Pharmacokinetics of Dolutegravir and Rilpivirine in Combination with SMV/SOF

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Background

Anti-HCV treatment with direct-acting antivirals (DAAs)-based regimens is a priority in patients co-infected by HIV-1 and HCV with advanced liver disease.

With the availability of DAAs, drug-drug interactions (DDIs) became a relevant issue in the management of HIV/HCV patients eligible to anti-HCV treatment, especially when an HCV protease inhibitors(PI) in included in the antiviral regimen. Since many patients are burdened by a long history of antiretroviral therapy (ART), the therapeutic options may be limited in this setting. Moreover, advanced liver disease and liver cirrhosis may further limit treatment options, since due to less predictable pharmacokinetic increased toxicity may be possible.

Integrase inhibitors (InIs) are burdened by significant less DDIs than other antiretrovirals (ARVs) and the availability of dolutegravir (DTG), thanks to a higher genetic barrier and the lower probability of selecting resistance-associated variants, further increases the importance of this class in order to limit DDIs in ART-experienced patients. Among non-nucleosidic reverse transcriptase inhibitors (NNRTIs), rilpivirine (RPV) appear to be well tolerated and with few interactions with other drugs. Moreover, both of these molecules do not require adjustment in compensated advanced liver disease.

Thanks to its safety profile and the limited DDIs, the combination of DTG and RPV, with or without nucleos(t)idic reverse transcriptase inhibitors (NRTIs), represents an appealing regimen in these patients. However, no data are currently available on its efficacy in experienced patients nor on the pharmacokinetics of these molecules in concomitant DAAs-based treatment in patients with advanced liver disease.

Aim

To evaluate the plasma through concentrations of DTG and RPV used in combination with simeprevir (SMV) plus sofosbuvir (SOF) in HIV/HCV co-infected pts with advanced liver disease.

Methods

Patients co-infected with HCV and HIV-1, with advanced liver disease (defined as a METAVIR F3-F4 by transient elastography and/or liver biopsy) and on antiretroviral with DTG-RPV-including regimens therapy with HIV-RNA<50 copies/mL, who started anti-HCV treatment with SMV-SOF (with or without ribavirin) for 12 weeks were considered.

Demographic, clinical, biochemical and immuno-virological (regarding both HIV and HCV infection) were recorded at anti-HCV treatment baseline (BL), on treatment week 4 (W4), week 12 (EOT = end of treatment) and at post-treatment (PT) weeks 4 (PTW4), 12 (PTW12) and 24 (PTW24).

Plasma trough concentrations (C_{trough}) of antiretrovirals DTG and RPV and of DAAs SOF (as active metabolite GS-331007) and SMV were evaluated with a HPLC validated method[1] at BL (only DTG, RPV) and at on-treatment week 2 (W2) and week 4 (W4). Plasma HCVRNA and HIVRNA were determined using Abbott Molecular Real-Time PCR.

Patients' characteristics were described as median value (IQR) or frequency (%), as appropriate. Geometric means were calculated to summarize C_{trough} values.

Linear mixed-effect models were fitted to log10 transformed C_{trough} to assess changes over the first 4 weeks. From these models after back-transformation, 95% confidence intervals (CIs) around the geometric mean (GM) of C_{trough} of antiretrovirals DTG and RPV and of DAAs SOF and SMV were computed. The statistical analysis was performed using SAS software, release 9.2 (SAS Institute).

Results

Eleven patients were evaluated. The main demographic, clinical, biochemical and immunological characteristics at BL are summarized in Table 1.

Table 1. Main characteristics of the study patients

Age *years*	53 (52-54)
Gender *male*	8 (73%)
BMI *kg/m²*	24 (23-26)
Duration of HIV infection *years*	23 (22-25)
Time on antiretroviral therapy *years*	21 (19-23)
Liver stiffness *KPa*	19 (13-34)
History of liver decompensation	1 (9%)
Previous diagnosis of hepatocellular carcinoma	0
Child-Turcotte-Pugh score *B*	1 (9%)
ALT *U/L*	53 (43-90)
Bilirubin *mg/dL*	0.67 (0.51-1.18)
eGFR CKD-EPI *mL/min/1.73m²*	101 (79-105)
Platelet count *10⁹/L*	103 (60-136)
White blood cells *10⁹/L*	4.4 (3.9-5.6)
Haemoglobin *g/dL*	14 (12.3-15.2)
Albumin g/dL	4 (3.6-4.2)
INR	1.01 (0.97-1.18)
Pseudocholinesterases *KU/L*	4.1 (3.4-7.3)
CD4 count *cells/mcL* %	515 (357-722) 34 (25-40)
Nadir CD4 count *cells/mcL*	181 (109-326)
ARV regimens DTG+RPV DTG+RPV+NRTIs	 5 (45%) 6 (55%)
History of anti-HCV therapy naive relapser partial responder null responder	 4 (36%) 1 (9%) 2 (18%) 4 (36%)
HCVRNA *Log IU/mL*	6.15 (5.57-6.43)
HCV Genotype 1a 1b 4	 9 (82%) 1 (9%) 1 (9%)
Ribavirin included in anti-HCV regimen	8 (73%)

Geometric means (95%CI) of antiretrovirals and DAAs concentrations during the anti-HCV treatment are shown in Figure 1 and Figure 2: baseline (antiretrovirals only), week 2 and week 4 (*in black*), and overall data (*in red*) for each drug.

Figure 1. C_{trough} of RPV (A) and DTG (B)

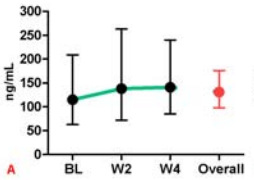
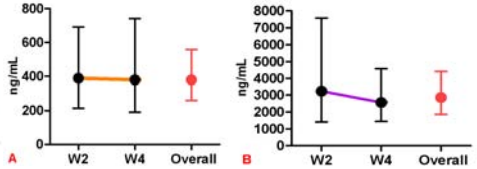


Figure 2. C_{trough} of GS-331007 (A) and SMV (B)



No significant changes were observed during the first 4 weeks in DTG and RPV C_{trough} (p=0.292 and p=0.523, respectively).

GS-331007 and SMV C_{trough} did not vary between week 2 and week 4 (p =0.636 and p=0.219, respectively).

The few available data from previous studies (blank line), in non-cirrhotic patients, are reported in the following table together with the results of our study (green line):

	RPV	DTG	GS-331007	SMV
Overall mean ±SD C_{trough} *ng/mL*	160 ±81	1808 ±1037	469 ±381	3820 ±2515
Previously reported C_{min} *ng/mL*	67 ±30[2] [mean ±SD]	1100 (45)[3] [mean CV%]	330 ±214[4] [mean ±SD]	1936 ±2640[5] [mean ±SD]

All patients completed the full course anti-HCV treatment. No serious adverse events were reported.

The rate of virological response to anti-HCV therapy and of HIV virological suppression and the absolute CD4 count with its relative change from BL are described in Figure 3, Figure 4 and Figure 5, respectively.

Figure 3. Virological response to anti-HCV therapy

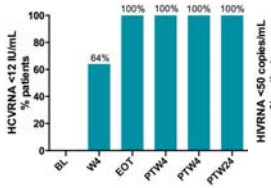


Figure 4. HIV virological suppression

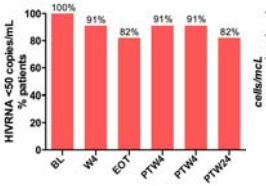
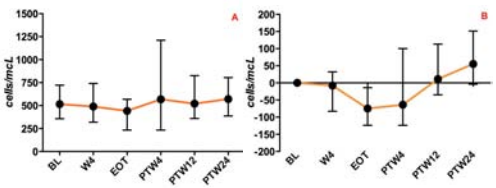


Figure 5. CD4 absolute count (A) and relative change from BL (B)



Conclusions

We presented the first data on the pharmacokinetics of dolutegravir plus rilpivirine-based antiretroviral regimen in patients treated with simeprevir plus sofosbuvir for chronic hepatitis C and advanced liver disease. Plasma concentrations of all the four antivirals are in the expected range, even though they tend to be slightly higher compared to those previously reported in non-cirrhotic patients. The advanced liver disease may influence plasma exposure of these drugs. On the contrary, dolutegravir and rilpivirine plasma exposure appeared not to be affected by concomitant DAAs-based therapy. Dolutegravir plus rilpivirine-based regimen appeared to be safe and effective in this group of experienced HIV-infected patients with advanced liver disease, even though it warrants further evaluations in larger samples of HIV/HCV co-infected subjects treated with DAAs.

[1]D'Avolio A, Baietto L, Siccardi M, et al. An HPLC-PDA method for the simultaneous quantification of the HIV integrase inhibitor raltegravir, the new nonnucleoside reverse transcriptase inhibitor etravirine, and 11 other antiretroviral agents in the plasma of HIV-infected patients. *Ther Drug Monit* 2008; 30(6):662-9. [2]Hoetelmans R, Kestens D, Marien K, et al. Effect of food and multiple dose pharmacokinetics of TMC278 as an oral tablet formulation. Abstract TuPe31B10. Presented at the Third International AIDS Society Conference on HIV Pathogenesis and Treatment; July 24–27, 2005; Rio de Janeiro, Brazil. [3] Tivicay US Prescribing Information, ViiV Healthcare, August 2013. [4] Bonora P, Torino Cohort, submitted. [5] FDA Antiviral Drugs Advisory Committee Meeting Briefing Document: Simeprevir. October 2013