Minimal Removal of Raltegravir by Hemodialysis in HIV-Infected Patients with End-Stage Renal Disease[▽]

José Moltó,^{1†*} José Sanz-Moreno,^{2†} Marta Valle,³ Samandhy Cedeño,⁴ Jordi Bonal,⁵
Hanane Bouarich,⁶ and Bonaventura Clotet^{1,4}

Lluita contra la Sida Foundation, HIV Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain¹; Internal Medicine Department, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain²; Centre d'Investigació del Medicament, Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, Spain³; IrsiCaixa Foundation, HIV Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain⁴; Nephrology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain⁵; and Nephrology Department, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain⁶

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Little is known about raltegravir removal by hemodialysis in patients with end-stage renal disease (ESRD). We therefore measured raltegravir concentrations in plasma in pre- and postdialyzer blood samples from 2 ESRD HIV-infected patients. The hemodialysis extraction ratio and raltegravir hemodialysis clearance were 5.5% and 9.1 ml/min in patient 1 and 9.5% and 19.1 ml/min in patient 2, respectively. Our results suggest minimal raltegravir removal by hemodialysis with no specific raltegravir dosage adjustments required in HIV-infected patients undergoing hemodialysis.

The prevalence of chronic renal disease in HIV-infected patients has been estimated to be 5% to 40% (1, 6), depending on the definition applied in each study, and on the racial composition and comorbidity of the population studied. In any case, the progressive aging of the HIV-infected population together with the presence of some comorbid diseases (such as diabetes or hypertension), as well as direct toxicity derived from the antiretroviral drugs, provides a basis for growing concern that the prevalence of chronic renal disease and end-stage renal disease (ESRD) may increase in the future (8). This means that an increasing number of HIV-infected patients will need renal replacement therapy.

Raltegravir is an integrase inhibitor of HIV with demonstrated efficacy in naïve and treatment-experienced HIV-infected patients (5, 9). It is mainly metabolized by glucuronidation through UGT1A1 in the liver, with only 9% of the raltegravir dose excreted unchanged in the urine. Raltegravir is approximately 83% bound to plasma proteins, has a low molecular weight, and presents a relatively high solubility in water (blood-to-plasma partition coefficient, 0.6) (4). These characteristics make it possible for hemodialysis to remove raltegravir from plasma in patients with ESRD. As a result, subtherapeutic concentrations of raltegravir after the dialysis sessions might be possible.

Here we report two cases of ESRD HIV-infected patients undergoing routine hemodialysis who were receiving antiretroviral therapy with raltegravir. To evaluate the effect of hemodialysis on raltegravir clearance, predialyzer and postdialyzer blood samples were collected at the beginning and end of a single dialysis session. Both patients gave their oral informed consent before sampling.

Blood samples for raltegravir determinations were collected into potassium and EDTA-containing 10-ml tubes. Plasma was isolated by centrifugation ($3,200 \times g$ for 15 min) and stored at -20°C until analysis. Raltegravir concentrations in plasma were determined by high-performance liquid chromatography with a fluorescence detector (HPLC multifluorescence detector 2475; Waters) according to a validated method (7). Chromatographic separation was performed on a Sunfire C₁₈ column (5 μm ; 4.6 by 150 mm) (Waters). The mobile phase was phosphate buffer-acetonitrile (25 mM, pH 3). The fluorescence detector was set at 299 and 396 nm for excitation and emission wavelengths, respectively. The drug was extracted from plasma by liquid-liquid extraction with *tert*-butyl methyl ether. The method was linear over the range of 10 to 5,000 ng/ml, with quality controls at 840 ng/ml, 360 ng/ml, and 60 ng/ml. At least 98% of raltegravir was recovered at the three levels of concentration assessed. The intra- and interday coefficients of variation were less than 10%.

The hemodialysis extraction ratio (ER) for raltegravir was calculated at the beginning of the dialysis session as $\text{ER} = (C_{\text{in}} - C_{\text{out}})/C_{\text{in}}$ (2), where C_{in} is predialyzer raltegravir concentration in plasma (i.e., blood entering the kidney machine) and C_{out} is postdialyzer raltegravir concentration in plasma (i.e., blood leaving the kidney machine).

Raltegravir dialysis clearance (CL_{D}) in terms of plasma was calculated as $\text{CL}_{\text{D}} = \text{ER} \times Q_p$ (2), where Q_p is plasma flow through the dialyzer.

Because raltegravir is minimally distributed into red blood cells (4), correction for hematocrit was made according to the equation $Q_p = Q_b(1 - H)$ (2), where Q_b is the blood flow through the dialyzer and H is the patient's hematocrit.

Patient 1 was a 53-year-old man who was diagnosed with HIV infection in 1984. The patient had received multiple antiretroviral regimens and at the time of the study had been receiving therapy with nevirapine (200 mg twice daily) and raltegravir (400 mg twice daily) for the previous 6 months. HIV-1 RNA load in plasma was <50 copies/ml, and CD4^{+}

* Corresponding author. Mailing address: Fundació Lluita contra la SIDA, Hospital Universitari Germans Trias i Pujol, Ctra de Canyet s/n, 08916 Badalona, Barcelona, Spain. Phone: 34 93 497 88 87. Fax: 34 93 465 76 02. E-mail: jmolto@flsida.org.

† These two authors have contributed equally to this paper.

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TABLE 1. Raltegravir concentrations in plasma in pre- and postdialyzer samples during the hemodialysis session^a

Time and concn	Patient 1	Patient 2
Beginning of dialysis session		
TPD (h)	13.0	6.75
C _{in} (ng/ml)	655	337
C _{out} (ng/ml)	619	305
End of dialysis session		
TPD (h)	17.0	10.0
C _{in} (ng/ml)	211	186
C _{out} (ng/ml)	224	199

^a TPD, time postdose; C_{in}, predialyzer concentration; C_{out}, postdialyzer concentration.

T-cell count was 863 cells/mm³. His most relevant underlying diseases included hepatitis C virus (HCV) coinfection, hypertension, hyperlipidemia, and severe ischemic heart disease. The patient had ESRD and had been undergoing hemodialysis three times a week (Fresenius F8HPS) for the previous 2 years. Each hemodialysis session lasted approximately 4 h. On hemodialysis days, the patient delayed the morning raltegravir dose until the end of the dialysis session. Dialysate and blood flows were held constant at 500 ml/min and 300 ml/min, respectively.

Patient 2 was a 50-year-old man who was diagnosed with HIV infection in 1992. He had been receiving antiretroviral therapy with efavirenz (600 mg once daily) plus tipranavir-ritonavir (500/200 mg twice daily, respectively) and raltegravir (400 mg twice daily). HIV-1 RNA load in plasma was <50 copies/ml, and CD4⁺ T-cell count was 976 cells/mm³. He had been diagnosed with hypertension. The patient had been undergoing 4-hour hemodialysis sessions three times a week (Polyflux 17C). Dialysate and blood flows were 500 ml/min and 300 ml/min, respectively.

Table 1 summarizes raltegravir concentrations in plasma in pre- and postdialyzer samples at the beginning and end of the dialysis session. At the end of the session, raltegravir concentrations had decreased by 68% in patient 1 and by 45% in patient 2. However, the hemodialysis extraction ratio and raltegravir hemodialysis clearance were only 5.5% and 9.1 ml/min in patient 1 and 9.5% and 19.1 ml/min in patient 2, respectively. Both patients maintained raltegravir concentrations in plasma higher than the protein-binding-adjusted 95% inhibitory concentration of 15 ng/ml at the end of the dialysis session (M. Miller, M. Witmer, K. Stilmock, P. Felock, L. Ecto, J. Flynn, W. Schleif, G. Dornadula, R. Danovich, and D. Hazuda, presented at the 16th International AIDS Conference, 2006).

While raltegravir has some characteristics that might favor its removal by hemodialysis, the small differences between raltegravir concentrations in plasma in pre- and postdialyzer samples together with the low hemodialysis clearance of raltegravir observed in these two patients suggest minimal removal of raltegravir by hemodialysis in HIV-infected patients with

ESRD. Consistent with the results of Giguère et al. (3), raltegravir concentrations during the hemodialysis session decreased in both patients in this study. However, such a decrease can be explained by the hepatic metabolism of raltegravir rather than by its removal by the dialyzer machine.

In conclusion, our results show minimal removal of raltegravir by hemodialysis. Although therapeutic drug monitoring for HIV-infected patients with altered renal function is advised by current treatment guidelines, raltegravir dosage adjustments seem to be unnecessary in HIV-infected patients with ESRD undergoing hemodialysis.

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The authors declare no competing interests.

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