Boceprevir for Previously Treated HCV-HIV Coinfected Patients: The ANRS-HC27 BocepreVIH Trial

P-N4

Isabelle Poizot-Martin[1,2], Eric Bellissant[3,4], Philippe Colson[5,6], Alain Renault[3,4], Lionel Piroth[7], Caroline Solas[8,9], Marc Bourlière[10], Rodolphe Garraffo[11], Philippe Halfon[12], Jean-Michel Molina[13,14] And the ANRS HC27 BOCEPREVIH Study Group.

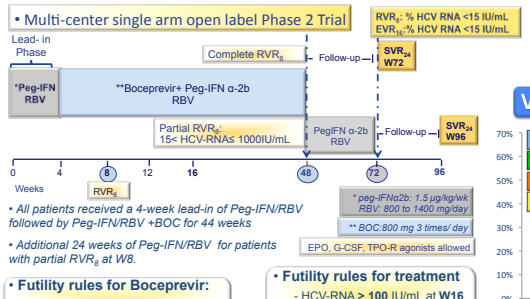
1-Aix Marseille University, APHM Sainte-Marguerite, Service d'Immuno-hématologie clinique, Marseille, France. 2- Inserm U912 (SESSTIM) Marseille, France. 3- Rennes 1 University, Rennes, France. Rennes University Hospital, Department of Clinical Pharmacology, Rennes, France. 4- INSERM 0203 CIC-P Clinical Investigation Centre, Rennes, France. 5-Aix Marseille University, AP-HM Timone, Fédération de Microbiologie Hospitalière, Marseille, France. 6- URMITE UM 63 CNRS 7278 IRD 198 INSERM 1095, Marseille, France. 7-Infectious Diseases Department, University Hospital, Dijon, France. 8-Aix Marseille Univ, APHM Timone, Service de Pharmacocinétique et Toxicologie, Marseille, France. 9- CRO2 INSERM U911, Marseille, France. 10-Service d'Hépato-Gastro-Entérologie, Hôpital Saint- Joseph, Marseille, France, 11-Faculty of Medecine of Nice, Hôpital Pasteur, Laboratoire de pharmacologie, Nice, France. 12-Hôpital Européen, Marseille, France. 13-Infectious Diseases Unit, Assistance Publique Hôpitaux de Paris (AP-HP) - Saint-Louis Hospital , Paris, France. 14-Paris VII - Denis Diderot University, Paris, France.

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Background

- Previous trials in HCV genotype 1 mono-infected patients [1-3] and in naive HCV/HIV- co-infected patients[4] have clearly demonstrated that addition of BOC to peg-IFN/RBV significantly increases sustained virological response rate (SVR).
- We report the SVR12 virological response rate and tolerance data for the HIV-HCV genotype 1 coinfected patients who previously failed peg-IFN/RBV and were enrolled in the ANRS-HC27 BOCEPREVIH Trial.
- As a significant drug interaction between BOC and ritonavir (rtv) in combination with atazanavir (ATV) was reported in healthy volunteers[5], patients treated with ATV/r were monitored with a monthly plasma HIV viral load measurement during BOC exposure. ATV Ctrough was also determined at screening, W48, or in case of HCV or HIV breakthrough. The PK sub-study performed in this trial pointed out a trend towards a lower ATV PK parameters only significant for AUC and a substantial variability in RAL PK parameters with a trend towards higher RAL AUC 0-8h. BOC PK was slightly affected [6].

Study Design



• Futility rules for Boceprevir:
HCV-RNA > 1000 IU/mL at W8 or W12
➡ **Peg-IFN/RBV 72 weeks**- SVR_{24} W96

• Futility rules for treatment
- HCV-RNA **> 100** IU/mL at **W16**
- HCV RNA **detectable** at **W28**
- HCV **breakthrough since W12**

Main eligibility criteria

- **Main inclusion criteria**
  - Patients ≥ 18 years, with body weight ≥ 40 Kg and ≤ 125 Kg,
  - Chronic HCV genotype 1,
  - HIV-1 co-infection,
  - Previous virological failure after ≥ 12 weeks PegIFN+RBV≥ 600 mg/day
  - Stable ART for at least 3 months, with at least three molecules among: **ATV* (rtv boosted or not)**, RAL, TDF, ABC, FTC, 3TC
  - CD4 ≥ 200 cells/mm³ (≥ 15%)
  - HIV-RNA< 50cp/mL ≥ 6 months,
  - liver biopsy ≤ 3 years or cirrhosis on any previous biopsy
- **Main exclusion criteria**
  - HBV coinfection, HIV-2 infection
  - Child B-C cirrhosis, past history of decompensated cirrhosis,
  - **Previous Null Response with cirrhosis**

Patients

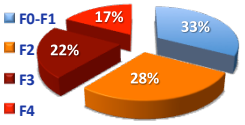
Patients' Characteristics at Baseline	N (%)/ Median [IQR], n= 64
Age, years	49 [46- 52]
Male	48 **(75%)**
IDU	47 **(73%)**
BMI ≥ 25 Kg/m²	18 (28%)
CDC stage C	14 (22%)
CD4, cells/mm³	**728** [527- 923]
HIV-RNA <50 copies/ml	61 **(95.3%)**
2 NRTIs*- ATVr	32 **(50%)**
2 NRTIs- RAL	27 **(42%)**
Other**	5 (8%)
HCV **genotype 1a**	50 **(78%)**
HCV-RNA, log IU/mL	6.4 [5.9-6.7]
IL28*** CC/CT/TT	22/ 31/ 10
HCV-RNA > 800 000 IU/mL	48 **(75%)**
Relapse	20 (31%)
Breakthrough	5 (8%)
Partial response	18 (28%)
Null-response	21 **(33%)**

*** NRTIs: TDF+ FTC (TVD): n=57 (89%); **Other cART regimen:** TDF+ ATV/r+ RAL= 2; TVD+ ATV/r + RAL= 1; TVD+ ATV + RAL= 1; FTC+ ATV/r + RAL= 1; *** Missing data for one patient

• Sixty nine patients were screenend and **sixty four were enrolled** but **only sixty two patients started boceprevir after the lead-in phase** (treatment was stopped for SAE in one case and for patient's decision in the other one).

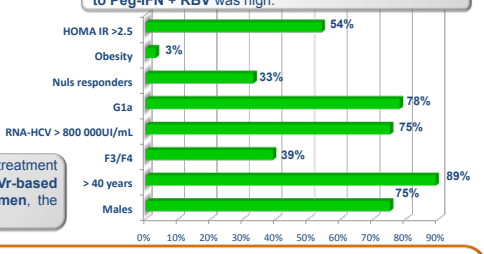
Patients' characteristics according cART	ATV/r n= 32	RAL n= 27	Others n= 5
Previous response			
Relapse	6 (19%)	**13 (48%)**	1 (20%)
Breakthrough	4 (13%)	1 (4%)	0
Partial Response	9 (28%)	7 (26%)	2 (40%)
Null response	**13 (41%)**	6 (22%)	2 (40%)
Fibrosis stage			
F0-F1	8 (25%)	11 (41%)	2 (40%)
F2	12 (38%)	6 (22%)	0
F3	9 (28%)	4 (15%)	1 (20%)
F4	3 (10%)	6 (22%)	2 (40%)
HCV Subtype 1a	23 (72%)	22 (82%)	5 (100%)
IL28 CC**	11 (34%)	9 (35%)	2 (40%)
IL28 CT	14 (44%)	14 (54%)	3 (60%)
IL28 TT	7 (22%)	3 (12%)	0
HOMA IR >2.5*	18 (56%)	14 (52%)	4 (80%)

*Missing Data: ATV/r: n= 4 (13%); RAL: n= 5(19%);Others: n= 1 (20%)
** Missing data : RAL: n= 1 (4%)



• The rate of **null responders** to the previous treatment was **higher among patients treated with ATVr-based** regimen (41%) whereas in **RAL-based regimen**, the rate of **relapser was higher** (48%).

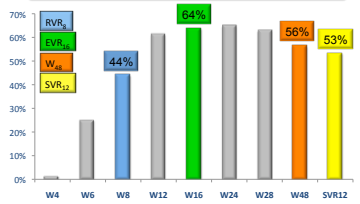
• At baseline, prevalence of **predictive negative factors to Peg-IFN + RBV** was high.



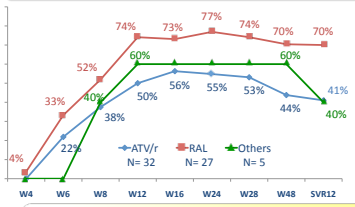
Results

• The W8-VL was <15 IU/mL in 26 patients, between 15 and 1000 IU/mL in 21 and >1000 in 17.
• The **W12 SVR** was achieved in **34/64 patients** (53%) including 7 patients who stopped prematurely HCV treatment for AE or patient/ investigator's decision. The W12 SVR seemed to vary according to **ART regimen, previous response, HCV subtype** but not to fibrosis stage nor IL28 polymorphism.
• **During BOC exposure, 6 patients** (3 with ATVr - and 3 with RAL-cART based regimen) presented **one blip of HIV VL**. **No case of HIV breakthrough or death** was observed at this time of analysis.

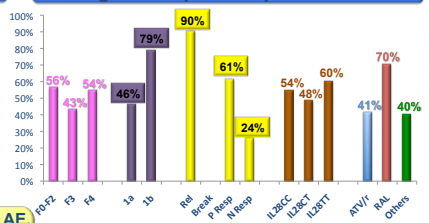
Virological Response (ITT n=64)



%HCV RNA <15UI according to cART



Virological Response by characteristics



Patients status according to previous response

	Relapse N = 20	Breakthrough N = 5	Partial response N = 18	Null response N = 21	All N = 64
SVR12	18*(90%)	0	11** (61 %)	5 (24%)	34 (53%)
Relapse	0	0	0	0	0
Breakthrough	0	2 (40%)	0	5 (24%)	7 (11%)
Virological failure	0	2 (40%)	3 (17%)	4 (19%)	9 (14%)
Treatment stopped for AEs:	2 (10%)	1 (20%)	1 (6%)	2 (10%)	6 (9%)
SAE	*1*	*1*	*1*	*1*	*4*
AEs	*1*	*0*	*0*	*1*	*2*
Treatment stopped for Patient'decision	0	0	3 (17%)	5 (24%)	8 (13%)

• * included patients who stopped treatment for 2 SAE (W29, W37), 1 AE (W26) and 1 patient's decision (W46)
•** included patients who stopped treatment for 1 SAE (W68), 1 AE (W50) and 1 investigator's decision (W52)

SAE (grade 4) according to fibrosis score

	F0/F1	F2	F3	F4
Number of SAE: n= 32	**6**	**4**	**10**	**12**
General Disorders				6
Cholecystis	1			
Acute pancreatitis		1		
Depression				1
Pneumonia		1		
Pyelonephritis				2
Abcess/ cellulitis			1	
Septicemia	1			
Pulmonary Hypertension	1			
Vaso vagal episode			1	
Gastro intestinal bleeding			1	
ASAT/ALAT elevation	1			
GGT elevation		1	4	
Hypophosphoremia		1		
Anemia (<7g/dL)			1	2
Neutropenia (<750/mm³)	1		2	1
Thrombopenia (<20 G/L)	1			

• **20 patients presented at least one grade 4 AE.**
• **10 patients stopped HCV treatment for AEs:** infections in 3(5%), general disorders in 4(6%), acute pancreatitis in 1, neutropenia in 1 and thrombopenia in 1.

Haematological toxicity management

	Number of patients
EPO use	38
RBC Transfusion	8
RBV dose reduction	9
GCSF use	7
PegIFN dose reduction for grade 3/4 thrombocytopenia	3

Resistance

• Full-length HCV NS3 protease gene was sequenced by Sanger population sequencing from serum samples of **13 patients exhibiting virological failure on BOC+PR, among whom 11 (85%) were infected with HCV-1a.**
• **Clinically-relevant BOC-resistance** associated amino acid substitutions were detected in serum samples from **7 patients (54%),** whereas they were **absent at baseline**. **Six of these 7** patients were infected with HCV of **subtype 1a.**

36	54	55	155	156	170	HCV Genotype	HCV RNA (LogUI/mL)	Reason for discontinuous therapy	Response to previous treatment
V	T	V	R	A	I				
M	T	V	K	A	I	1a	7,41	Patient's decision	Nul responder
M	T	V	K	A	I	1a	7,12	Virological failure	Nul responder
V/M	T	V	R/T/K	A	I	1a	6,39	Virological failure	Nul responder
V/A	T/A	V	R/K	A	I/V	1a	5,57	Virological failure	Breakthrough
V	T	V	K	A	I	1a	5,88	Patient's decision	Nul responder
V/M	T	V	R	A	I	1a	6,36	Virological failure	Nul responder
V	S	V	R	S	V	1b	6,7	Virological failure	Nul responder

The amino acid substitutions included mostly R155K (in 5 cases (38%); both wild-type and mutant amino acids were observed in 2 cases) and V36M or A (in 4 cases and 1 case, respectively; both wild-type and mutant amino acids were observed in 3/5 cases).

Conclusion

W12 SVR rate was similar to that described in previously treated patients with chronic HCV-1-monoinfection[3] (SVR rate: 59 to 66%; SVR rate among patients with prior relapse (69% to 75%). Discontinuation for AE was low in this trial.

Reference
1. F Poordad et al., N Engl J Med 2011;364:1195-1206;
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5. http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm#sa 8 february 2012;www.ema.europa.eu/docs 16 february 2012
6. R Garraffo et al. 14th IWCPHT, Amsterdam 22-24 April 2013, Abstract 015.