Addition of boceprevir to PEG-interferon/ribavirin in HIV-HCV-Genotype-1-coinfected, treatment-experienced patients: efficacy, safety, and pharmacokinetics data from the ANRS HC27 study

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Isabelle Poizot-Martin[1,2,*], Eric Bellissant[3,4], Rodolphe Garraffo[5], Philippe Colson[6,7], Lionel Piroth[8], Caroline Solas[9,10], Alain Renault[3,4], Marc Bourlière[11], Philippe Halfon[12], Jade Ghosn[13,14], Laurent Alric[15], Alissa Naqvi[16], Patrizia Carrieri[2,17], Jean-Michel Molina[18] for the ANRS HC27 BOCEPREVIH Study Group.

1. Aix-Marseille University, AP-HM Sainte-Marguerite, Service d'Immuno-Hématologie Clinique, Marseille, France
2. INSERM, UMR 912 (SESSTIM), Marseille, France.
3. Rennes 1 University, Pontchaillou University Hospital, Service de Pharmacologie, Rennes, France
4. INSERM, CIC 1414 Clinical Investigation Centre, Rennes, France
5. Nice University, Pasteur University Hospital, Laboratoire de Pharmacologie et de Toxicologie Médicale, Nice, France
6. Aix-Marseille University, AP-HM Timone, Fédération de Microbiologie Hospitalière, Marseille, France
7. URMITE, UM63, CNRS 7278, IRD 198, INSERM 1095, Marseille, France.
8. Bourgogne University, Bocage University Hospital, Département d'Infectiologie, UMR 1347, Dijon, France
9. Aix-Marseille University, AP-HM Timone, Service de Pharmacocinétique et Toxicologie, Marseille, France
10. INSERM, UMR 911 (CRO2), Marseille, France
11. AP-HM Saint-Joseph, Service d'Hépato-Gastro-Entérologie, Marseille, France
12. European Hospital, Marseille, France
13. Paris Descartes University, PRES Sorbonne Paris-Cité, EA 7327, Paris, France.

14. Paris-Sud University, AP-HP Bicêtre Hospital, Service de Médecine Interne, Le Kremlin-Bicêtre, France
15. Toulouse 3 University, Purpan University Hospital, Service de Médecine Interne, Toulouse, France
16. Nice University, Archet University Hospital, Service d'Infectiologie, Nice, France
17. ORS PACA, Observatoire Régional de la Santé Provence-Alpes-Côte d'Azur, Marseille, France
18. Paris 7 - Denis Diderot University, AP-HP Saint-Louis Hospital, Service des Maladies Infectieuses et Tropicales, Paris, France

***Corresponding author's address:** Service d'Immuno-hématologie Clinique, CHU Sainte Marguerite, 270 Boulevard de Sainte Marguerite, 13009 Marseille, France. Phone: + 33.4.91.74.61.63; isabelle.poizot@mail.ap-hm.fr.

Running title: Boceprevir in HIV/HCV-coinfected relapsers

Abbreviations:

PEGylated-interferon (PEG-IFN); ribavirin (RBV); sustained virological response (SVR); HCV-genotype-1 (HCV-G1); direct acting antiviral drug (DAA); boceprevir (BOC); atazanavir combined with ritonavir (ATV/r); abacavir (ABC); emtricitabine (FTC); lamivudine (3TC); raltegravir (RAL); tenofovir (TDF).

Abstract

Background: Scarce data exist on the efficacy and safety of the PEGylated-interferon/ribavirin/boceprevir regimen in HIV/HCV-coinfected patients who failed to respond to PEGylated-interferon/ribavirin treatment.

Objectives: To evaluate the efficacy and safety of this drug regimen .and the impact of the addition of boceprevir(BOC) on atazanavir(ATV) or raltegravir(RAL) pharmacokinetic parameters in a subgroup of patients.

Methods: In this single-arm phase 2 trial, HIV-1/HCV-genotype-1-coinfected patients received PEGylated-interferonα2b(1.5µg/kg/week)+ribavirin(800-1400mg/day) alone until W4 and with BOC(800 mgTID) until W48. Based on virologic response at W8, the three drugs were stopped or PEGylated-interferon/ribavirin was continued alone until W72. The primary endpoint was SVR at W24 off-therapy (SVR_{24}).

Results: 64 patients were included. SVR_{24} was achieved in 53% of patients ($CI_{90\%}$: 43-63%) and in 90% of previous relapsers. In univariate analysis, SVR_{24} was associated with response to previous HCV-treatment, HCV-1b subtype, HCV-RNA decline, ribavirin-C_{trough} at W4, and HCV-RNA at W8 but not to fibrosis score, *IL28B* genotype, or boceprevir-C_{trough} at W8. In multivariate analysis, SVR_{24} remained associated with response to previous HCV-treatment [non-responders versus null-responders: OR= 5.0(1.3-20.0); relapsers versus null-responders: OR= 28.8(4.9-169.5)]. HCV treatment was discontinued for adverse events in 17% of patients. A 51% decrease in ATV/r-AUC_{0-8h} ($p < 0.01$) and a 57% increase in RAL-AUC_{0-8h} ($p < 0.01$) were observed, although atazanavir/r or raltegravir did not affect BOC-AUC_{0-8h} significantly. The ATV mean $C_{through}$ fell from 763.8 ng/mL (CI 95%: 230.3-1297.3) without BOC to 507.7 ng/mL (CI 95%: 164-851.4) with BOC.

Conclusions: Boceprevir-based regimen demonstrated a high SVR24 rate in treatment-experienced HIV-HCV genotype 1 coinfected relapsers.

Keywords: HIV/HCV coinfection; HCV retreatment; boceprevir; direct acting antiviral drug.

Introduction

With the use of last generation direct active antiviral (DAA) drugs, the majority of HCV monoinfected and HIV/HCV coinfected patients will hopefully be cured [1], and in the majority of cases, with an interferon-free regimen. However, interactions between DAA and antiretroviral drugs remains an issue for HCV/HIV coinfected patients, and to date, access to interferon (IFN)-free regimens remains limited in many parts of the world. The objective of the ANRS HC27-BOCEPREVIH trial was to evaluate the efficacy and safety of the NS3 HCV protease inhibitor boceprevir (BOC) in combination with PEG-IFN/RBV in HIV/HCV-G1-coinfected patients who failed to respond to PEG-IFN/RBV. This trial included a pharmacokinetic sub-study evaluating the drug interaction between BOC and ritonavir-boosted atazanavir (ATV/r) or raltegravir (RAL) in order to further investigate previous observations in healthy volunteers regarding HIV protease inhibitors and to elucidate this issue with the integrase inhibitor RAL[2].

Methods

Study design

This single-arm, multicenter, open-label, phase 2 trial, enrolled HIV-1/HCV-G1 coinfected patients who had previously failed a treatment with PEG-IFN (α-2a or α-2b)/RBV (≥ 600 mg/day) during < 12 weeks. Other inclusion criteria included stable (> 3 months) antiretroviral therapy with at least three drugs (among which abacavir, emtricitabine, lamivudine, tenofovir, ATV or ATV/r, and RAL), CD4 cell count > 200 /mm^3 and > 15%, and HIV-RNA < 50 copies/mL for at least 6 months. The primary exclusion criteria were HBV coinfection, Child-Pugh score B or C, and history of decompensated cirrhosis. Virological failure to previous therapy was classified as relapse, (i.e., undetectable HCV-RNA at end of treatment and detectable HCV-RNA thereafter), breakthrough (i.e., undetectable HCV-RNA at least once during treatment, becoming detectable thereafter under treatment), and non-response including partial-response (i.e., > 2 $\log_{10}$ HCV-RNA decline at W12 and still detectable HCV-RNA at W24) and null-response (i.e., <2 $\log_{10}$ HCV-RNA decline at W12). The fibrosis score

was documented by a liver biopsy. Inclusion of non-cirrhotic null-responders was limited to 34% of patients. Cirrhotic patients with a previous null-response were excluded. The study protocol (EUDRACT number 2010-023450-36) was approved by Ethical Committee *CPP-Sud-Méditerranée-1 (*Marseille, France) and the French Regulatory Authority *ANSM* (previously *Afssaps*, Paris, France). The protocol was registered in the ClinicalTrials.gov database under reference NCT01335529. It was conducted in compliance with the Declaration of Helsinki and ICH-GCP guidelines. All participants provided written informed consent.

Procedures

All patients received a lead-in phase with PEG-IFNα-2b/RBV during 4 weeks. BOC was added at the end of W4 (Figure 1). Total treatment duration was defined according to a patient's status regarding rapid virological response (RVR) at the end of W8 (RVR_8). A complete RVR_8 was defined as HCV-RNA < 15 IU/mL and a partial RVR_8 as HCV-RNA between 15-1000 IU/mL. For patients with complete RVR_8, total treatment duration was 48 weeks; SVR was evaluated at W72 (SVR_{24}). For patients with partial RVR_8, BOC was stopped at W48 but PEG-IFN/RBV was maintained for a total of 72 weeks, and SVR_{24} was evaluated at W96. A dosage of 800mg BOC was prescribed (in 200 mg capsules) 3 times per day (7-9 hour interval between intakes) during meals. PEG-IFN (1.5 µg/kg) was administered subcutaneously once a week. Oral RBV was given at 800-1400 mg/day (weight-based) BID during meals. Erythropoietin (EPO), granulocyte-colony-stimulating factor (G-CSF) and thrombopoietin-receptor (TPO-R) agonists were allowed. Blood transfusions and RBV dose reduction were allowed only if EPO failed to maintain a hemoglobin concentration above 100 g/L. Futility rules for BOC were defined as an HCV-RNA > 1000 IU/mL at W8 or W12. For these patients, PEG-IFN/RBV was maintained until W72, and SVR_{24} was evaluated at W96. BOC, PEG-IFN and RBV were interrupted if HCV-RNA was > 100 IU/mL at W16, if HCV-RNA was still detectable at W28 or at any time in the case of virological breakthrough.

We defined virological breakthrough as confirmed HCV-RNA detection after prior undetectability. All non-responders (failure or breakthrough) received follow-up until W72 or W96 depending on the

HCV-RNA at W8. Virological relapse was defined as HCV-RNA undetectable at EOT, then detectable at the end of follow-up, without evidence of new HCV reinfection.

Virological analysis

HCV-RNA was quantified on site by real-time-PCR assays using RealTime-HCV (Abbott Diagnostics) or COBAS TaqMan-HCV (Roche Diagnostics) assays (lower limits of detection (LLD) of 12 and 15 IU/mL, respectively) and carried out by the same laboratory and assay throughout the study. For virological response assessment, detectable HCV-RNA was defined as HCV-RNA > 15 IU/mL. Detectable HCV-RNA below LLD was considered positive with a value equal to LLD. Genotypic drug resistance testing was performed for all patients with virological failure, breakthrough, or relapse post-treatment. HCV-RNA was extracted from 200 µl serum with the EZ1-Virus Mini Kit v2.0 using the BioRobot EZ1 Workstation (Qiagen) following the manufacturer's instructions. PCR amplification and direct population sequencing of the full-length HCV-*NS3* protease gene were performed using in-house protocols as described previously [3]. Amino-acid diversity was analyzed at sites associated with reduced susceptibility to BOC. HIV-RNA was measured with RealTime-HIV (Abbott Diagnostics) or COBAS TaqMan-HIV (Roche Diagnostics) assays. HIV viral load (VL) was considered detectable at > 50 copies/mL. A blip in HIV viral load was defined as a positive detectable HIV viral load lower than 1000 copies/mL becoming undetectable in a next measurement performed after a delay of 4 weeks.

IL28B genotype (SNP rs12979860) was determined in all patients using peripheral blood mononuclear cell DNA by Sanger population sequencing [4, 5].

Pharmacokinetic analysis

Plasma RBV-C_{trough} was determined at W4 using a high performance liquid chromatography-diode array detector (HPLC-DAD). A pharmacokinetic (PK) sub-study evaluating the drug interaction between BOC and ATV/r, or BOC and RAL was planned in a sub-group of 30 patients. Blood samples were collected at baseline for antiretroviral (ARV)and at W8 for both ARV and BOC. BOC-C_{trough} was

determined by a liquid-chromatography tandem-mass spectrometry method. PK parameters [C_{max}, C_{trough} and the area under the curve ($AUC_{à\text{-}!h}$)] were determined at steady-state based on the PK profiles obtained with blood samples drawn at 0 (before ARV ± BOC intake), 1, 2, 3, 4, 6 and 8 h during an 8-hour interval after intake of drugs with a standardized meal. PK analysis was performed by a non-compartmental method (PK fit Software, Montpellier, France). The reported C_{max}, T_{max} and C_{trough} are the values observed in individual PK profiles. Statistical analyses were performed by comparing mean PK parameters at baseline and W8 for ARV, and with historical data of BOC alone for BOC. Patients were classified according to RBV-$C_{trough\text{-}W4}$ and BOC-$C_{trough\text{-}W8}$ to evaluate the impact on SVR_{24}. A 2 µg/mL threshold was chosen for RBV according to the minimum recommended C_{trough} reported under PEG-IFN/RBV [6]. Because no efficacy threshold was established for BOC-C_{trough}, the cut-off was set at the median value observed in our study (127 µg/L).

Safety analysis

Adverse events (AE) were graded by investigators according to the "ANRS-scale to grade the severity of adverse events in adults". Non-life threatening AEs were managed by means of a dose reduction of PEG-IFN or RBV similarly to those previously described [7, 8]. Monthly monitoring of HIV-VL during BOC exposure was initiated in March 2012 associated with ATV-C_{trough} measurement at screening, at W48, or in case of HCV- or HIV-breakthrough, according to FDA and EMEA recommendations. An independent data and safety monitoring board regularly evaluated the safety and side-effects of study regimens.

Statistical analysis

The primary efficacy endpoint was SVR_{24} rate measured at W72 or W96 according to treatment duration. The analysis of the main endpoint was performed with a test comparing an observed to a theoretical proportion conducted in unilateral formulation with a type I error of 5%. The rate of SVR_{24} below which the therapy would have no interest was fixed at 20% (null hypothesis). The rate of SVR_{24} above which the therapy would bring a real benefit was fixed at 35% (alternative hypothesis). To

guarantee 90% power to detect such a 15% benefit and considering the statistical hypotheses, a minimum of 22 (out of 77) participants with a SVR_{24} were required to conclude that SVR rate is above 20%. An intent-to-treat analysis was performed for all patients who initiated treatment. Cases of missing data for the primary endpoint were considered treatment failures. Secondary efficacy endpoints included RVR_8 and SVR_{12}. Safety endpoints included treatment-emergent AEs, laboratory abnormalities and deaths. Anemia and HCV- and HIV- breakthroughs were cautiously monitored. Data are presented as counts and percentages, or median and inter-quartile range (IQR), as appropriate. Association of baseline characteristics with SVR_{24} as well as pharmacological data (RBV-$C_{trough\text{-}W4}$, BOC-$C_{trough\text{-}W8}$) were analyzed using Wilcoxon, Chi^2 or Fisher's exact tests with a significant threshold of $p < 0.05$. Multivariate analysis was subsequently conducted using a logistic regression model. For this analysis, continuous variables were broken into two classes on the basis of their median values, except for pharmacological data, where the threshold was optimal (i.e., optimizing sensitivity and specificity). Statistical analyses were performed using SAS statistical software (version 9.4;Cary, NC, USA).

Results

Sixty-nine patients were screened from May 2011 to April 2012, 64 patients were enrolled and started PEG-IFN/RBV, and 62 patients started BOC after the lead-in phase. The analysis was performed on these 64 patients (Fig. 1). The baseline characteristics of patients are presented in Table 1. Most were men (75%), with a median age of 49 years, most were infected with HCV-G1a (78%), and 39% had severe fibrosis or cirrhosis. The HCV viral load was more than 800,000 IU/mL in 77% of cases and *IL28B* CT/TT genotypes were detected in 64%. Thirty-three percent of patients were previous null-responders, and 31% were relapsers. Half were treated with 2 NRTI+ATV/r, 42% with 2 NRTI+RAL and 8% with other authorized ART combinations. Among NRTIs, 92% were treated with tenofovir + emtricitabine. HIV-VL was detectable in 2 patients treated with an ATV/r-based regimen (60 and 176 copies/mL, respectively) and in 1 patient treated with an RAL-based regimen (80 copies/mL). For

these 3 patients, HIV-VL was undetectable at screening and at W4, and remained undetectable throughout the follow up.

Efficacy

Sixty-two patients reached W4 (fig 1). At this time, one patient achieved undetectable HCV-RNA, while 28 patients (44%) had an HCV-RNA decrease $\geq$ 1 $\log_{10}$. Sixty-one patients reached W8, of whom 26 had a complete RVR_8 and were assigned to continue PEG-IFN/RBV/BOC until W48. The rate of RVR_8 was 27.3% among cirrhotic patients versus 24.5% among patients without cirrhosis. A partial RVR_8 was observed in 21 patients and was re-evaluated at W12, and 14 participants had to stop BOC and continue PEG-IFN/RBV until W72. All of these 14 patients stopped the three drugs before W20 because of AE in one case, lack of efficacy in 7 and patient's decision in 6. At W12, twenty patients with partial RVR_8 had a partial response and were assigned to PEG-IFN/RBV/BOC until W48 and then to PEG-IFN/RBV until W72. However, 14 patients stopped the treatment before W72 because of AE in four cases, lack of efficacy in 2, breakthrough in 6 and patient's decision in 2. One patient had to stop BOC and continue PEG-IFN/RBV until W72, but he decided to stop PEG-IFN/RBV before W16. No patient died after the EOT.

Overall, thirty-seven patients (58%) discontinued treatment either before (n = 3) or after (n = 34) W8, due to AEs in 11 patients (17%), virological breakthrough in 7 (11%), lack of efficacy in 9 (14%), patient's decision in 9 (14%; 7 before W16), and investigator's decision in 1. Thus, 27 patients (42%) terminated the study protocol.

SVR_{24} was achieved in 34/64 patients (53%; 90% CI: 43%-63%; p = 0.002), including 7 patients who stopped HCV treatment prematurely following AEs (n = 5) or patient/investigator's decision (n = 2), and was similar to SVR_{12}. The SVR_{24} rate was 90% in relapsers and 79% in patients with HCV-G1b. Table 2 shows SVR_{24} according to baseline characteristics, virological response at W4 and at W8, RBV-$C_{trough\text{-}W4}$ and BOC-$C_{trough\text{-}W8}$. Among baseline characteristics, response to previous treatment,

RAL-based regimen, HCV-G1b, HCV-RNA < 6.4 log_{10} and HOMA > 2.5 were significantly associated with virological outcome. HCV-RNA decrease ≥ 1 log_{10} at W4, HCV-RNA < 15 IU/mL at W8 and RBV-C_{trough} ≥ 2 µg/mL at W4 were also significantly associated with virological outcome. In multivariate analysis, response to previous treatment was the only significant variable associated with SVR_{24} for previous non responders versus null-responders (OR 5.0; CI: 1.3; 20.0) and for relapsers versus null-responders (OR 28.8; CI: 4.9; 169.5).

Resistance

The full-length HCV-*NS3* protease gene was sequenced for 13 patients out of 23 who stopped treatment after HCV breakthrough, partial response, or patient's/investigator's decision. Eleven were infected with HCV-G1a. Clinically relevant amino-acid substitutions, absent at baseline, were detected in 7 patients (Table 3). They included mostly R155K and V36M/A, and substitutions T54A and T54S were observed in 1 case each. V36A, T54A and R155K were concurrently detected in HCV-G1a from 1 patient.

Pharmacokinetics

The median RBV-C_{trough} was 1.70 µg/mL (IQR: 1.39; 2.13) and was not significantly different (p = 0.36) between patients who achieved SVR_{24} and those who did not: 1.75 µg/mL (IQR: 1.39; 2.66) versus 1.70 µg/mL (IQR: 1.45; 1.91), respectively. However, 72.2% of patients who achieved SVR_{24} had a, RBV-C_{trough} up to 2 µg/mL versus 27.8% of patients who did not (p = 0.03). The median BOC-C_{trough} was 127 µg/L (IQR: 104; 308) and was not significantly different (p = 0.40) between patients who achieved SVR_{24} or not: 163 µg/L (IQR: 100; 458) versus 125 µg/L (IQR: 104; 255), respectively. Moreover, 52.4% of patients who achieved SVR_{24} had a BOC-C_{trough} up to 127 µg/L versus 47.6% of patients who did not achieve SVR_{24} (p = 0.63).

Twelve patients (10 males) fully completed the PK study, 7 on ATV/r and 5 on RAL, associated with

tenofovir + emtricitabine (Table 4). A decrease in ATV/r-$AUC_{0\text{-}8h}$ of 51% ($p < 0.01$) and an increase in RAL-$AUC_{0\text{-}8h}$ of 57% ($p < 0.01$) were observed at W8. ATV and RAL-C_{trough} were, respectively, 34% and 54% lower after initiation of BOC, but these variations did not reach statistical significance and the values remained above target concentrations for both drugs. ATV/r or RAL did not significantly affect BOC-$AUC_{0\text{-}8h}$, compared with historical controls [9]. Variations in BOC-C_{trough} and C_{max} were observed when associated with ATV/r or RAL, but they did not reach statistical significance.

Safety

AEs, dose modifications, and study drug discontinuation are summarized in Supplementary Tables 1 and 2. The AEs most commonly observed were asthenia and flu-like symptoms. Grade 4 AEs occurred in 20 patients and included leukoneutropenia (6%), infections (6%), anemia (3%) and general disorders (3%). Although they were more frequent in patients with a severe fibrosis score, such events were observed in 23.8% and 22.2% of patients with F0/F1 and F2 fibrosis score, respectively."Eleven (17%) patients discontinued treatment due to an AE. Four suspected unexpected serious adverse reactions (SUSAR) were reported. Two participants experienced sepsis, one had a generalized rash, and the other experienced acute pyelonephritis. All resolved. The two cases of sepsis were considered as strongly related to PEG-IFN even when they were observed under the combination of PEG-IFN/RBV and BOC. The investigator and sponsor considered those events as possibly related to study medication. No death occurred. Three patients reported anemia as a serious AE (SAE) but did not discontinue the study. Most patients with anemia received EPO (38 patients) or had a PEG-IFN or RBV dose reduction (in 2 and 13 patients, respectively), and 8 received a transfusion. G-CSF was administered to 7 patients for neutropenia. Two patients discontinued the study drug because of neutropenia (neither was infection-related) or thrombocytopenia.

During BOC exposure, 6 patients (ATV/r- and RAL-based regimen, n = 3 each) presented with one blip of HIV-VL, but no HIV breakthrough was observed. The median CD4 cell count decreased in absolute value from 728/mm^3 [527-923] to 452/mm^3 [301-639] at W48, but this value increased in percentage from 36% (IQR: 30-42) to 41% (IQR: 35-45). At W96, the percentage of CD4 cells

returned to baseline (35%; IQR: 31-40) but remained lower in absolute value (641/mm^3 (483-895).

Discussion

In this trial, the addition of BOC to PEG-IFN/RBV in HIV/HCV-coinfected patients who previously failed PEG-IFN/RBV led to an SVR_{24} rate of 53%, quite similar to that observed in both naive HCV-monoinfected (59 to 66%) and HIV/HCV-coinfected (63%) patients [10, 11]. More interestingly, the SVR_{24} rate reached 90% in patients who had previously relapsed after PEG-IFN/RBV therapy and 61% in patients with previous partial response. These rates are higher than those observed in previously treated HCV-monoinfected patients (up to 75% and 52%, respectively) [10].

Interestingly, among 28 patients with a decrease in HCV-RNA < 1 $\log_{10}$ at W4, addition of BOC allowed for the achievement of SVR_{24} in 21 (75%) cases. Moreover, patients with undetectable HCV-RNA at W8 were shown to have an SVR_{24} rate of 88.5%, including 2 patients who stopped treatment prematurely (at W26 and W29) following AEs. Thus, patients who had an early response could benefit from shorter treatment. This hypothesis is consistent with recent reports of a response-guided shortening of BOC-based tri-therapy in HIV/HCV-coinfected patients [12]. However, the design of this study did not allow us to assess this hypothesis.

The limited impact of *IL28B* polymorphism was already described in naive coinfected patients treated with BOC[10]. As already reported, patients with HCV-G1 subtype 1b tended to achieve slightly higher SVR rates, as well as relapsers and previous partial-responders compared to other patients [13]. The fact that the SVR_{24} was significantly higher among patients with insulin resistance confirms that the negative predictive factors previously determined for PEG-IFN/RBV therapy are no longer relevant with DAA. In contrast, some differences in SVR rates were observed among ART regimens (higher in patients treated with an RAL-based regimen = 70%), but patients were not randomized according to their cART regimen. Moreover, this result could be explained by a higher proportion of null-responders among patients treated with ATV/r-based regimen (41% versus 22%).

We report a significant impact of RBV-$C_{trough\text{-}W4}$ on SVR_{24}, confirming that a threshold of ≥2 µg/mL remains crucial for optimizing the virological response to an RBV-based therapy. In contrast, BOC-$C_{trough\text{-}W8}$ did not appear significantly to affect the rate of SVR_{24}. This could be explained by the large pharmacokinetic variability of BOC observed among our patients.

Twenty patients (33%) reported at least one SAE, and 17% discontinued treatment following an AE. Furthermore, no drug interactions occurred and the observed safety was consistent with previous reports [10, 11]. Similar to the CUPIC study [14], the rate of SAE was higher in patients with severe fibrosis. Significant hematological toxicity resulting in treatment withdrawal was observed in only 2 patients (3%), as a result of a proactive management of anemia (59% of patients). The prevalence and distribution of amino-acid substitution detected in 7 patients were similar to those previously reported [3].

A few sets of ART regimens were allowed in this trial because data on BOC-ART interactions were not available at the beginning of the study. Nevertheless, no HIV breakthrough was observed. The results of our PK sub-study are consistent with observations made in healthy volunteers. A trend towards lower ATV exposure when combined with BOC, with a significant AUC reduction, was observed. This was neither significant nor clinically relevant, as ATV-C_{trough} still remained largely above the 200 ng/ml recommended threshold. However, even though ATV-C_{trough} remained largely above the 200 ng/ml recommended threshold and we did not observe any HIV virological failure, our data suggest careful HIV RNA monitoring in patients receiving combinations of BOC with ATV/r. The substantial variability in RAL-PK parameters also suggest the need for careful monitoring of tolerance, even if we did not observed related adverse events in our trial. There was also a substantial variability in RAL-PK parameters without any clinical significance. Pending more data, we suggest careful HIV-RNA monitoring in patients receiving combinations of BOC with ATV/r and, to a lesser extent, RAL.

There are several limitations to this trial. First, it is a non-randomized trial with a small sample size. Concerning the PK study, we could not include the number of planned patients. Finally, only 27

patients (42%) completed the study according to the protocol, with a high number of discontinuations due to patient's decision.

In conclusion, addition of BOC to PEG-IFN/RBV for HIV/HCV-coinfected patients who previously failed PEG-IFN/RBV led to an SVR_{24} rate of 53%, but this group included up to 90% in patients who previously relapsed after PEG-IFN/RBV therapy. Severe adverse events were reported in 20 patients and were more frequent in patients with severe fibrosis, and proactive management of anemia should be performed for patients administered this therapeutic combination. The pharmacological data justify maintaining a close monitoring of HIV-VL for patients treated with an ATV/r-based regimen, and a shorter regimen might be considered for patients with RVR_8. Such a therapeutic option might be considered in countries where treatment of hepatitis C infection with the newer direct-acting antiviral drugs remains difficult because of the lack of availability, as recently emphasized [15].

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Table 1: Baseline demographics and clinical characteristics

	N (%), n=64
Age, year, median [IQR]	49 [46-52]
Gender, Male	48 (75%)
Ethnicity, Non-Black	61 (95%)
IVDU	47 (73%)
BMI ≥25 Kg/m^2	18 (28%)
Response to previous HCV-treatment	
Relapse	20 (31%)
Breakthrough	5 (8%)
Partial response	18 (28%)
Null-response	21 (33%)
CDC stage C	14 (22%)
CD4, cells/mm^3, median [IQR]	728 [527-923]
Nadir <200/mm^3	35 (55%)
HIV-RNA <50 copies/mL	61 (95%)
Antiretroviral treatment	
2 NRTIs*+ATV/r	32 (50%)
2 NRTIs+RAL	27 (42%)
Other **	5 (8%)
HCV-genotype	
1a	50 (78%)
1b	14 (22%)

	N (%), n=64
HCV-RNA, log IU/mL, median [IQR]	6.4 [5.9-6.7]
HCV-RNA >800 000 IU/mL	49 (77%)
HOMA (n=54), median [IQR]	3.2 [1.9-6.2]
> 2.5	36 (67%)
IL28B-genotype (n=63)	
CC	22 (35%)
CT	31 (49%)
TT	10 (16%)
Fibrosis score	
F0/F1	21 (33%)
F2	18 (28%)
F3	14 (22%)
F4	11 (17%)

* NRTIs: TDF+FTC=57; ABC+3TC=2;

** Other ART regimens: TDF+ATV/r+RAL=2; FTC+ATV/r+RAL=1; TDF+FTC+ATV/r+RAL=1; TDF+FTC+ATV+RAL=1

Data are n (%) unless otherwise specified.. IQR = Inter Quartile Range. IVDU = Intra-Venous-Drug-Use. BMI = Body-Mass Index. HCV = Hepatitis C Virus. CDC = Center for Diseases Control. NRTI = Nucleoside Reverse Transcriptase Inhibitor. ABC = abacavir. ATV = atazanavir. ATV/r = ritonavir- boosted atazanavir. FTC = emtricitabin. 3TC = lamivudin. RAL = raltegravir. TDF = tenofovir. HOMA = Homeostasis Model Assessment. IL28B = Interleukin-28B.

Table 2: SVR_{24} rate according to baseline characteristics, week 4 and week 8 virological responses, ribavirin C_{trough} at week4 and BOC C_{trough} at week8

		SVR_{24} n=34	No SVR_{24} n=30	p-value*
Age	< 50 years	19 (52.8%)	17 (47.2%)	0.9497 (a)
	≥ 50 years	15 (53.6%)	13 (46.4%)	
Gender	Male	24 (50.0%)	24 (50.0%)	0.3855 (a)
	Female	10 (62.5%)	6 (37.5%)	
Ethnicity	Black	2 (66.7%)	1 (33.3%)	1.0000 (b)
	Non-black	32 (52.5%)	29 (47.5%)	
IVDU	Yes	23 (48.9%)	24 (51.1%)	0.2642 (a)
	No	11 (64.7%)	6 (35.3%)	
BMI	< 25 Kg/m^2	23 (50.0%)	23 (50.0%)	0.4232 (a)
	≥ 25 Kg/m^2	11 (61.1%)	7 (38.9%)	
Response to previous HCV-treatment	Relapse	18 (90.0%)	2 (10.0%)	<0.0001 (b)
	Breakthrough	0 (0.0%)	5 (100.0%)	
	Partial response	11 (61.1%)	7 (38.9%)	
	Null-response	5 (23.8%)	16 (76.2%)	
CDC stage	A/B	26 (52.0%)	24 (48.0%)	0.7332 (a)
	C	8 (57.1%)	6 (42.9%)	
CD4, cells/mm^3	< 350	3 (60.0%)	2 (40.0%)	1.0000 (b)
	≥ 350	31 (52.5%)	28 (47.5%)	
Antiretroviral treatment (n=59)	2 NRTIs + ATV/r	13 (40.6%)	19 (59.4%)	0.0223 (a)
	2 NRTIs + RAL	19 (70.4%)	8 (29.6%)	

		SVR_{24}	No SVR_{24}	p-value*
		n=34	n=30	
HCV-genotype	1a	23 (46.0%)	27 (54.0%)	0.0309 (a)
	1b	11 (78.6%)	3 (21.4%)	
HCV-RNA, log IU/mL	< 6.4	21 (65.6%)	11 (34.4%)	0.0451 (a)
	≥ 6.4	13 (40.6%)	19 (59.4%)	
HOMA (n=54)	≤2.5	5 (27.8%)	13 (72.2%)	0.0209 (a)
	>2.5	22 (61.1%)	14 (38.9%)	
IL28B-genotype (n=63)	CC	12 (54.5%)	10 (45.5%)	0.7897 (a)
	CT	15 (48.4%)	16 (51.6%)	
	TT	6 (60.0%)	4 (40.0%)	
Fibrosis score	F0-F2	22 (56.4%)	17 (43.6%)	0.5107 (a)
	F3-F4	12 (48.0%)	13 (52.0%)	
HCV-RNA decrease at	< 1 log	13 (38.2%)	21 (61.8%)	0.0038 (a)
W4 (n=62)	≥ 1 log	21 (75.0%)	7 (25.1%)	
HCV-RNA-W8	Undetectable	15 (93.8%)	1 (6.3%)	0.0002 (a)
	Detectable	19 (39.6%)	29 (60.4%)	
RBV-C_{trough}-W4 (μg/mL)	< 2	17 (41.5%)	24 (58.5%)	0.0296 (a)
(n=59)	≥ 2	13 (72.2%)	5 (27.8%)	
BOC-C_{trough}-W8 (μg/L)	< 127	9 (45.0%)	11 (55.0%)	0.6365 (a)
(n=41)	≥ 127	11 (52.4%)	10 (47.6%)	

Chi-square test (a) or Fisher exact test (b) Data are n (%) unless otherwise specified; IVDU = Intra-Venous-Drug-Use. CDC = Center for Diseases Control. NRTI = Nucleoside Reverse Transcriptase Inhibitor. ATV/r = ritonavir-boosted atazanavir. RAL = raltegravir. HCV = Hepatitis C Virus. HOMA = Homeostasis Model Assessment. RBV = ribavirin. BOC = Boceprevir

Table 3: Resistance profile in patients with virological failure

Patient	Response to previous treatment	HCV Genotype	Baseline Mutations	Time of failure	log HCV RNA (IU/mL)	Emerging Mutations	Reason for therapy discontinuation
1	Null responder	1a	WT	W12	7,41	V36M, R155K	Patient's decision
2	Null responder	1a	WT	W16	7,12	V36M, R155K	Virologic failure
3	Null responder	1a	WT	W8	6,39	V36V/M, R155R/T/K	Virologic failure
4	Breakthrough	1a	WT	W8	5,57	V36V/A, T54T/A, R155R/K, I170I/V	Virologic failure
5	Null responder	1a	WT	W8	5,88	R155K	Patient's decision
6	Null responder	1a	WT	W8	6,36	V36V/M	Virologic failure
7	Null responder	1b	WT	W28	6,7	T54S, A56S, I170V	Virologic failure

All patients had wild type at baseline.

WT = wild type.

Table 4 : Pharmacokinetic parameters of ritonavir-boosted atazanavir, raltegravir and boceprevevir

	$AUC_{0\text{-}8h}$ (µg/L.h)	p-value	C_{trough} (µg/L)	p-value	C_{max} (µg/L)	p-value
ATV/r -BL	13212 ± 6620	<0.01	764 ± 754	NS[2]	2413 ± 1514	NS[2]
ATV/r -W8 with BOC[1]	6533 ± 3178		508 ± 486		1418 ± 793	
RAL –BL	5901 ±6167	<0.01	338 ± 348	NS[2]	1387 ± 1478	NS[2]
RAL-W8 with BOC[1]	9249 ±3032		154 ± 115		3556 ± 1408	-
BOC-W8 with ATV/r[3]	4170 ± 1048	NS[2]	154 ± 89.2	NS[2]	1315 ± 458	NS[2]
BOC-W8 with RAL[3]	5310 ± 2643	NS[2]	118 ± 79.5	NS[2]	1040 ± 574	NS[2]

[1] ATV/r and RAL mean PK parameters were compared between baseline and W8

[2] NS: not statistically significant; BL: Baseline

[3] BOC mean PK parameters were compared with published data [29].

Figure 1: Flow chart