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Virologic response and haematologic toxicity of boceprevir- and telaprevir-containing regimens in actual clinical settings

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SUMMARY

Effectiveness, safety and tolerability of boceprevir (BOC) and telaprevir (TPV) in actual clinical settings remain unknown. We determined rates of sustained virologic response (SVR) and haematologic adverse effects among persons treated with BOC- or TPV-containing regimens, compared with pegylated interferon/ribavirin (PEG/RBV). Using an established cohort of hepatitis C virus (HCV)-infected persons, Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), we identified those treated with a BOC- or TPV-containing regimen and HCV genotype 1-infected controls treated with PEG/RBV. We excluded those with HIV co-infection and missing HCV RNA values to determine SVR. Primary endpoints were SVR (undetectable HCV RNA 12 weeks after treatment completion) and haematologic toxicity (grade 3/4 anaemia, neutropenia and thrombocytopenia). We evaluated 2288 persons on BOC-, 409 on TPV-containing

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TRANSPARENCY DECLARATIONS

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SUPPORTING INFORMATION

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

Table S1 Virologic response in HCV genotype 1 infected persons treated with boceprevir or telaprevir based regimens compared with historic controls treated with pegylated interferon and ribavirin: results overall and by prior treatment status using an “intent-to-treat” type analysis where all missing SVR values are treated as non-SVR.

Table S2 Virologic response by in HCV genotype 1 infected persons treated with boceprevir or telaprevir based regimens compared with historic controls treated with pegylated interferon and ribavirin: results by prior treatment status and presence of cirrhosis at baseline using an “intent-to-treat” type analysis where all missing SVR values are treated as non-SVR.

regimen and 6308 on PEG/RBV. Among these groups, respectively, 31%, 43% and 9% were treatment-experienced; 17%, 37% and 14% had baseline cirrhosis; 63%, 54% and 48% were genotype 1a. SVR rates among noncirrhotics were as follows: treatment naïve: 65% (BOC), 67% (TPV) and 31% (PEG/RBV); treatment experienced: 57% (BOC), 54% (TPV) and 13% (PEG/RBV); (P -value not significant for BOC vs TPV; $P < 0.0001$ for BOC or TPV vs PEG/RBV). Haematologic toxicities among BOC-, TPV- and PEG/RBV-treated groups were as follows: grade 3/4 anaemia 7%, 11% and 3%; grade 4 thrombocytopenia 2.2%, 5.4% and 1.7%; grade 4 neutropenia 8.2%, 5.6% and 3.4%. SVR rates are higher and closer to those reported in pivotal clinical trials among BOC- and TPV-treated persons compared with PEG/RBV-treated persons. Haematologic adverse events are frequent, but severe toxicity is uncommon.

Keywords

boceprevir; directly acting antiviral agents; ERCHIVES; haematologic toxicity; sustained virologic response; telaprevir

INTRODUCTION

Treatment options for hepatitis C virus (HCV) have grown rapidly since 2011. In addition to interferon and ribavirin, five oral directly acting antiviral agents (DAAs) and one fixed dose combination of DAAs are now approved by the Food and Drug Administration in the United States. In key pivotal trials, treatment regimens containing the first-generation DAAs, which include boceprevir and telaprevir, were associated with significantly higher rates of virologic response compared with pegylated interferon alpha and ribavirin (PEG/RBV) combination [1–3]. However, pill burden and adverse events associated with use of the first-generation DAAs remained significant. Approved second-generation DAAs include sofosbuvir and simeprevir, which lead to higher virologic response rates, are better tolerated and have lower pill burden, but are very costly [4–7]. Recent guidelines for the treatment of HCV no longer support use of first-generation DAAs [8]. However, use of newer DAAs may not be economically feasible for many HCV-infected persons worldwide. In the United States, a 24-week course of sofosbuvir plus RBV costs approximately US \$169 000, while a 12 week course of sofosbuvir plus simeprevir costs approximately \$150 000 [9]. In some settings, first-generation DAAs may still be of considerable value to patients, care providers, payers of health care and policymakers. Therefore, it is important to understand real-world effectiveness and safety issues associated with the use of these agents.

Information on treatment response and adverse events for DAAs is mostly derived from randomized clinical trials. Such trials may not always be true representations of population response in actual clinical settings. We undertook this study to quantify treatment response, tolerability and occurrence of haematologic adverse events among persons treated with boceprevir- and telaprevir-containing regimens and compare them with historic controls treated with PEG/RBV in actual clinical settings, using a national cohort of HCV-infected veterans.

METHODS

Data sources

We used the third iteration of the Electronically Retrieved Cohort of HCV Infected Veterans Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES 3.0) to identify newly diagnosed HCV-infected subjects and HCV-uninfected controls between 1 October 2001 and 30 June 2013. The earlier versions of ERCHIVES have been previously defined [10–16]. In ERCHIVES 3.0, we identified all HCV-infected persons in the Veterans Affairs healthcare system from 1 October 2001 through 30 June 2013. HCV-infected subjects were identified based on a positive HCV antibody test. Clinical and demographic information was retrieved from the National Patient Care Database, pharmacy information from the Pharmacy Benefits Management database and laboratory data from the Corporate Data Warehouse. Pharmacy data were available through 30 June 2013 and laboratory data through April 2014.

Study population

Hepatitis C virus-infected persons were classified within one of three treatment groups: (i) those treated with a boceprevir-containing regimen; (ii) those treated with a telaprevir-containing regimen; and (iii) historical controls treated with a PEG/RBV regimen. As boceprevir and telaprevir are approved for treatment of HCV genotype 1-infected persons only, we limited the PEG/RBV group to HCV genotype 1-infected persons only. HCV treatment was defined as receipt of a prescription for the corresponding regimen for >14 days. Cumulative days of prescription were computed from the Pharmacy Benefits Management database. Duration of treatment was calculated based on actual days of prescriptions written. For boceprevir-containing regimen, the 4-week lead-in period with PEG/RBV was included when calculating treatment duration. Full course of treatment was defined per labelling guidelines, based on prior treatment status. We excluded HIV-coinfected persons and those in whom HCV RNA was not available at baseline or to calculate sustained virologic response (SVR) rate 12 weeks after completion of therapy (defined in more detail below). Within each treatment group, we categorized subjects as treatment naïve or treatment experienced based on any prior therapy with PEG/RBV for >14 days. We used the first course of treatment for treatment-naïve analyses and last course of treatment for treatment-experienced subjects.

Study outcomes

Early virologic response (EVR) was defined as the proportion of subjects with undetectable HCV RNA at week 8 of treatment for boceprevir-containing (including the PEG/RBV lead-in) and PEG/RBV regimens and at week 4 of treatment for telaprevir-containing regimens. End-of-treatment response (ETR) was defined as the proportion of subjects with undetectable HCV RNA at the end date of last HCV prescription. Sustained virologic response was defined as the proportion of subjects who had at least one undetectable HCV RNA 12 weeks after the last dose of study medication. Anaemia, neutropenia and thrombocytopenia were defined and graded as per WHO classification of severe adverse events [17].

Data collection

We collected demographic (age, race, sex), anthropometric (height and weight to calculate body mass index) and selected laboratory and pharmacy data from the data sources listed above. We categorized subjects as having cirrhosis or no cirrhosis at baseline using the FIB-4 score, which was calculated as follows:

$$\text{FIB-4} = \text{age [years]} \times \text{AST [IU/L]} / \text{platelet count [platelets} \times 10^9/\text{L]} \times \left(\text{ALT}^{\frac{1}{2}} [\text{IU/L}] \right)$$

Based on previously published data, a cut-off value of 3.5 was used to estimate the presence of baseline cirrhosis [18]. We also retrieved information on prescriptions of erythropoiesis-stimulating agents (ESA, erythropoietin and darbopoietin) and HMG-CoA reductase inhibitors (statins). Subjects were considered to have diabetes if they met any of the following criteria: (i) glucose ≥ 200 mg/dL on two separate occasions; (ii) ICD-9 codes (two or more outpatient OR one or more inpatient) PLUS treatment with an oral hypoglycaemic or insulin for ≥ 30 days; (iii) ICD-9 codes (two outpatient OR one inpatient) PLUS glucose ≥ 126 mg/dL on two separate occasions; and (iv) glucose ≥ 200 mg/dL on one occasion PLUS treatment with an oral hypoglycaemic or insulin for ≥ 30 days [19].

Analysis

Baseline demographic, clinical and laboratory variables were compared using chi-square or *t*-test, as appropriate. SVR was compared in each of the three treatment groups, stratified by prior treatment status and presence of cirrhosis at baseline. Predictors of SVR, including demographic variables, prior treatment status, presence of cirrhosis, select baseline laboratories, completion of treatment and use of ESA and statins, were determined using univariable and multivariable logistic regression analyses. Counts and proportions of subjects developing anaemia and grade 3 and 4 neutropenia and thrombocytopenia were determined and compared between treatment groups. A *P*-value of <0.05 was considered significant where comparisons were made. We used SAS® (SAS Institute Inc., Cary, NC, USA) and Stata® version 11 (Stata Corp, College Station, TX, USA) for statistical analyses.

We performed additional sensitivity analyses to determine SVR on an 'intent-to-treat' basis, whereby all missing SVR values were treated as non-SVR.

Regulatory approvals

The study was approved by the Institutional Review Board at VA Pittsburgh Healthcare System. Appropriate approvals were also obtained from each of the databases from where data were retrieved.

RESULTS

Among 305 257 HCV-infected persons included within ERCHIVES between October 2001 and June 2013, we identified 4191 persons who received any treatment with boceprevir- or telaprevir-containing regimen and 27 968 persons who received PEG/RBV therapy. After excluding HIV-coinfected persons, nongenotype 1 (among the PEG/RBV group) infected

and those with missing HCV RNA values, we had 2288 persons in the boceprevir group, 409 in the telaprevir group and 6308 in the PEG/RBV group (Fig. 1).

Baseline characteristics of the study groups are provided in Table 1. The telaprevir group was more likely to be treatment experienced and had a higher proportion of persons with cirrhosis and diabetes.

Virologic response

Virologic response rates are provided in Figs 2–4. SVR in the treatment-naïve persons were 62.5% for boceprevir-containing regimen, 63.6% for the telaprevir-containing regimen and 29.2% for the PEG/RBV-containing regimen. Respective SVR rates among treatment-experienced persons were 52.7%, 51.7% and 11.7% for the three treatment groups. Among treatment naïve with no cirrhosis at baseline, SVR rates were 65.0%, 66.9% and 31.0%, respectively, while among treatment naïve with cirrhosis at baseline, SVR rates were 49.6%, 59.2% and 17.6%, respectively. Among treatment experienced with no cirrhosis at baseline, SVR rates were 57.1%, 54.5% and 13.0%, while among treatment experienced with cirrhosis at baseline, SVR rates were 35.8%, 45.4% and 5.9%, respectively. For all of the SVR results, there was no statistically significant difference between boceprevir- and telaprevir-containing regimen, but *P*-value was <0.0001 for both when compared with PEG/RBV regimen.

In a multivariable logistic regression model, following factors were associated with a lack of SVR: Black race (OR 0.72; 95% CI 0.59–0.87), cirrhosis at baseline (OR 0.42; 95% CI 0.34–0.53), prior treatment for HCV (OR 0.76; 95% CI 0.63–0.91) and higher pretreatment HCV RNA (OR 0.91; 95% CI 0.87–0.94 per log₁₀ increase). Factors associated with achieving SVR included completion of a full course of treatment (OR 2.52; 95% CI 2.12, 3.00) and development of anaemia while on treatment (OR 1.95; 95% CI 1.34, 2.83) (Table 2).

Haematologic adverse events

Anaemia was observed in 86–96% of the treated persons, with higher rates in the boceprevir- and telaprevir-containing groups compared with PEG/RBV treatment group. The difference was not significant between boceprevir vs telaprevir groups (Table 3). Grade 3/4 anaemia was observed in 6.7% of boceprevir, 11% of telaprevir and 3.4% of PEG/RBV group. Time from treatment initiation to lowest haemoglobin was shortest in the telaprevir group (86 ± 66 days), followed by boceprevir group (98 ± 71 days) and longest in the PEG/RBV group (161 ± 108 days) ($P < 0.01$ for all comparisons). Grade 4 neutropenia was observed in 8.2% of boceprevir, 5.6% of telaprevir and 3.4% of PEG/RBV group, while grade 4 thrombocytopenia was observed in 2.2%, 5.4% and 1.7%, respectively. While the drops in haemoglobin, neutrophil count and platelet counts were substantial in each group while on therapy, all parameters improved substantially after completion of treatment (Table 4).

We performed additional analyses to determine SVR among all persons initiated on treatment, with missing values treated as non-SVR (akin to ‘intent-to-treat’ analyses in clinical trials). Overall SVR rates were lower than those reported in our primary analysis;

however, comparison between three treatment groups yielded similar trends. These results are provided in supplementary tables.

DISCUSSION

To our knowledge, our study is one of the largest to date to report real-life experience on the effectiveness and safety of first generation of DAAs and historical controls among the same population who were treated with PEG/RBV regimen. The larger proportion of boceprevir-treated persons in the DAA groups is a reflection of boceprevir being the preferred formulary agent at the VA, with telaprevir being available upon the request of treatment providers. Early studies in the VA healthcare system indicated that overall SVR rates in persons treated with boceprevir- or telaprevir-containing regimens were 50–52%, substantially lower than the 63–79% SVR rates reported from clinical trials, while haematologic adverse events were higher than reported from clinical trials [20,21]. Our overall SVR rates of 6–64% in the treatment-naïve DAA-treated group and 52–53% in the treatment-experienced DAA-treated group are closer to the SVR rates reported in the pivotal clinical trials. This difference is partly due to intent-to-treat analysis in a previously reported study by Backus *et al.* [20], while we analysed only those who had HCV RNA available to determine SVR. In our sensitivity analysis, where we classified missing SVR values as non-SVR, the overall SVR rate in our DAA-treated group was 38%. The reason for higher rates of haematologic toxicity is likely due to a more heterogeneous population with higher comorbidity burden in real-life settings compared with clinical trials. Our study underscores the significant SVR achieved among persons who received treatment with either boceprevir- or telaprevir-containing regimen, and the superiority of these regimens to the PEG/RBV regimen in real-life settings. While 2 newer DAAs have been approved after boceprevir and telaprevir, with several more in phase 3 clinical trials, demonstrating even better efficacy, tolerability and safety profiles, the newer regimens are extremely costly and may not be available to all those in need of treatment. In such cases, boceprevir- and telaprevir-based regimens may still be a viable option to eradicate HCV in select groups of patients.

As is well known from multiple studies, prior treatment for HCV and presence of cirrhosis are associated with lower SVR rates. We found that persons treated with either boceprevir- and telaprevir-containing regimens achieved SVR rates 3–7 times higher than similar persons treated with PEG/RBV, regardless of the prior treatment status or the presence of cirrhosis. However, these factors remained strong predictors of SVR, with cirrhosis associated with 58% lower and prior treatment associated with 24% lower likelihood of achieving SVR. Among those with cirrhosis at baseline, SVR among treatment-naïve persons was 50%, 59% and 18%, respectively, while among the treatment-experienced groups, SVR achieved was 36%, 45% and 6% in the three groups, respectively. While there was no statistically significant difference between the boceprevir- and telaprevir-containing regimens, clinical relevance of a difference of 10% SVR is unclear. These results might be useful in determining which first-generation DAA to use in a particular patient when newer DAAs are not available or not an option.

Frequency of haematologic adverse events was very high, with vast majority of treated persons developing at least one adverse event. However, severe haematologic toxicity was

relatively uncommon. We were not able to determine the effect of dosage of various regimens upon such toxicities. Severe haematologic adverse events, as measured by time to lowest respective laboratory value, occurred mostly 3 or more months after initiation of treatment and returned closer to baseline after completion of treatment. Use of ESA was similar in all groups and was associated with a slightly lower but statistically insignificant SVR rates in the multivariable model. Association of ESA with SVR has been inconsistent in previous studies, and it is very difficult to separate the effect of ESA itself from the underlying reason for prescribing ESA in the first place. While anaemia at baseline was associated with a significantly lower likelihood of achieving SVR, anaemia on treatment was associated with a 95% increased likelihood of achieving SVR. Association of on-treatment anaemia with SVR has also been inconsistent in the past, but results from our study suggest that association of anaemia on treatment with higher likelihood of achieving SVR may be due to higher RBV exposure.

While our study provides crucial real-life effectiveness and safety data on the use of boceprevir- and telaprevir-containing regimens, several limitations need to be noted. All data were gathered in the setting of actual clinical care, so the time-points for clinical and laboratory evaluations were not always consistent. We used predefined time windows around each measurement based on clinical experience and kept them consistent for all study groups to minimize this effect. We did not perform intent-to-treat analysis as our primary analysis because we wanted to determine the real-life value of the regimens studied; however, these were performed in sensitivity analyses, and while the overall SVR rates were lower, the comparisons between three groups yielded similar results. We were not able to study the effect of ribavirin dose reduction upon incidence of anaemia. We were also not able to determine adherence to study medications due to the observational nature of our data. Finally, we did not further classify treatment-experienced persons into relapsers, partial responders or null responders.

In conclusion, use of BOC- and TPV-containing regimens is superior than PEG/RBV for treatment of HCV genotype 1-infected persons. The virologic response rates for these regimens in real-life settings are closer to the clinical trials compared with the PEG/RBV regimens. Severe haematologic toxicity is uncommon. Precise role of these regimens in view of the newer approved drugs requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BOC	boceprevir
DAAs	directly acting antiviral agents
ERCHIVES	Electronically Retrieved Cohort of HCV Infected Veterans) Study
ESA	erythropoiesis-stimulating agents
ETR	End-of-treatment response
EVR	Early virologic response
HCV	hepatitis C virus
PEG	pegylated interferon
RBV	ribavirin
SVR	sustained virologic response
TPV	telaprevir

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Fig. 1.

Creation of the Study Data set. ERCHIVES, Electronically Retrieved Cohort of HCV Infected Veterans; PEG, pegylated interferon alpha; RBV, ribavirin; SVR, sustained virologic response.

Fig. 2.

Early, end-of-treatment and sustained virologic responses in HCV genotype 1-infected persons, by prior treatment status. EVR, early virologic response; ETR, end-of-treatment response; SVR, sustained virologic response; BOC, boceprevir-containing regimen; TPV, telaprevir-containing regimen; PEG/RBV, pegylated interferon alpha plus ribavirin.

P = nonsignificant for comparison between BOC and TPV except for EVR in treatment experienced where $P = 0.02$;

$P < 0.0001$ for comparisons between both BOC and TPV vs PEG/RBV regimen except for EVR in treatment experienced where $P = 0.002$ for comparison between BOC and PEG/RBV and $P = 0.9$ for comparison between TPV and PEG/RBV.

Fig. 3.

Early, end-of-treatment and sustained virologic responses in treatment-naïve HCV genotype 1-infected persons, by presence of cirrhosis at baseline. EVR, early virologic response; ETR, end-of-treatment response; SVR, sustained virologic response; BOC, boceprevir-containing regimen; TPV, telaprevir-containing regimen; PEG/RBV, pegylated interferon alpha plus ribavirin. P = nonsignificant for comparison between BOC and TPV except for EVR in treatment naïve with cirrhosis where $P = 0.04$ for BOC *vs* TPV; $P < 0.0001$ for all comparisons between both BOC and TPV *vs* PEG/RBV regimen.

Fig. 4.

Early, end-of-treatment and sustained virologic responses in treatment-experienced HCV genotype 1-infected persons, by presence of cirrhosis at baseline. EVR, early virologic response; ETR, end-of-treatment response; SVR, sustained virologic response; BOC, boceprevir-containing regimen; TPV, telaprevir-containing regimen; PEG/RBV, pegylated interferon alpha plus ribavirin. P = nonsignificant for comparison between BOC and TPV except for EVR in treatment experienced with no cirrhosis where $P = 0.02$; $P < 0.0001$ for comparisons between both BOC and TPV vs PEG/RBV regimen for ETR and SVR; For EVR in treatment experienced with no cirrhosis, $P = 0.002$ for comparison between TPV vs PEG/RBV;

P = nonsignificant for EVR comparisons in treatment experienced with cirrhosis.

Table 1

Baseline characteristics of the study groups

	Group A PEG+RBV+BOC (N = 2288)	Group B PEG+RBV+TPV (N = 409)	Group C PEG+RBV (N = 6308)	P-value		
				A vs B	A vs C	B vs C
Mean age, years (SD)	57.11 (6.33)	57.87 (5.88)	52.84 (6.4)	0.03	<0.0001	<0.0001
Sex, male	96.4%	95.6%	95.9%	0.45	0.28	0.8
Race/ethnicity						
White	57.2%	57.7%	61.7%	0.99	<0.0001	0.01
Black	26.0%	25.7%	22.6%			
Hispanic	3.2%	3.2%	5.5%			
Other	13.7%	13.4%	10.2%			
Body mass index, mean, kg/m ²	29.16 (4.99)	29.1 (4.78)	28.98 (6.41)	0.83	0.17	0.63
Body mass index ≥ 30 kg/m ²	37.8%	36.2%	35.1%	0.54	0.02	0.65
Cirrhosis (FIB-4 > 3.5)	17.5%	37.4%	13.9%	<0.0001	<0.0001	<0.0001
Treatment experienced	31.4%	43.5%	8.8%	<0.0001	<0.0001	<0.0001
HCV RNA, log IU/mL	6.31 (2.19)	6 (2.56)	6.3 (1.93)	0.02	0.85	0.02
Genotype 1a	63.2%	54.5%	48.4%	0.005	<0.0001	0.04
1a (N)	1135	157	3051			
1b (N)	405	68	1652			
Not specified or mixed (N)	255	63	1605			
Missing (N)	493	121	0			
Alanine aminotransferase, U/L	81.03 (62.75)	91.41 (66.78)	89.01 (76.34)	0.003	<0.0001	0.5
Aspartate aminotransferase, U/L	64.08 (45.18)	78.19 (54.37)	66.82 (55.46)	<0.0001	0.02	<0.0001
Haemoglobin, g/dL	16.65 (5.59)	17.02 (6.38)	16.67 (5.53)	0.27	0.88	0.28
Anaemia (Haemoglobin <13 for men, <12 for women)	5.55%	7.33%	6.33%	0.16	0.19	0.42
Platelets, K/L	192 (64.74)	157.37 (61.05)	207.03 (71.98)	<0.0001	<0.0001	<0.0001
Absolute neutrophil count	3.7 (1.64)	3.32 (1.51)	3.84 (1.63)	<0.0001	0.004	<0.0001
Mean duration of treatment, weeks, SD	44.17 (30.28)	48.96 (32.76)	37.82 (18.63)	0.006	<0.0001	<0.0001
Completed full course of treatment	57.3%	46.9%	29.7%	<0.0001	<0.0001	<0.0001
Diabetes	18.6%	21.3%	15.3%	0.21	0.0002	0.001
ESA use	27.6%	28.8%	28.9%	0.61	0.25	0.98
Use of statins while on treatment	12.0%	8.8%	8.8%	0.06	<0.0001	0.98
G-CSF use	10.4%	4.9%	9.0%	0.0005	0.04	0.005

PEG, pegylated interferon alpha; RBV, ribavirin; BOC, boceprevir-containing regimen; TPV, telaprevir-containing regimen; ESA, erythropoiesis-stimulating agent; G-CSF. Use of statins and ESA is not at baseline but while on treatment for HCV.

Table 2

Predictors of sustained virologic response among those treated with boceprevir- or telaprevir-based regimens

	Odds ratio univariable	95% CI	Odds ratio multivariable	95% CI
Age, for each 10 year increase	0.85	0.76, 0.95	0.94	0.83, 1.07
Sex, male vs female	1.04	0.7, 1.56	1.03	0.66, 1.61
Race/ethnicity				
White	1			
Black	0.67	0.56, 0.8	0.72	0.59, 0.87
Hispanic	1.24	0.78, 1.96	1.3	0.78, 2.15
Other	1.13	0.89, 1.43	1.19	0.92, 1.54
Body mass index, each one unit increase in kg/m ²	0.99	0.97, 1.004	0.99	0.96, 1.01
Body mass index				
<30 vs 30 kg/m ²	1.1	0.94, 1.29	1.05	0.79, 1.39
Cirrhosis	0.54	0.45, 0.65	0.42	0.34, 0.53
Treatment experienced Ms treatment naive	0.66	0.56, 0.78	0.76	0.63, 0.91
Completed full course of treatment	2.63	2.24, 3.08	2.52	2.12, 3.00
HCV RNA, log IU/mL	0.91	0.88, 0.94	0.91	0.87, 0.94
Baseline alanine aminotransferase level, U/L	1.002	1.001, 1.004	1.004	1.002, 1.01
Presence of diabetes	0.78	0.64, 0.95	0.89	0.72, 1.11
ESA use	0.93	0.78, 1.1	0.85	0.70, 1.03
Use of statins	1.18	0.92, 1.5	1.29	0.99, 1.70
Anaemia at baseline	0.56	0.41, 0.78	0.75	0.52, 1.07
Anaemia on treatment	2.04	1.49, 2.78	1.95	1.34, 2.83
Genotype (1a is the comparator group)				
1b	1	0.81, 1.24	1.06	0.85, 1.33
Not specified	1.1	0.85, 1.41	1.14	0.87, 1.49
BOC vs TPV (TPV is the comparator group)	1.04	0.84, 1.29	0.82	0.65, 1.05

BOC, boceprevir-containing regimen; TPV, telaprevir-containing regimen; ESA, erythropoiesis-stimulating agent.

Table 3

Anaemia and use of erythropoiesis-stimulating agents (ESA) among study subjects

	Treatment group			P-value		
	Group A Boceprevir	Group B Telaprevir	Group C PEG/RBV	A vs B	A vs C	B vs C
Anaemia						
Haemoglobin 6.5–7.9 g/dL	5.86%	10.02%	2.92%	0.002	<0.001	<0.001
Haemoglobin <6.5 g/dL	0.83%	0.98%	0.52%	0.77	0.1	0.23
Lowest haemoglobin g/dL	10.21 (2.56)	10.24 (2.68)	11.49 (3.81)	0.84	<0.001	<0.001
Days from treatment initiation until lowest haemoglobin	98.18 (70.81)	86.38 (65.95)	161.35 (108.37)	0.002	<0.001	<0.001
Thrombocytopenia						
Baseline platelet count (K/ μ L)	192 (64.74)	157.37 (61.05)	207.03 (71.98)	<0.001	<0.001	<0.001
Platelets 25–49.9 (K/ μ L)	11.28%	18.34%	6.02%	<0.001	<0.001	<0.001
Platelets <25 (K/ μ L)	2.23%	5.38%	1.71%	0.0003	0.12	<0.001
Lowest platelet count (K/ μ L)	97.85 (46.97)	83.79 (43.89)	122.03 (55.7)	<0.001	<0.001	<0.001
Days from treatment initiation until lowest platelets	108.62 (75.75)	91.05 (72.91)	135.03 (106.92)	<0.001	<0.001	<0.001
Neutropenia						
Baseline ANC (K/ μ L)	3.7 (1.64)	3.32 (1.51)	3.84 (1.63)	<0.001	0.004	<0.001
ANC 0.5–0.75 (K/ μ L)	15.03%	15.65%	9.62%	0.75	<0.001	0.0001
ANC <0.5 (K/ μ L)	8.22%	5.62%	3.44%	0.07	<0.001	0.02
Lowest ANC (K/ μ L)	1.02 (0.61)	1.17 (0.75)	1.26 (0.8)	0.0002	<0.001	0.04
Days from treatment initiation until lowest ANC	91.34 (71.25)	106.06 (83.47)	104.14 (110.39)	0.003	<0.001	<0.001

On-treatment anaemia is measured by the lowest recorded Hb while on treatment.

Table 4

Haematologic toxicities after completion of treatment

	Group A Boceprevir	Group B Telaprevir	Group C PEG/RBV	<i>P</i> -value		
				A vs B	A vs C	B vs C
Mean post-treatment haemoglobin, g/dL	14.76 (1.49)	14.56 (1.61)	15.05 (1.43)	0.02	<0.0001	<0.0001
Mean difference between post-treatment and lowest on-treatment haemoglobin, g/dL	4.68 (2.14)	4.3 (2.73)	4.05 (2.41)	0.01	<0.0001	0.08
Mean difference between post-treatment and pretreatment haemoglobin, g/dL	-1.69 (5.25)	-2.32 (6.21)	-1.1 (4.75)	0.06	<0.0001	0.0002
Post-treatment platelets, (K/ μ L)	199.88 (67.07)	168.62 (66.32)	214.74 (76.64)	<0.0001	<0.0001	<0.0001
Mean difference between post-treatment and lowest on-treatment platelets, (K/ μ L)	102.89 (54.53)	86.2 (53.44)	94.95 (59.25)	<0.0001	<0.0001	0.003
Mean difference between post-treatment and pretreatment platelets, (K/ μ L)	8.97 (47.63)	12.24 (54.54)	10.14 (51.24)	0.28	0.36	0.45
Post-treatment ANC, (K/ μ L)		3.95 (1.91)	4.3 (1.95)	0.09	0.01	0.003
Mean difference between post-treatment and lowest on-treatment ANC, (K/ μ L)	3.14 (1.8)	2 (53.44)	3.11 (1.83)	0.007	0.64	0.01
Mean difference between post-treatment and pretreatment ANC, (K/ μ L)	0.47 (0.63)	0.66 (1.92)	0.53 (1.87)	0.11	0.26	0.28

PEG/RBV, pegylated interferon and ribavirin combination therapy; ANC, absolute neutrophil count. Post-treatment values represent the highest value between 12 and 48 weeks after completion of treatment. Values in parentheses represent standard deviation.