who was unaware of the assignment to BOC or placebo.

Study Regimens. PegIFN was administered subcutaneously at 1.5 μg/kg once weekly; RBV was dosed according to body weight at 600-1,400 mg/day (divided twice daily dose). BOC was administered orally at a dose of 800 mg three times daily (to be taken with food and with an interval of 7-9 hours between doses) in four capsules of 200 mg each. Placebo was matched to BOC. The study was double-blinded regarding the administration of BOC.

A total of 1,097 patients were randomized and treated. All patients received PegIFN/RBV during the 4-week lead-in period (Supporting Fig. 1). Patients randomized to control received PegIFN/RBV treatment for 44 weeks after the lead-in period, as well as placebo three times daily beginning at week 5 (PR48). Patients randomized to the response-guided therapy (RGT) regimen received PegIFN/RBV plus BOC for a total of 24 weeks after the lead-in period. If HCV RNA levels were undetectable from week 8 through week 24, treatment was considered complete; however, if HCV RNA levels were detectable at any visit from week 8 up to but not including week 24, PegIFN/RBV was continued, and placebo was administered at week 28 through week 48 (abbreviated at BOC/RGT). Patients randomized to the third regimen received PegIFN/RBV plus oral BOC for 44 weeks after the lead-in period (abbreviated as BOC/PR48). In all groups, patients with detectable HCV RNA at week 24 were discontinued for virologic futility.

Management of Anemia. The management of anemia was identical for all three arms. RBV dose reduction (in 200 mg increments) was recommended when the Hb level was <10 g/dL and RBV dose interruption or discontinuation was recommended when the Hb level was <8.5 g/dL. At the discretion of the study investigator, RBV could be increased to full dose directly or in steps, respectively, when the AE subsided. The use of EPO was at the discretion of the investigator. The sponsor provided EPO to patients as well as guidelines for its use in the study protocol, which is available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1010494/suppl_file/nejmoa1010494_appendix.pdf.[18,19] The recommended initial EPO dose was 40,000 U subcutaneously once weekly. EPO was not to be administered when Hb was ≥12 g/dL. EPO was to be reduced by 25%-50% for Hb increases of >1 g/dL within 2 weeks, or for Hb increases >2 g/dL within 4 weeks.

Statistics. The trial was designed as a superiority study to detect differences in SVR rates between either of the two BOC regimens (BOC/RGT or BOC/PR48) and standard therapy (PR48). The data analysis plan is available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1010494/suppl_file/nejmoa1010494_appendix.pdf. The primary analyses used all patients who had received ≥1 dose of any study medication.

The efficacy analyses presented here are based on all patients who underwent an Hb measurement at baseline and at least once during the treatment phase and up to 7 days after treatment end date. Plasma HCV RNA levels were measured using the TaqMan 2.0 assay (Roche Diagnostics), which has lower limits of quantification and detection of 25 and 9.3 IU/mL, respectively; the lower limit of detection was used for decision making at various points throughout the study and for analysis of SVR.

As the proportion of patients who became anemic during treatment and the proportion of patients who used EPO during treatment were similar in the BOC/RGT (49% [179/368] and 43% [159/368]) and BOC/PR48 arms (50% [184/366] and 43% [159/366]) these treatment groups were combined for subsequent analysis (abbreviated as BOC/PR). SVR by anemia status (yes, no) and by anemia management strategy (EPO use only, RBV dose reduction only, both, or neither) was also summarized. The proportion of patients who achieved SVR, relapse, or undetectable HCV-RNA at various time points by EPO use and anemia management strategy were also summarized for patients who received BOC/PR.

Hb decline during treatment and follow-up was summarized for five groups: (1) all patients; (2) patients randomized to the PR48 arm; (3) patients randomized to the BOC/RGT arm who were early responders (undetectable HCV RNA at week 8); (4) patients randomized to the BOC/RGT arm who were late responders (detectable HCV RNA at week 8 but undetectable by week 24); and (5) patients randomized to the BOC/PR48 arm.

Safety data are summarized separately for the BOC/RGT and BOC/PR48 arms by EPO use.

Results

Patient Characteristics. The study randomized and treated 1,097 patients, 1,080 of whom had at least one Hb measurement during the treatment phase and

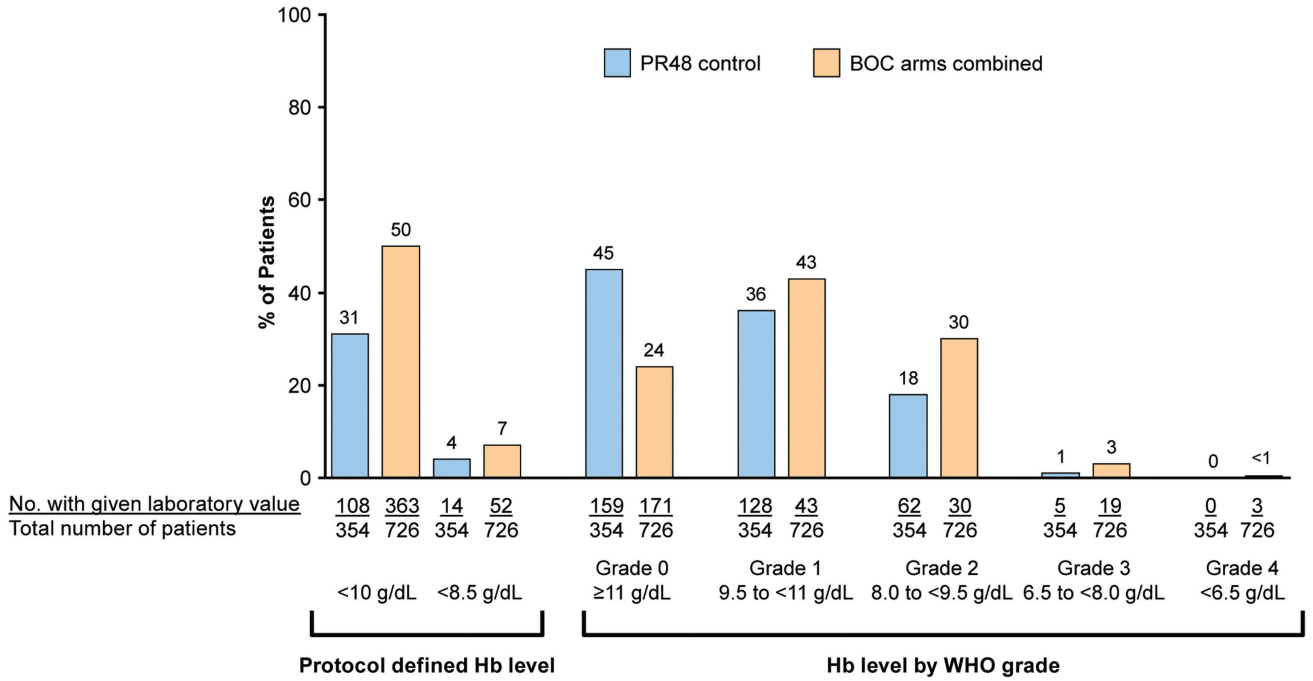

Fig. 1. Hemoglobin levels.

up to 7 days after treatment end date (PR48, 354 patients; BOC/PR, 726 patients). Overall, the incidence of anemia (Hb <10 g/dL) was 50% in the BOC/PR arms (363/726) and 31% in the PR48 arm (108/354) ($P < 0.001$). Severe anemia (Hb <8.5 g/dL) was less common, occurring in 4% (14/354) and 7% (52/726) of patients in the PR48 and BOC/PR arms, respectively ($P = 0.04$) (Fig. 1).

Among patients who developed anemia, the maximum mean Hb decline was −4.8 g/dL (SD 1.3) and −5.3 g/dL (SD 1.4) in the PR48 and BOC/PR arms, respectively. After the addition of BOC or placebo, the mean maximum Hb decline between weeks 4 and 8 was 1.3 g/dL among patients treated with BOC and 0.6 g/dL among those treated with placebo. After 4 weeks of therapy with PR, the change in Hb level from baseline was predictive of subsequent anemia after the addition of BOC; however, the negative post-test probability for the development of anemia with an observed Hb decline ≤2 g/dL was relatively high (28.5%-37.2%). The negative predictive value of the magnitude of hemoglobin declined after 2 weeks of BOC/PR (treatment week 6) and subsequent anemia was similar (Supporting Tables 1 and 2). After discontinuation of therapy at 28 weeks for patients in the RGT arm who met criteria for early discontinuation or at 48 weeks for all other patients, Hb returned to pre-treatment levels; no difference in the magnitude or rate of return was detected in the PR48 and BOC/PR48 arms (Fig. 2).

Baseline demographics and clinical characteristics of patients with and without incident anemia who received BOC/PR are shown in Table 1. Anemia occurred more frequently in women (65%) and patients >40 years old (53%) compared with men (41%) and patients <40 years old (33%). In addition, patients who became anemic during BOC/PR treatment had significantly lower baseline Hb levels (Supporting Fig. 2), had lower estimated creatinine clearance, and were more likely to be taking statins.

Multivariate analysis included the following baseline factors as predictors of incident anemia among patients who received BOC; statin use, baseline Hb level

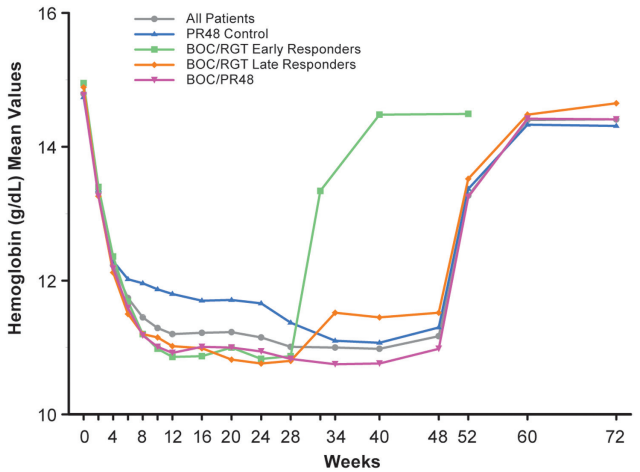

Fig. 2. Mean hemoglobin concentration over time by treatment arm. The *x* axis numbers are not to scale.

Table 1. Characteristics According to Treatment-Related Anemia

Characteristics	BOC Arms Combined (n = 726)		P
	Hb ≥10 g/dL (n = 363)	Hb <10 g/dL (n = 363)	
Sex, n/m (%)			
Female	99/280 (35)	181/280 (65)	<0.0001
Male	264/446 (59)	182/446 (41)	<0.0001
Race, n/m (%)			
White	310/593 (52)	283/593 (48)	0.12
Black/African American	40/105 (38)	65/105 (62)	0.001
Other	13/28 (46)	15/28 (54)	0.60
Age			
≤40 years, n/m (%)	73/109 (67)	36/109 (33)	<0.0001
>40 years, n/m (%)	290/617 (47)	327/617 (53)	0.04
Baseline weight, kg, mean (SD)	82.2 (16.8)	81.7 (17.6)	0.68
Baseline HCV subtype,* n/m (%)			
1a	241/464 (52)	223/464 (48)	0.24
1b	113/240 (47)	127/240 (53)	0.20
Missing data	9/22 (41)	13/22 (59)	0.23
Baseline HCV-RNA viral load, n/m (%)			
≤2,000,000 IU/mL	105/229 (46)	124/229 (54)	0.08
>2,000,000 IU/mL	258/497 (52)	239/497 (48)	0.23
Baseline statin use, n/m (%)	5/16 (31)	11/16 (69)	0.04
Baseline METAVIR fibrosis score, n/m (%)			
F0/F1/F2	317/625 (51)	308/625 (49)	0.61
F3/F4	32/75 (43)	43/75 (57)	0.07
Missing	14/26 (54)	12/26 (46)	0.58
Baseline steatosis, n/m (%)			
Absence	108/212 (51)	104/212 (49)	0.70
Presence	255/514 (50)	259/514 (50)	0.80
Missing	14/26 (54)	12/26 (46)	0.58
Baseline Hb, g/dL	15.2 (1.2)	14.4 (1.2)	<0.0001
Baseline serum creatinine, mg/dL, mean (SD)	0.831 (0.15)	0.823 (0.16)	0.49
Estimated creatinine clearance, mL/min, mean (SD)	124.9 (33.7)	116.4 (38.8)	0.002
Baseline RBV dose, mg/kg/day			
Mean (SD)	12.1 (2.1)	11.5 (2.1)	<0.0001
Median (IQR)	12.6 (2.1)	11.9 (2.8)	–
RBV dose reduction due to AE during treatment, n/m (%)†	26/219 (12)	193/219 (88)	<0.0001
Nadir Hb level, g/dL			
Mean (SD)	11.2 (1.0)	9.1 (0.7)	<.0001
Median (IQR)	10.9 (1.3)	9.2 (0.8)	–
Maximum Hb decline, g/dL			
Mean (SD)	−4.1 (1.4)	−5.3 (1.4)	<.0001
Median (IQR)	−4.1 (1.7)	−5.3 (1.8)	–
Time to anemia, days, median (IQR)	NA	71 (70)	–
Time to Hb nadir, days			
Mean (SD)	127 (76)	137 (78)	0.08
Median (IQR)	113 (108)	114 (121)	

The data include all randomized patients who underwent Hb measurement at baseline and at least once during the treatment phase up to 7 days after treatment end date. n = number of patients matching the given characteristic; m = number of patients with the indicated Hb level.

Abbreviation: NA, not applicable.

*HCV subtype was ascertained via sequencing of the nonstructural 5B region.

†Includes patients with RBV dose reduction due to anemia.

(continuous variable), estimated baseline creatinine clearance (continuous variable), and sex. Only lower baseline Hb level was predictive of incident anemia (odds ratio, 0.58; 95% confidence interval, 0.51-0.67; $P < 0.0001$) whereas lower baseline creatinine clearance was borderline significant (odds ratio, 0.9955; $P = 0.0524$).

Anemia, Hb Decline, and Virologic Response. For patients treated with BOC/PR, the magnitude of Hb decline during therapy and the development of anemia were associated with virologic response. Among patients treated with BOC/PR who did not develop anemia, HCV RNA was undetectable at the end of treatment (EOT) in 67% (245/363), whereas among patients who developed anemia, EOT virologic response was observed in 81% (293/363) (Table 2). Similarly, the observed SVR rate was higher in patients with incident anemia during treatment with BOC/PR

Table 2. Virologic Response, SVR, and Treatment Discontinuation Due to an AE by Anemia Management Strategy

	BOC Arms Combined					
		Hb <10 g/dL (n = 363): Anemia Management Strategy				
	Hb ≥10 g/dL (n = 363)	Total (n = 363)	EPO Alone (n = 137)	RBV Dose Reduction Alone (n = 29)	Both (n = 145)	Neither (n = 52)
Week 4 undetectable, n (%)	22 (6)	17 (5)	8 (6)	0	8 (6)	1 (2)
Week 8 undetectable, n (%)	191 (53)	221 (61)	84 (61)	20 (69)	88 (61)	29 (56)
Week 12 undetectable, n (%)	238 (66)	288 (79)	110 (80)	27 (93)	114 (79)	37 (71)
Week 24 undetectable, n (%)	233 (64)	285 (79)	102 (74)	25 (86)	116 (80)	42 (81)
EOT response, n (%)	245 (67)	293 (81)	113 (82)	24 (83)	115 (79)	41 (79)
SVR, n (%)	212 (58)	263 (72)	102 (74)	21 (72)	102 (70)	38 (73)
Relapse, n/m (%)	23/245 (9)	25/293 (9)	8/113 (7)	2/24 (8)	12/115 (10)	3/41 (7)
Discontinuation due to AE, n (%)	47 (13)	123 (34)	44 (32)	9 (31)	52 (36)	18 (35)
Treatment duration, days, median (IQR)	197 (163)	203 (141)	199 (142)	278 (141)	238 (141)	197 (142)
RBV received, mg/kg/day						
Mean (SD)	12.1 (2.1)	11.5 (2.1)	12.1 (1.9)	11.6 (2.1)	10.8 (2.1)	11.7 (2.2)
Median (IQR)	12.6 (2.1)	11.9 (2.8)	12.5 (2.1)	12.0 (1.7)	11.0 (3.2)	12.2 (3.0)
Time to first RBV dose modification, n (%)[a]*						
≤4 weeks	0	9 (2)	NA	0	9 (6)	NA
>4-8 weeks	2 (1)	53 (15)	NA	3 (10)	50 (34)	NA
>8-12 weeks	0	44 (12)	NA	2 (7)	42 (29)	NA
>12-16 weeks	0	24 (7)	NA	7 (24)	17 (12)	NA
>16 weeks	3 (1)	43 (12)	NA	17 (59)	26 (18)	NA
Mean (SD), days	118 (65)	88 (61)	NA	134 (66)	79 (56)	NA
Median (IQR), days	123 (125)	72 (64)	NA	123 (80)	61 (44)	NA
Distribution of maximum RBV dose reduction, n† (%)						
200 mg	4 (1)	83 (23)	NA	20 (69)	63 (43)	NA
400 mg	0	44 (12)	NA	3 (10)	41 (28)	NA
600 mg	0	17 (5)	NA	1 (3)	16 (11)	NA
800 mg	0	7 (2)	NA	1 (3)	6 (4)	NA
1,200 mg	0	1 (<1)	NA	0	1 (1)	NA
RBV dose interruption, n† (%)						
Any interruption	0	58 (16)	NA	7 (24)	51 (35)	NA
3-4 days	0	9 (2)	NA	1 (3)	8 (6)	NA
5-7 days	0	9 (2)	NA	1 (3)	8 (6)	NA
8-14 days	0	19 (5)	NA	3 (10)	16 (11)	NA
15-28 days	0	9 (2)	NA	1 (3)	8 (6)	NA
>28 days	0	12 (3)	NA	1 (3)	11 (8)	NA
Percent intended BOV doses delivered‡						
Mean (SD)	71.6 (31.8)	77.4 (27.9)	78.5 (28.7)	81.7 (22.7)	75.5 (27.5)	77.4 (30)
Median (IQR)	88.7 (52)	91.7 (39)	95.7 (39)	90.9 (20)	87.4 (43)	94 (30)
Percentage of intended RBV doses delivered§						
Mean (SD)	67.3 (32.6)	71.3 (26)	75.5 (27.0)	73.6 (20.5)	66.6 (24.2)	72.3 (29.1)
Median (IQR)	81.1 (59.2)	78.7 (43)	88.7 (43)	81.5 (36)	73.7 (37)	82.9 (46)
Percentage of intended PegIFN doses delivered§						
Mean (SD)	68.4 (32.1)	76.2 (26.9)	76.8 (27.4)	77.7 (22.1)	76.1 (26.0)	74.3 (30.9)
Median (IQR)	81.3 (59)	89.6 (45.8)	92.9 (46)	83.3 (30)	86.0 (44)	87.5 (44)

Abbreviation: NA, not applicable.

*One patient who received both RBV dose reduction and EPO had missing data for time of first RBV dose reduction. n = number of patients administered the given dose; m = number of patients with the indicated Hb level.

†Only dose reductions/dose interruptions of at least 7 days were included.

‡Percentage of intended BOC doses delivered was calculated as follows: total dose of BOC received divided by the expected total based on actual treatment duration. BOC dosing data was collected from patient e-diaries and drug dispensed/returned at the study site. (Excludes 77 patients with missing e-diary data.)

§Percentage of intended RBV and PegIFN doses delivered was calculated as follows: total dose received divided by the expected total dose.

(72% [263/363]) compared with those who did not have incident anemia (58% [212/363]). The magnitude of the maximum Hb decline from baseline in patients treated with BOC/PR was also associated with the likelihood of achieving SVR. Higher SVR rates were observed in patients who experienced a maximum Hb decline >3 g/dL during therapy compared with those with a maximum decline of <3 g/dL (Table 3).

Management of Anemia and Virologic Response. Among patients who did not develop anemia (defined as Hb <10 g/dL) during treatment with BOC/PR (n = 363), RBV dose reduction due to anemia as defined by the study investigator as an AE occurred in

Table 3. EOT and SVR by Maximum Hb Decline During Treatment

Maximum Hb Decline from Baseline, g/dL	BOC Arms Combined, n = 734	
	EOT, n/m (%)	SVR, n/m (%)
≤ 1	3/17 (17.6)	3/17 (17.6)
>1-2	2/21 (9.5)	1/21 (4.8)
>2-3	32/48 (66.6)	26/48 (54.2)
>3-4	116/160 (72.5)	103/160 (64.4)
>4-5	138/189 (73.0)	119/189 (63.0)
>5	247/299 (82.6)	223/299 (74.6)

The analysis includes eight patients with missing data. n = number of patients with EOT or SVR; m = number of patients with the indicated Hb level.

1% (5/363), EPO was used in 10% (36/363), and the median daily RBV dose received during therapy was 12.6 mg/kg (interquartile range [IQR] of 2.1). For the 36 patients who were prescribed EPO in the absence of protocol-defined anemia, the mean Hb level was 10.7 g/dL and the mean Hb decline from baseline was 4.5 g/dL. For the five patients who underwent RBV dose reduction due to anemia as defined by the study investigator as an AE, the median time to the first RBV dose reduction was 123 days (Table 2) and the maximum reduction was 200 mg/day. An additional 21 patients underwent an RBV dose reduction due to other AEs, such as flu-like symptoms and rash (Table 1). Among the nonanemic patients, discontinuation of all treatment due to an AE occurred in 13% of patients (47/363).

For patients who developed anemia during treatment with BOC/PR (n = 363), anemia was managed by the site investigators as follows: EPO without RBV dose reduction, 38% (n = 137); RBV dose reduction without EPO, 8% (n = 29); both EPO with RBV dose reduction, 40% (n = 145); and neither RBV dose reduction nor EPO, 14% (n = 52). Among anemic patients, EPO was prescribed in 78% (n = 282) and the RBV dose was reduced in 48% (n = 174). Among those patients who had their RBV dose reduced, the overall median daily RBV dose received during treatment was 11.3 mg/kg (IQR of 3.0) which was lower than the median daily RBV dose received by patients who did not undergo RBV dose reduction (12.4 mg/kg, IQR of 2.5). For patients who had their RBV dose reduced for more than 7 days, the majority had a maximum dose reduction of 200 mg (55%, n = 83) and 16% (n = 25) had a maximum dose reduction of ≥600 mg. Among anemic patients, discontinuation of all therapy due to an AE occurred in 34% (123/363) of patients. Thirteen patients in the BOC/PR arm discontinued all therapy due to an investigator assessment of anemia as an AE.

The SVR rate was similar (70%-74%) for anemic patients regardless of the approach used to manage the anemia. Overall, patients with incident anemia were more likely to achieve virologic response than those who did not develop anemia, including those who underwent RBV dose reduction. The EOT, SVR and relapse according to the anemia management strategy are shown in Table 2. The observed pattern of SVR was consistent with that observed in the overall population for smaller subgroups of patients including African Americans (Supporting Table 3). Time to initial RBV dose reduction was correlated with SVR. Among the 145 patients who received both RBV dose reduction and EPO, SVR rates were 44% (4/9), 62% (31/50), 76% (32/42), 71% (12/17), and 85% (22/26) when the time to first RBV dose reduction was ≤4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, and >16 weeks.

Anemia, EPO Use, and Safety. Of those who used EPO, most patients with anemia initiated therapy within the first 4-12 weeks of treatment and continued to use EPO for the duration of therapy (Table 4). Of note, the median duration of EPO use was substantially shorter in the BOC/RGT arm than in the BOC/PR48 arm (BOC/RGT, 85 days; BOC/PR48, 149 days). The incidence of treatment discontinuation due to an AE, serious/life-threatening AEs and death was similar in patients who were treated with EPO and those who did not receive EPO (Table 4). In particular, no difference was observed in the frequency of cardiovascular and/or thromboembolic events in patients who did and did not use EPO. One case of pure red blood cell aplasia (PRCA) occurred in a 56-year-old Caucasian woman who was treated with BOC/PR and received high-dose EPO (40,000 units TIW) for treatment-emergent anemia (Hb nadir, 9.0 g/dL). After approximately 36 weeks of BOC/PR therapy and 32 weeks of EPO, the patient developed new-onset pancytopenia; the diagnosis of PRCA was made based on the presence of anti-EPO antibodies, and a bone marrow biopsy was consistent with the disease. The patient had complete resolution of PRCA following treatment with rituximab, intravenous immunoglobulin, and methylprednisilone.

Discussion

Based on clinical trials demonstrating greater efficacy, treatment with the HCV NS3/4A PIs boceprevir and telaprevir in combination with PegIFN/RBV has emerged as the standard of care for persons infected with HCV genotype 1 who have never been treated

Table 4. Safety and Tolerability According to EPO Use

	BOC/RGT (n = 368)		BOC/PR48 (n = 366)	
	EPO (n =159)	No EPO (n = 209)	EPO (n = 159)	No EPO (n = 207)
Duration of EPO use, n (%)				
≤4 weeks	33 (21)	NA	13 (8)	NA
>4-12 weeks	46 (29)	NA	30 (19)	NA
>12-24 weeks	63 (40)	NA	44 (28)	NA
>24-36 weeks	9 (6)	NA	39 (25)	NA
>36 weeks	8 (5)	NA	33 (21)	NA
Mean (SD)	93.5 (70.6)	NA	156.4 (90.7)	NA
Median	85	NA	149	NA
Minimum-Maximum	1-294	NA	1-305	NA
Serious AE, n (%)	21 (13)	21 (10)	19 (12)	26 (13)
Death, n (%)	0	1 (<1)	0	1 (<1)
Life-threatening AE, n (%)	1 (1)	4 (2)	3 (2)	1 (<1)
Study drug discontinuation (any drug) due to AE, n (%)	18 (11)	27 (13)	30 (19)	30 (14)
Clinically relevant AE, n (%)				
Fatigue	97 (61)	99 (47)	109 (69)	100 (48)
Dyspnea	38 (24)	30 (14)	41 (26)	43 (21)
Cardiovascular and thromboembolic AE	21 (13)	22 (11)	22 (14)	25 (12)
Malignancy/malignancy-related condition	1 (1)	1 (<1)	1 (1)	1 (<1)

Abbreviation: NA, not applicable.

previously.[15,16,20,21] Not unexpectedly, the HCV PI-based treatment has been associated with a greater incidence of AEs that may limit their tolerability; in particular, incident anemia was more common in patients treated with HCV PIs plus PegIFN/RBV compared with PegIFN/RBV alone.[15,16,20,21] Indeed, in the clinical trials of BOC in combination with PegIFN/RBV, anemia was identified as one of the most common and clinically important adverse effects.[15,16] As such, our findings related to the incidence of anemia and the impact of its management with RBV dose reduction and/or adjuvant EPO have important implications for the use of this regimen in clinical practice.

The addition of BOC to PegIFN/RBV was associated with greater decline in the Hb level above that observed with PegIFN/RBV combination therapy, leading to incident anemia in ~50% of patients receiving triple therapy compared with 31% of those treated with PegIFN/RBV alone. While the baseline Hb level was predictive of subsequent anemia, the magnitude of decline in Hb level at the end of the PR lead-in phase and after 2 weeks of BOC had only modest ability to predict which patients would remain free of anemia. Thus, close monitoring of Hb levels during BOC/PR therapy is needed to identify anemia patients. Importantly, among patients in the BOC/PR arm, the SVR rate was higher in patients who developed anemia (72%) compared with those who did not (58%). This relationship was similar to that observed in the patients in the PR48 arm of this study (data not shown) and in previous studies. In two large clinical trials of PegIFN/RBV, the IDEAL study (n = 3070) and the CHARIOT study (n = 871), HCV genotype 1, treatment-naïve patients who developed anemia, defined as an Hb level <10 g/dL during treatment, were more likely to achieve SVR than those who did not develop anemia. In both studies, anemic patients achieved higher SVR rates than nonanemic patients despite the receipt of less RBV due to frequent RBV dose reduction up to 50% in many patients (600 mg/day). Because the decline in Hb level in patients treated with PegIFN/RBV is strongly correlated with plasma RBV concentration, these analyses led to the hypothesis that the higher SVR rate observed among anemic patients may be due to higher RBV exposure in these patients compared with nonanemic patients despite lower ingested RBV doses.

The observation of higher SVR rates among anemic patients treated with BOC in combination with PegIFN/RBV, compared with nonanemic patients, may also reflect differences in exposure to RBV and, perhaps, BOC. In an analysis of the relationship of measured plasma concentrations of both BOC and RBV (steady-state AUC_t) performed by pharmacologists at the US Food and Drug Administration (FDA), there was a significant relationship between incident anemia and the RBV AUC_t among patients treated with BOC in combination with PegIFN/RBV (n = 113, $P < 0.0001$) and those treated with PegIFN/RBV alone (n = 51, $P = 0.001$).[22] In the same analysis, there was also a trend toward increasing incidence of anemia and higher BOC AUC_t; however, this relationship did not reach statistical significance. As such, in the summary

of these studies of BOC and RBV concentration and incident anemia, researchers at the FDA concluded that these data derived from the BOC registration trials support the hypothesis that the higher SVR rates observed in patients with anemia compared with those without anemia are due to higher RBV exposure, and that RBV dose reduction may be an appropriate strategy to management anemia with triple therapy.[22] Based on this FDA analysis and other data, the US prescribing information for BOC in combination with PegIFN/RBV recommends that anemia be managed with RBV dose reduction and/or discontinuation, as has been the standard practice with PegIFN/RBV treatment regimens.

In this study, approximately half (48%) of the patients who developed anemia in the BOC/PR arms underwent RBV dose reduction and, as expected, had a lower median daily dose of RBV ingested during therapy (11.3 mg/kg/day) compared with patients who did not develop anemia (12.6 mg/kg/day) and those who developed anemia but were not managed with RBV dose reduction (12.4 mg/kg/day). Despite these differences in ingested RBV over the course of therapy, SVR rates were higher in anemic patients who did not reduce their RBV dose (74%) and anemic patients who reduced their RBV dose (71%) compared with those who did not develop anemia (58%). These observations suggest that following RBV dose reduction for anemia, the dose does not need to be titrated to pre-anemia levels. Further, these data support the hypothesis that the physiologic effect of RBV, hemolytic anemia, is a better reflection of RBV exposure than the ingested dose over the course of therapy. As such, these data provide reassurance to clinicians that RBV dose reduction in 200-mg increments for the management of anemia during treatment with BOC/PR does not substantially impair the likelihood of SVR in such treatment-naïve patients. Further research is needed to assess this approach in other patient populations such as those with prior treatment failure or cirrhosis.

While RBV dose reduction represents the standard approach to anemia during HCV treatment, the use of ESA such as epoetin alfa to reverse anemia is more controversial. In this study of HCV treatment-naïve patients, 43% of all patients receiving BOC/PR and 78% of those who became anemic on this regimen were treated with adjuvant EPO and the median duration of EPO use was substantially shorter in the BOC/RGT arm than in the BOC/PR48 arm. However, in this study, the rate of EPO use among patients treated with PegIFN/RBV alone was also high, ~24% of all treated patients.[15] In contrast, in the large, US phase 3b IDEAL study of PegINF/RBV therapy; the frequency rate of EPO use was lower at 16.3% of patients. In addition, approximately 38% of patients received EPO without a RBV dose reduction, though current guidelines recommend RBV dose reduction prior to the addition of EPO. The frequent use of EPO may be due to an important difference in the provision of the drug in the two studies. In the IDEAL study, EPO was not provided by the sponsor and was typically obtained through third party health insurance.[23] In contrast, in the current study, EPO was provided directly by the sponsor at no cost to the patient. Thus, the ease with which EPO could be accessed for patients and the placebo-controlled nature of this study may have influenced the frequency of its prescription for the management of anemia. While in this study, anemic patients who received EPO were more likely to achieve SVR than those without anemia and the incidence of adverse events was similar in patients treated or not treated with EPO, the true impact of EPO on the efficacy and safety of BOC in combination with PegIFN/RBV is difficult to interpret because most anemic patients took EPO and no apparent difference was detected compared with those anemic patients who did not receive EPO.

In an earlier randomized, placebo controlled trial, the use of ESAs for the management of PegIFN/RBV induced anemia has been associated with the partial reversal of treatment-related Hb decline, the maintenance of the prescribed RBV dose, and the improvement in the quality of life compared to management of anemia with RBV dose reduction alone.[11] In addition, in the retrospective analysis of the IDEAL study, patients who rapidly developed anemia (within 8 weeks of starting PegIFN/RBV) had higher SVR rates if they received ESAs, largely attributable to lower rates of treatment discontinuation in early anemic patients who received ESAs compared with those who did not get ESAs. There was no apparent benefit of ESAs observed in those who developed anemia after treatment week 8. These data suggest that the primary role of ESAs may be to prevent treatment discontinuation in patients with severe symptoms attributed to anemia. However, the role of ESAs in the treatment of HCV with PegIFN/RBV-based therapy has remained controversial due to its high cost and the potential for additional AEs. In other patient populations such as patients with cancer and end-stage renal disease, ESAs have been linked to increased risk of serious cardiovascular events, tumor progression, thrombosis, and death. In addition, PRCA due to neutralizing

antibodies to native EPO has been reported in patients treated with ESA including HCV-infected patients treated with PegIFN/RBV. Indeed, in this study, one patient developed PRCA during therapy with BOC/PR and EPO. Taken together with the finding that RBV dose reduction was not associated with decreased likelihood of SVR, these data support the recommendation that anemia during therapy with BOC/PR should be managed primarily with RBV dose reduction, and the role of EPO should be limited to situations in which this strategy is not effective. Results from a randomized controlled trial of the management of anemia with RBV dose reduction alone or the use of ESAs as first line management is expected to provide more definitive guidance on the use of EPO in this setting (ClinicalTrials.gov Identifier: NCT01023035).

In conclusion, the addition of BOC to PegIFN/RBV therapy is associated with greater risk of anemia compared with PegIFN/RBV alone. Approximately half of the HCV genotype 1–infected patients treated with BOC/PR developed anemia, which was managed with RBV dose reduction, the prescription of EPO, or both interventions. However, the SVR rate was higher (70%-74%) in patents with incident anemia compared with those without anemia irrespective of the anemia management strategy. Additional studies are underway to further evaluate these strategies to manage treatment emergent anemia; until such data is available, RBV dose reduction should remain the primary approach to anemia management during BOC/PR therapy for treatment-naïve patients.

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Appendix

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