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Boceprevir/Telaprevir-Based Therapy in HIV-Infection: Interim Analysis of a Multicenter Cohort

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ABSTRACT (updated)

BACKGROUND: Clinical trials on triple therapy against HCV infection including telaprevir (TVR) or boceprevir (BOC) plus pegylated interferon and ribavirin (PR) have reported considerably higher response rates than with PR alone. However, there is little information about the response to triple therapy used in clinical practice in these patients. This study was aimed to evaluate the efficacy and safety of triple therapy including TVR or BOC in HIV/HCV-coinfected patients in real-life conditions.

METHODOLOGY: HIV/HCV genotype 1-coinfected patients seen at 22 centers throughout Germany and Spain who received therapy including TVR or BOC plus PR and who had reached treatment week (TW) 4 were included in this study.

RESULTS: 183 patients have been included in this study so far: 84.2% were male, 71.1% were IL28B rs12979860 genotype CT or TT and 56.9% individuals presented cirrhosis. Infection with HCV genotype 1a was observed in 67.3% and 79.2% showed a baseline HCV RNA load >600000 IU/mL. The most commonly used ARV drugs were tenofovir/emtricitabine [117 (63.9%) patients], raltegravir [83 (45.4%)] patients) and boosted atazanavir [66 (36.1%) patients]. One-hundred and twenty-five (68.3%) patients had received previous HCV treatment: 27.3% had been null responders, 11.5% partial responders and 17.5% had relapsed. 151 (82.5%) subjects initiated treatment based on TVR and 32 (17.5%) on BOC. During therapy, proportions of patients with undetectable HCV RNA, according to the time-point of follow-up were 62.3% (114/183) at TW4, 74.4% (61/82) at TW8, 78% (128/164) at TW12, 70.9% (107/151) at TW24 and 68.9% (62/90) at TW48. 60 (32.8%) patients discontinued HCV therapy [24 (13.1%) because they fulfilled stopping rules, 19 (10.4%) individuals due to adverse events, 4 (2.2%) were lost to follow-up and 2 (1.1%) patients died, one of them due to hepatic decompensations]. Rash associated with TVR was observed in 16 cases (10.6%) and 57 (31.1%) individuals showed hemoglobin levels below 10mg/dl at some point of treatment. In an intention-to-treat analysis restricted to 78 patients who had a 60 week or longer follow-up after starting therapy, sustained virologic response 12 weeks after treatment discontinuation was observed in 50 (64.1%) patients. 5 (9.1%) out of 55 who had response at end of therapy and reached W12 after treatment relapsed.

CONCLUSIONS: Response rates to triple therapy with TVR or BOC plus PR in HIV/HCV-coinfected patients under real-life conditions, and therefore, including a high proportion of poor responders, pretreated patients and of subjects with cirrhosis, are near that found in naïve patients in clinical trials. The safety profile of BOC and TVR-based therapy is comparable to that shown in clinical trials.

BACKGROUND

- Treatment strategies aimed to achieve sustained virologic response (SVR) are of the highest priority in patients infected with HIV and hepatitis C virus (HCV). Until recently, therapy against HCV was based on pegylated interferon plus ribavirin (PR), however, in the setting of HIV/HCV genotype 1 (HCV-1)-coinfected patients, SVR rates to this regimen do not exceed 25% in the clinical practice.
- Considerable increases of SVR to triple therapy including the first generation HCV-protease inhibitors boceprevir (BOC) and telaprevir (TVR) in combination with PR have been observed in clinical trials and this triple regimen has become the standard therapy for HIV/HCV-1-coinfected patients[1,2]. However, the tolerability, the increased cost, pharmacologic interactions with antiretroviral therapy and the complexity of the treatment are issues of concern.
- Furthermore, data on safety and efficacy of PI-based therapy are mainly derived from clinical trials, which are highly selective, often fail to reflect patient management in the daily clinical routine and tend to lack difficult-to-treat individuals, such as those who failed previous treatment and who bear cirrhosis.
- Studies obtained in real-life settings are scarce[3] and include almost exclusively HCV-monoinfected patients. Remarkably, some of them have reported evidence of tolerability and efficacy of BOC and TVR-based treatment in the clinical practice being lower than observed in pivotal trials. However, the data are not consistent and information on response rates and safety profiles of DAAs in the HIV/HCV-coinfected population are urgently needed.

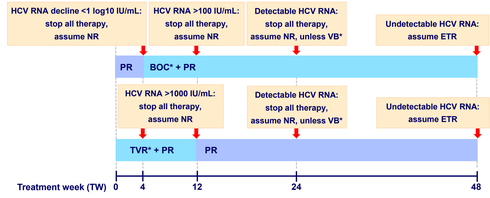
[1]Sulkowski M et al. Lancet Infect Dis 2013; 13: 597-605; [2]Sulkowski M et al. Ann Intern Med 2013; 159: 86-96; [3]Lacombe K et al. AIDS 2013; 27: 1356-1359.

OBJECTIVE

To evaluate the efficacy and safety of triple therapy including TVR or BOC in combination with PR in a multicenter population of HIV/HCV-coinfected patients under real-life conditions.

PATIENTS AND METHODS

- **Design:** Multicentric, international study (ClinicalTrials.gov: NCT02057003: RIS-HEP07).
- **Study population:** Patients who consecutively attended 22 health care centers throughout Germany and Spain and who fulfilled the following criteria:
  - ✓ Infection with HCV genotype 1.
  - ✓ Coinfection with HIV.
  - ✓ Initiation of triple therapy including BOC or TVR in combination with PR.
  - ✓ At least 4 weeks of follow-up.
  - ✓ Therapy not part of a clinical trial.
- **Dosing and scheduled treatment duration:**
  - ✓ BOC: 800 mg every 8 hours following a 4-week lead-in phase with PR alone.
  - ✓ TVR: 1125 mg every 12 hours or 750 mg every 8 hours during the first 12 weeks.
  - ✓ PR: 180 µg pegylated interferon α-2a once per week or 1.5 µg/kg α-2b once per week, respectively, plus 800-1200 mg oral ribavirin twice a day, during all therapy.
  - ✓ Scheduled treatment duration for all patients: 48 weeks.
- **Futility rules and definition of response to triple therapy (*Figure 1*):**



NR: no response; VB: virological breakthrough, defined as increase in plasma HCV-RNA by 1 $\log_{10}$ following a decline at any timepoint; requires discontinuation of all therapy. Relapse: detectable HCV-RNA following end-of-treatment response (ETR).

*5 patients received BOC without lead-in and 7 patients received TVR following a lead-in phase.

- **Statistical analysis:** Descriptive statistics were performed. The response during therapy was assessed for all patients who had reached the corresponding time point. SVR 12 weeks after the scheduled end of therapy (SVR12) was evaluated in an intention-to-treat analysis in the subgroup of patients who have reached week 60 of follow-up. The relationship between SVR12 and previous response, liver damage, HCV subtype and IL28B genotype was analyzed by means of the Chi-square test in a per-protocol analysis.

RESULTS

***Table 1*: Baseline characteristics of the study population, n=183**

Parameter	BOC (n=32)	TVR (n=151)
Age (years)*	46 (43-51)	48 (45-51)
Male gender, no. (%)	26 (81)	128 (85)
IL28B rs12979860 CT/TT, no. (%)‡	19 (68)	99 (72)
HCV subtype 1a, no. (%)#	15 (58)	88 (69)
Plasma HCV RNA >600 IU/µL, no. (%)	27 (84)	118 (78)
Cirrhosis, no. (%)¶	21 (75)	74 (53)
Liver stiffness	19.5 (11.7-25.7)	14.8 (10.2-26.5)
Platelets (cells/µL)	136 (90-217)	159 (102-205)
Albumin (g/dL)	4 (3.6-4.15)	4.1 (3.9-4.4)
Alanine aminotransferase, IU/mL*	56 (39-90)	63 (40-97)
Previous response to anti-HCV therapy		
Naives, no. (%)	14 (54)	44 (39)
Null responders, no. (%)	5 (16)	45 (29)
Partial responders, no. (%)	0	21 (14)
Relapsers, no. (%)	7 (22)	25 (17)
Other, no. (%)	6 (19)	16 (11)
CD4 cell count (mm^{-3})*	475 (351-661)	550 (373-716)
Undetectable HIV RNA , no. (%)	27 (84)	128 (84)
Tenofovir/emtricitabine, no. (%)	22 (69)	95 (63)
Ritonavir-boosted atazanavir, no. (%)	3 (9.4)	63 (42)
Raltegravir, no. (%)	21 (66)	62 (41)

*Median (interquartile range); ‡available in 166 patients; #available in 159 patients; ¶determined by liver biopsy (F=4 according to the Scheuer Index) or by transient elastometry (cut-off value: 14.6 kPa); available in 167 patients; null response: lack of 2 log10 decline of HCV RNA or below the detection threshold at treatment week 12; partial response: response at week 12 without achieving undetectable HCV RNA at week 24; relapse: undetectable HCV RNA at the end of treatment without reaching SVR.

A total of 151 (82%) patients initiated therapy including TVR: 40 (26.5%) received TVR bid and 7 (4.6%) had a lead-in phase. BOC was administered without lead-in in 5 (16%) individuals. An HCV RNA decline <1 log10 IU/mL after lead-in was observed in 12/34 (35%) individuals and 5 (4.3%) subjects presented undetectable HCV-RNA at this timepoint.

***Figure 2*: On-treatment response to triple therapy including BOC or TVR plus PR.**

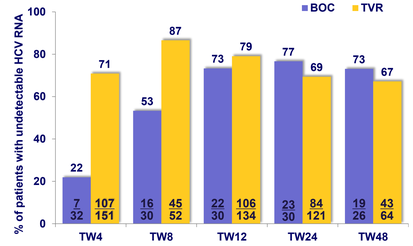
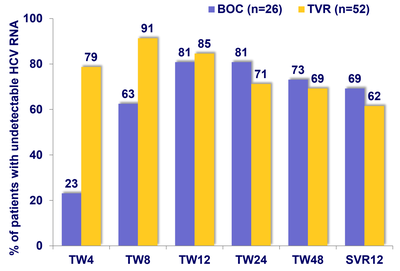


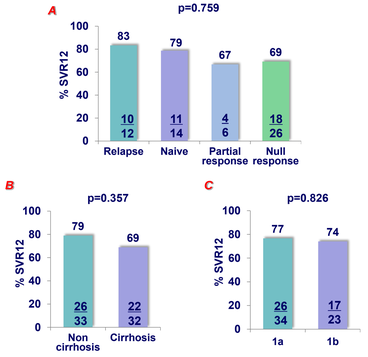
***Figure 3*: Intention-to-treat analysis of the response to treatment among those patients who have reached the SVR12 evaluation point (n=78). Intention-to-treat analysis.**



Overall SVR12: 50/78 (64.1%)

Five (9.1%) of the 55 patients who had ETR and reached the SVR12 evaluation point relapsed.

***Figure 4*: SVR12 rates according to prior response to PR (*A*), presence of cirrhosis at baseline (*B*) and HCV subtype (*C*). Per-protocol analysis.**



Sixty (32.8%) individuals stopped therapy before reaching TW48.

***Table 3*: Reasons for treatment discontinuation before the scheduled end of treatment.**

Event	BOC (n=32)	TVR (n=151)
Stopping rules	5 (16)	19 (13)
Discontinuation due to adverse events	2 (6.3)	17 (11)
Virological breakthrough	2 (6.3)	9 (6)
Voluntary drop-out	1 (3.1)	3 (2)
Death	1 (3.1)	1 (0.7)
- due to hepatic failure	1 (3.1)	0

***Table 4*: Main safety events observed among patients receiving BOC- or TVR-based triple therapy**

Event	BOC (n=32)	TVR (n=151)
Discontinuation due to adverse events	2 (6.3)	17 (11.3)
Hepatic decompensations	3 (9.4)	5 (3.3)
Rash (grade II-IV)	0 (0)	16 (10.6)
Anemia (< 10 mg/dL)	12 (37.5)	45 (29.8)
Neutropenia (<1000 cells/mL)	15 (47)	48 (32)
Thrombocytopenia (< 50000 cells/mL)	6 (18.8)	33 (21.9)
Blood transfusion	4 (12.5)	11 (7.3)
Use of erythropoietin	6 (18.8)	19 (12.6)

CONCLUSIONS

- Response rates to triple therapy with BOC or TVR plus PR in HIV/HCV-coinfected patients under real-life conditions, and therefore, including a high proportion of poor responders, pretreated patients and of subjects with cirrhosis, are close to that found in naïve patients in clinical trials.
- The safety profile of BOC and TVR-based therapy is comparable to that shown in clinical trials.

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