Removal of Dolutegravir by Hemodialysis in HIV-Infected Patients with End-Stage Renal Disease

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Data on dolutegravir removal by hemodialysis are lacking. To study this, we measured dolutegravir plasma concentrations in samples of blood entering and leaving the dialyzer and of the resulting dialysate from 5 HIV-infected patients with end-stage renal disease. The median dolutegravir hemodialysis extraction ratio was 7%. The dolutegravir concentrations after the dialysis session remained far above the protein-binding-adjusted inhibitory concentration. Our results show minimal dolutegravir removal by hemodialysis, with no specific dolutegravir dosage adjustments required in this setting. (This study is registered at ClinicalTrials.gov under registration number NCT02487706.)

Progressive improvement in the life expectancy of HIV-infected patients after the introduction of combined antiretroviral therapy (cART) has been accompanied by an increase in the prevalence of other non-AIDS-defining comorbidities, including chronic kidney disease (CKD) (1, 2). Nowadays, CKD may be considered an epidemic among HIV-infected patients, and the number of patients with end-stage renal disease (ESRD) requiring hemodialysis as renal replacement therapy is increasing, especially among those of older age (1). HIV drugs differ in the extent of their removal from blood by hemodialysis, and separate dosing recommendations may be required (3).

Dolutegravir is an integrase inhibitor of HIV with demonstrated efficacy in naive and treatment-experienced HIV-infected patients (4–8). According to Weller et al. (9), no dolutegravir dosage adjustment is necessary for patients with severe renal function impairment (i.e., creatinine clearance, <30 ml/min). However, little is known about dolutegravir removal from plasma by hemodialysis. Our aim, therefore, was to evaluate the effect of hemodialysis on dolutegravir concentrations in HIV-infected patients with ESRD.

This study (registered at ClinicalTrials.gov under registration no. NCT02487706) was a single-center single-arm open-label pilot study in HIV-infected patients with ESRD undergoing routine hemodialysis. After enrollment (day 1), dolutegravir (Tivicay; ViiV Healthcare) at 50 mg once daily was added to their stable cART regimen for 5 days. Patients were told to take dolutegravir in the morning, separately from other drugs that might interfere with dolutegravir absorption (e.g., antacids, multivitamins, chelating agents, etc.). On day 5, blood samples were collected from each patient at the beginning and end of a dialysis session. Additionally, paired samples of blood entering (in) and leaving (out) the dialyzer and the resulting dialysate were collected 1 h after the start the dialysis session.

Blood samples were collected into 5-ml tubes containing potassium and EDTA. Plasma was isolated by centrifugation (3,200 × g for 15 min) and stored at –80°C until analysis. Dialysate samples (20 ml) were directly collected from the dialysate port of the dialyzer. Dolutegravir concentrations in both plasma and the dialysate were determined using high-performance liquid chromatogra-

phy-tandem mass spectrometry (LC-MS/MS) at the Department of Molecular and Clinical Pharmacology of the University of Liverpool, Liverpool, United Kingdom, according to a validated method. The method was linear over the range of 10 to 4,000 ng/ml (intra- and interday variation, <10%). The laboratory subscribes to the external quality assurance program organized by the Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology of Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

The hemodialysis extraction ratio (ER) for dolutegravir was calculated as (10): $ER (\%) = (C_{in} - C_{out})/C_{in} \times 100$, where C_{in} is predialyzer dolutegravir concentration (i.e., blood entering the dialyzer) and C_{out} is postdialyzer dolutegravir concentration (i.e., blood leaving the dialyzer).

Due to the high protein binding of dolutegravir, postdialyzer concentrations (C_{out}) were corrected for hemoconcentration by a factor F based on total protein (TP) concentration predialyzer (TP_{in}) and postdialyzer (TP_{out}) (10): $F = TP_{in}/TP_{out}$.

The trial was performed according to the stipulations of the Declaration of Helsinki, and the protocol was approved by the local ethics committee and by Spanish national regulatory authorities. Each participant gave written informed consent before being screened for eligibility criteria.

Five anuric HIV-infected patients, four men and one woman, undergoing routine hemodialysis thrice weekly were included in the study. The median (range) age and body weight were 53.0 years (41.3 to 69.5 years) and 77.1 kg (57.5 to 91.9 kg), respectively. Patients were known to be infected with HIV for a median

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TABLE 1 Dolutegravir concentrations during the dialysis session on day 5

Patient no.	Type of hemodialysis ^a	Dolutegravir concn (mg/liter) ^b			ER (%) ^c	Dolutegravir concn in plasma (mg/liter) ^d	
		<i>C</i> _{in}	<i>C</i> _{out}	Dialysate		<i>C</i> _{pre}	<i>C</i> _{post}
1	OL-HDF	0.47	0.98	0.02	1	0.48	0.86
2	Conventional	1.51	2.73	0.02	20	1.52	2.18
3	OL-HDF	1.90	3.90	0.03	7	1.62	2.77
4	Conventional	1.47	1.43	0.06	3	1.58	1.14
5	Conventional	2.13	2.59	0.04	25	2.90	2.52

^a OL-HDF, on-line hemodiafiltration.^b *C*_{in}, predialyzer concentration in plasma; *C*_{out}, postdialyzer concentration in plasma.^c ER, extraction ratio.^d *C*_{pre}, concentration in plasma at the beginning of the dialysis session; *C*_{post}, concentration in plasma at the end of the dialysis session.

of 14.1 years (7.1 to 20.5 years). The cART regimen included boosted protease inhibitors in three participants and nonnucleoside reverse transcriptase inhibitors in two participants. Additionally, four of the patients were receiving raltegravir at enrollment.

Conventional hemodialysis was used in three participants (Revaclear 400 capillary dialyzer; membrane area, 1.8 m²; BiCart bicarbonate cartridge; Gambro), while the two remaining participants underwent online hemodiafiltration (OL-HDF) (Polyflux 210H capillary dialyzer; membrane area, 2.1 m²; BiCart bicarbonate cartridge; Gambro). The Gambro Artis 230 V monitor was used for all participants. Each hemodialysis session lasted approximately 4 h. Blood flows were held constant at 300 ml/min for patients on conventional hemodialysis and at 400 ml/min for patients on OL-HDF. The dialysate flow was held constant at 500 ml/min for all participants.

Dolutegravir was well tolerated, and all participants completed the study. At the start of the dialysis session on day 5, the median (range) time after the last dolutegravir dose was 5.9 h (5.6 to 6.4 h). Table 1 summarizes dolutegravir concentrations in plasma and in the dialysate during the dialysis session. The median (range) hemodialysis extraction ratio was 7% (1 to 25%), with negligible dolutegravir concentrations in the dialysate. The dolutegravir concentrations in plasma at the end of the dialysis session remained at 34.1 times (13.4 to 43.2 times) the protein-binding-adjusted 90% inhibitory concentration (IC₉₀) against different strains of HIV, at 0.064 mg/liter (11).

The small differences between dolutegravir concentrations in plasma going in and coming out of the dialyzer machine, together with barely noticeable dolutegravir concentrations in dialysate in this study, suggest the minimal removal of dolutegravir by hemodialysis in HIV-infected patients with ESRD. These results are consistent with known physiochemical characteristics for dolutegravir. Dolutegravir is >99% bound to proteins in plasma and is minimally eliminated by the kidneys, with <1% of the dolutegravir dose excreted unchanged in the urine (11). Interestingly, no differences in dolutegravir extraction ratios were observed between patients undergoing conventional hemodialysis and those undergoing OL-HDF, even when OL-HDF combines diffusion with convection to enhance the removal of medium-molecular-weight substances (12).

Although the median dolutegravir extraction ratio was low, two patients exhibited a substantially higher extraction ratio. This finding might be explained by the reduced albumin-binding capacity present in some uremic patients (13), which in turn may lead to substantial changes in the free fraction of highly protein-

bound drugs, such as dolutegravir (6). Unfortunately, we were not able to confirm this hypothesis, since the free concentration of dolutegravir in plasma was not determined in this study.

In conclusion, based on the minimal extraction ratio of dolutegravir by hemodialysis, coupled with dolutegravir concentrations in plasma that were far above the protein-binding-adjusted IC₉₀ in this study, no dolutegravir dose adjustment seems to be necessary in HIV-infected patients with ESRD who are undergoing hemodialysis.

We declare no commercial or other conflicts of interest.

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