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Boceprevir plus pegylated interferon/ribavirin to re-treat hepatitis C virus genotype 1 in HIV–HCV co-infected patients: final results of the Spanish BOC HIV–HCV Study

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SUMMARY

Introduction: Boceprevir (BOC) was one of the first oral inhibitors of hepatitis C virus (HCV) NS3 protease to be developed. This study assessed the safety and efficacy of BOC + pegylated interferon-α2a/ribavirin (PEG-IFN/RBV) in the retreatment of HIV–HCV co-infected patients with HCV genotype 1.
Methods: This was a phase III prospective trial. HIV–HCV (genotype 1) co-infected patients from 16 hospitals in Spain were included. These patients received 4 weeks of PEG-IFN/RBV (lead-in), followed by response-guided therapy with PEG-IFN/RBV plus BOC (a fixed 44 weeks was indicated in the case of cirrhosis). The primary endpoint was the sustained virological response (SVR) rate at 24 weeks post-treatment. Efficacy and safety were evaluated in all patients who received at least one dose of the study drug.
Results: From June 2013 to April 2014, 102 patients were enrolled, 98 of whom received at least one treatment dose. Seventy-three percent were male, 34% were cirrhotic, 23% had IL28b CC, 65% had genotype 1a, and 41% were previous null responders. The overall SVR rate was 67%. Previous null-responders and cirrhotic patients had lower SVR rates (57% and 51%, respectively). Seventy-six patients (78%) completed the therapy scheme; the most common reasons for discontinuation were lack of response at week 12 (12 patients) and adverse events (six patients).
Conclusions: Response-guided therapy with BOC in combination with PEG-IFN/RBV led to an overall SVR rate of 67%, but an SVR rate of only 51% in patients with cirrhosis. The therapy was generally well tolerated. Although the current standards of care do not include BOC + PEG-IFN/RBV, the authors believe

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that this combination can be beneficial in situations where new HCV direct antiviral agent interferon-free therapies are not available yet.

1. Introduction

Liver disease caused by chronic hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality among HIV-infected patients in the developed world and represents an important health care problem in this population.[1,2] HCV genotype 1 is the most prevalent in this population.

The standard treatment for HCV infection until 2009 was the combination of pegylated interferon plus ribavirin (PEG-IFN/RBV) for 48 weeks. However, the sustained virological response (SVR) rate achieved in patients with genotype 1 is low with this combination, at less than 40%.[3–6] More than half of the patients fail to respond and these patients require retreatment.

In recent years, several drugs with direct antiviral activity against HCV have been developed (direct-acting antivirals, DAAs). The first DAAs used in combination therapy with PEG-IFN/RBV were the protease inhibitors of HCV NS3 telaprevir and boceprevir (BOC). The results of clinical trials with triple therapy in both monoinfected[7,8] and HIV co-infected patients[9–11] have been good. However, data on the efficacy of this regimen in patients who have not responded to previous PEG-IFN/RBV therapy are scarce.[12–17]

Although triple therapy achieves higher rates of SVR than conventional therapies, it may be more toxic and is clearly more expensive. There are data indicating that response-guided therapy (RGT) (32 weeks of triple therapy) in HCV monoinfected patients with previous failure to PEG-IFN/RBV therapy can be as effective as the standard triple therapy (44 weeks), but with lower toxicity and cost.[14]

Some studies have evaluated the efficacy and safety of triple therapy with protease inhibitors in HIV–HCV co-infected patients previously treated with PEG-IFN/RBV,[18,19] and one has evaluated RGT.[20]

This phase III study assessed the safety and efficacy of RGT with BOC + PEG-IFN/RBV in the retreatment of HIV–HCV genotype 1 patients who were non-responders or relapsers to PEG-IFN/RBV therapy.

2. Methods

2.1. Study design and participating centers

The study was a phase III, prospective, multicenter, open-label, single-arm trial performed in the specialized HIV units of 16 hospitals of Spain. The study was conducted in accordance with the principles of Good Clinical Practice. The institutional ethics committee of Hospital Clinic of Barcelona (coordinating center) and AEMPS (La Agencia Española de Medicamentos y Productos Sanitarios; Spanish drug agency) approved the study, having taken into account the opinions of the other Clinical research ethics committees involved in the project (16 hospitals in Spain). All patients provided written informed consent before entering the study. The clinical trial is registered in EudraCT (number 2012-003984-23). The study design is illustrated in Figure 1.

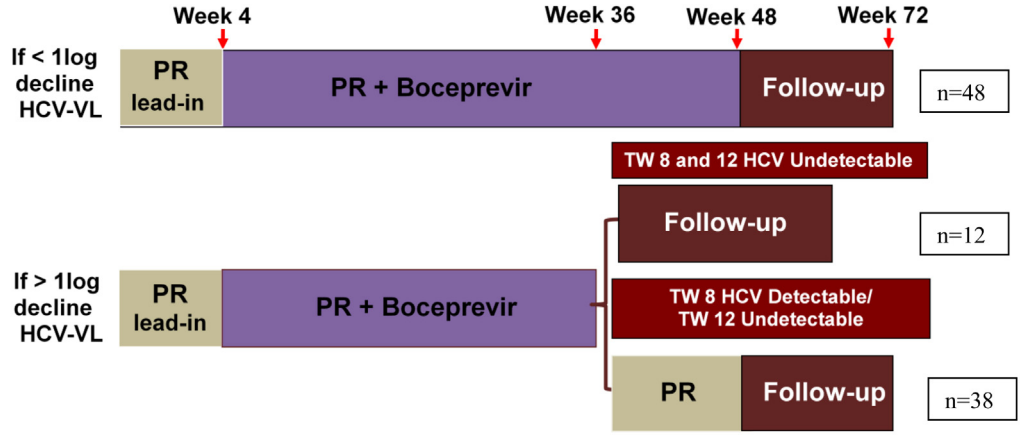
2.2. Patients

HIV–HCV co-infected patients who had received medical care for their HIV infection at any of the hospitals participating in the study were enrolled from June 2013 to April 2014. The patients had to fulfill the following inclusion criteria: previous non-responders or relapsers to PEG-IFN/RBV therapy; HIV infection with a CD4 cell count >100 cells/mm^3 and undetectable plasma HIV viral load (<50 copies/ml) for more than 6 months; the antiretroviral treatment had to contain raltegravir (at least during the last 6 weeks).

Cirrhosis was defined by a liver biopsy showing F4 liver fibrosis, or transient elastography showing a liver stiffness of >12.5 kPa. Exclusion criteria included the following: hepatitis B virus (HBV) infection or any other cause of clinically significant liver disease, decompensated liver disease, a severe psychiatric disorder, and active substance abuse.

2.3. Treatment and monitoring

Pegylated interferon-α2a was administered subcutaneously at a dose of 180 μg once weekly. Ribavirin was administered twice a



HCV-VL: Viral load of HCV. PR: Peg-Interferon plus Ribavirin; TW8: Therapy Week 8; TW12: Therapy Week 12

Figure 1. Study design (HCV-VL, viral load of hepatitis C virus; PR, pegylated interferon plus ribavirin; TW8, therapy week 8; TW12, therapy week 12).

day at a dose of 800 to 1200 mg per day on the basis of body weight. Boceprevir was administered at a dose of 800 mg three times daily. During the 4-week lead-in period, all patients received PEG-IFN/RBV. Subsequent treatment varied according to the degree of liver fibrosis and viral response at this point: (1) patients with an HCV RNA decrease of <1 $\log_{10}$ and all patients with cirrhosis received BOC + PEG-IFN/RBV for 44 weeks; (2) patients who achieved a ≥ 1 $\log_{10}$ drop in HCV RNA received a RGT regimen consisting of (a) BOC + PEG-IFN/RBV for 32 weeks if the HCV RNA level was undetectable at weeks 8 and 12 (completed therapy at week 36); (b) PEG-IFN/RBV for an additional 12 weeks if the HCV RNA level was detectable at week 8 (but undetectable at week 12) (Figure 1).

In all groups, failure to achieve an undetectable HCV RNA level at week 12 resulted in discontinuation of all treatments and advancement to follow-up. Plasma HCV RNA levels were measured using the VERSANT HCV RNA 1.0 Assay (kPCR) (Siemens Healthcare), which has a lower limit of quantification and detection of 15 IU/ml. Measurements were performed at the baseline visit, weeks 4, 8, 12, 24, 36, and 48, as well as at weeks 12 and 24 of the follow-up period.

2.4. Assessment of efficacy

The primary measure of efficacy was the SVR rate, defined as the proportion of patients with undetectable HCV RNA in serum at the end of follow-up (24 weeks after cessation of treatment), by an intent-to-treat (ITT) analysis of the whole population and also according to baseline characteristics. Possible predictors of SVR were also analyzed.

2.5. Assessment of safety

Adverse events were graded according to a modification of the World Health Organization scale. Therapy was permanently discontinued in patients who developed life-threatening events. In the case of hematological toxicity, the RBV or PEG-IFN dose was lowered according to the drug label recommendations, and full doses were restarted, if possible, when the hematological parameters had returned to previously normal levels for that patient. The use of granulocyte colony-stimulating factor (G-CSF) and erythropoietin was permitted in this study and used at the discretion of the physician responsible for each patient.

2.6. Statistical analysis

Analyses of the primary outcome (SVR) included data from all patients who received at least one dose of any study medication. Other efficacy analyses included the proportion of patients with an early response (i.e., undetectable HCV RNA level at weeks 4 and 8) in those who achieved SVR and the proportion of patients with a relapse.

The proportion of patients with SVR was expressed as a percentage with the 95% confidence interval (CI). Quantitative characteristics were described using the mean and standard deviation (SD) or median and interquartile range (IQR) and compared between groups with the *t*-test and Wilcoxon rank sum test, respectively. Qualitative variables were described using the absolute frequency and percentage and were compared between groups with the Chi-square test or Fisher's exact test. Logistic regression models were used to identify baseline factors influencing SVR. Characteristics were chosen on the basis of clinical judgment and statistical criteria (simple regression model p-value <0.1) and were evaluated in a stepwise fashion. All tests were two-tailed with the significance level set at 5%. The statistical software used for the analyses was Stata Release 13 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

A total of 102 patients were included in the study, of whom 98 received at least one treatment dose and were included in the analysis (Figure 2). The baseline demographic characteristics are shown in Table 1. The mean age of the patients was 49 years; 100% of the patients were Caucasian and 73% were male.

The prevalence of infection with HCV genotypes 1a and 1b was 65% and 35%, respectively. Polymorphism IL28B CC was present in 23% of patients. A total of 34% of patients had cirrhosis.

Most patients were non-responders to previous HCV therapy: 41% were null responders and 23% were partial responders. One third of patients included were relapsers.

In accordance with the inclusion criteria of the study, all patients had an undetectable HIV viral load and a high CD4 cell count (median 674, IQR 510–946 cells/mm^3).

Following the study design, patients were divided into three therapy groups: 48 patients (67% with cirrhosis) entered the long arm (BOC + PEG-IFN/RBV for 48 weeks) and 50 patients entered the RGT arm; the treatment duration could be shortened to 36 weeks in 12 of these latter patients.

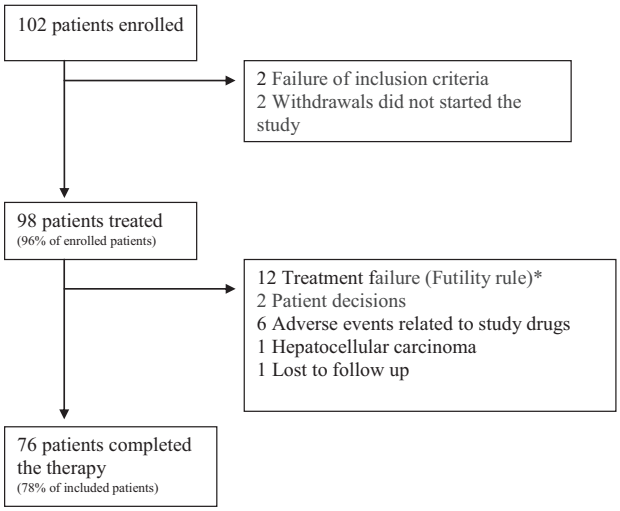
3.2. Efficacy

The global SVR rate was 67% (95% CI 57–76%). In particular, the SVR rate was 85% among patients with prior relapse and 57% among those with a previous null response. In cirrhotic patients, the SVR rate dropped to 51% (Table 2).

When an analysis was done by treatment arm, the SVR rate was 48% with the long treatment, 92% with the short RGT, and 84% in the group receiving long RGT.

Viral breakthrough occurred in only four patients. HCV relapsed during follow-up in 10 patients (13% of patients with HCV negative at the end of therapy); in three cases the relapse was delayed, occurring between weeks 12 and 24 of follow-up. Nine relapses occurred in the group of patients assigned to the fixed long arm therapy.

Sixty-nine patients (70%) had a good response to PEG-IFN/RBV, defined as a decrease in HCV RNA of ≥ 1 $1\log_{10}$ IU/ml after the



*patients with detectable HCV RNA at week 12 of therapy had to discontinue all therapy (futility rule established in the protocol)

Figure 2. Flow chart. *Patients with detectable HCV RNA at week 12 of therapy had to discontinue all therapy (futility rule established in the protocol).

Table 1
Baseline characteristics[a]

Variable		Summary statistics
Age, years		49 (SD 6)
Sex	Male	72 (73%)
	Female	26 (27%)
	Total	98 (100%)
IL28	CC	21 (23%)
	CT	65 (70%)
	TT	7 (8%)
	Total	93 (100%)
HCV viral load IU/ml	2 291 335 (758 209–4 303 728)	
HCV genotype	1a	61 (65%)
	1b	33 (35%)
	Total	94 (100%)
Previous response to HCV therapy	Breakthrough	6 (7%)
	Relapse	27 (30%)
	Null response	37 (41%)
	Partial response	21 (23%)
	Total	91 (100%)
Degree of liver fibrosis	F1	36 (38%)
	F2	11 (11%)
	F3	16 (17%)
	F4	33 (34%)
	Total	96 (100%)
% CD4	37.65 (29–999.9)	
CD4 count, cells/mm^3	674 (510–946)	
HIV viral load	25 (19–37)	

IL28, interleukin 28; HCV, hepatitis C virus.
[a] Results are reported as the arithmetic mean (standard deviation, SD), number (column percentage), or median (interquartile range).

4-week lead-in period; in the cirrhotic patients this response was worse (20 patients; 61%).

The decrease of 1 log HCV RNA at week 4 was associated with a higher rate of SVR; nevertheless, those patients who did not show a decrease of 1 log HCV RNA during this period had a very low SVR rate (17%). The positive predictive value (PPV) of achieving SVR in the group of patients with a response at 4 weeks was 84%; the PPV was lower in cirrhotic patients (70%).

Similarly, the 8-week response (decrease ≥2 log or HCV RNA undetectable at week 8 of therapy) was related to SVR; 66% of patients who had this response achieved SVR (PPV 73%). Of most importance at this point is the negative predictive value (100%); no patient without a response at 8 weeks achieved SVR.

Table 2
Sustained virological response (SVR) rate according to baseline characteristics and HCV RNA evolution during treatment

Variable		SVR, *n* (%)	*p*-Value
Sex	Male	47 (65)	0.4673[a]
	Female	19 (73)	
IL28	CC	14 (67)	0.1291[b]
	CT	45 (69)	
	TT	2 (28)	
HCV genotype	1a	40 (65)	0.4776[a]
	1b	24 (72)	
Previous response to PEG-IFN/RBV therapy	Breakthrough	5 (83)	0.0842[b]
	Relapse	23 (85)	
	Partial response	14 (66)	
	Null response	21 (57)	
Previous null response	No	42 (73)	0.0328[a]
	Yes	21 (57)	
Cirrhosis	No	48 (76)	0.0141[b]
	Yes	18 (51)	
Response at 4 weeks (HCV RNA decrease ≥1 log)	No	10 (17)	<0.0001[a]
	Yes	56 (81)	
Response at 8 weeks (HCV RNA undetectable or decrease ≥2 log)	No	0 (0)	0.0002[b]
	Yes	66 (72)	
Early response (HCV RNA undetectable at weeks 8 and 12)	No	56 (64)	0.0964[b]
	Yes	10 (91)	

IL28, interleukin 28; HCV, hepatitis C virus; PEG-IFN/RBV, pegylated interferon/ribavirin.
[a] Chi-square test.
[b] Fisher's exact test.

The simple logistic regression analysis identified three factors that were significantly associated with the achievement of SVR: previous response to PEG-IFN/RBV therapy (no null response vs. null response), 4-week response, and absence of cirrhosis. In this study, no positive relationship was found between SVR and sex, IL28b, or genotype 1 subtype (Table 3).

In the multiple model, the following factors remained independently associated with SVR: a good response at 4 weeks (vs. not presenting such a response, odds ratio (OR) 9.50, 95% CI 3.12–28.95; $p = 0.0001$) and the absence of cirrhosis (vs. cirrhosis, OR 3.22, 95% CI 1.05–9.89; $p = 0.0407$).

3.3. Safety

Seventy-six patients completed the assigned treatment schedule. Twelve patients discontinued treatment at week 12 of therapy due to the futility rule established in the protocol; this represents 55% of patients who prematurely stopped the therapy. The second reason for ending the study drugs was toxicity (six patients). Two other patients discontinued at weeks 8 and 12 of their own volition. One patient stopped after receiving a diagnosis of metastatic hepatocellular carcinoma and one patient was lost at week 36 of follow-up.

Adverse events (AEs) were very frequent; 93% of patients presented at least one AE, but the mean was seven AEs per patient. Most AEs were mild and known to be related to PEG-IFN/RBV and BOC therapy (flu-like symptoms, asthenia, neuropsychiatric symptoms, hematological toxicity, dysgeusia, and rash).

Due to hematological toxicity, the dose of RBV was decreased in 45% of patients and the dose of PEG-IFN was decreased in 23% of patients. No difference in the SVR rate was seen between patients who completed the whole therapy and those who needed a dose modification. Overall, 20% of patients required treatment with erythropoietin and 14% with G-CSF; two patients received transfusions. Regarding the degree of liver fibrosis, no more AEs were observed in cirrhotic patients; however, the need to reduce the dose of PEG-IFN and to use erythropoietin or drugs to treat dermatological toxicities was significantly greater in these patients.

Twenty-seven serious AEs (SAEs) were reported in 19 patients; these led to therapy discontinuation in six patients. The most frequent SAEs were hematological (thrombocytopenia, $n = 5$; neutropenia, $n = 8$; anemia, $n = 3$). SAEs were most frequent in patients with cirrhosis (30% vs. 13%, $p = 0.0358$).

4. Discussion

This appears to be the first phase III trial with BOC in HIV–HCV co-infected patients. The results of this study showed that RGT with BOC plus PEG-IFN/RBV achieved high rates of SVR in patients with a prior treatment failure. This was most evident in patients who had previously relapsed or had a breakthrough to PEG-IFN/RBV, who showed a SVR rate of up to 80%. On the other hand, the response was moderate in previously null responders. These results are in line with those reported in recent studies on the retreatment of HCV monoinfected patients,[14] and in series in co-infected patients.[18]

Data on RGT to re-treat HCV in HIV co-infected patients are scarce. A recent study in 21 patients showed good results with this strategy,[20] although most of the patients were treatment-naïve (71%) and no prior partial or null responders were included in that study, unlike the present one.

Table 3
Variables related to a sustained virological response (SVR)

Variable		Crude OR	(95% CI)	*p*-Value (simple model)	Adjusted OR	(95% CI)	*p*-Value (multiple model)
Sex	Female	1		0.9138			
(*n* = 83)	Male	0.94	(0.33–2.68)				
IL28	CC	1		0.2235			
(*n* = 79)	CT	1.22	(0.39–3.81)				
	TT	0.25	(0.04–1.77)				
HCV genotype	1a	1		0.7226			
(*n* = 80)	1b	1.20	(0.44–3.28)				
Cirrhosis	No	2.19	(1.38–3.49)	0.0106	3.22	(1.05–9.89)	0.0407
(*n* = 83)	Yes	1			1		
Previous null response	No	1		0.0266			
(*n* = 83)	Yes	0.34	(0.13–0.88)				
Early response	No	1		0.1964			
(*n* = 83)	Yes	4.08	(0.48–34.48)				
Response at 4 weeks	No	1		<0.0001	1		0.0001
(*n* = 83)	Yes	10.07	(3.43–29.57)		9.50	(3.12–28.95)	
Response at 8 weeks	No	1		-			
(*n* = 78)	Yes	1.00	-				

OR, odds ratio; CI, confidence interval; IL28, interleukin 28; HCV, hepatitis C virus.

In agreement with other studies,[7,14,16,17,21,22] the 4-week response was the best marker to determine the likelihood of SVR. Also, the lack of an 8-week response identified patients who did not benefit from this treatment, and allowed therapy discontinuation at this point. If the predictive value of this marker is confirmed in other studies, it could eventually change the futility rule from12 weeks to 8 weeks.

It is important to emphasize that only one patient relapsed in the short arm of RGT, showing that a shortened treatment duration in patients with a good initial response is safe and effective.

Patients with advanced liver disease, who usually have a mild response,[23–25] also achieved a satisfactory rate of SVR.

Although the safety profile was poor and a high number of AEs were reported, all of them have been described previously,[7,14,16,23,26] most were mild, and only six patients discontinued treatment for this reason. Cirrhotic patients did not report more AEs or interruptions of therapy compared to non-cirrhotic patients in this study, unlike those published by other authors.[24,25] However, cirrhotic patients in the present study had more SAEs and required more drug dose modifications and use of adjuvant therapy. Therefore, these patients should be followed closely to complete the therapy scheme and achieve a good response.

By trial design, SVR was determined at 24 weeks after the end of therapy. In fact three patients relapsed after 12 weeks of follow-up, which shows that according to this approach, the determination of SVR at 24 weeks may be more useful than at 12 weeks.

The most important limitation of this study is the lack of a control group. Phase III studies are often randomized with a group receiving the standard treatment; however, very difficult to treat HIV–HCV co-infected patients were included, for whom treatment options are limited. In this population, the use of a control group would have been difficult to justify from an ethical point of view because response rates to the PEG-IFN/RBV scheme are low. Finally, it is agreed that with the advent of interferon-free therapy , the treatment regimen evaluated herein has been rendered obsolete. However, these newer drugs are not available for all patients. Based on the high efficacy obtained in this study, especially in prior relapsers, it is believed that the scheme of RGT with BOC + PEG-IFN/RBV is a good therapeutic and cost-effective alternative in countries where new antiviral HCV drugs are not available.

In conclusion, response-guided therapy with boceprevir in combination with PEG-IFN/RBV leads to adequate SVR rates in HCV genotype 1 patients who are previous non-responders or relapsers to PEG-IFN/RBV therapy. The therapy was generally well tolerated.

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