

## Case Report

# Removal of Raltegravir by Continuous Ambulatory Peritoneal Dialysis

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**Objective** : The dosage of raltegravir (RAL) is not increased in patients receiving hemodialysis, but the appropriate dosage for patients receiving peritoneal dialysis is unknown. To evaluate the therapeutic effect and dosage of RAL in a patient who was being introduced to continuous ambulatory peritoneal dialysis (CAPD), we investigated the RAL concentration in the plasma and peritoneal dialysate.

**Methods** : Plasma samples were sampled before dosing (0 h) and at 3 h after RAL dosing. The dialysate was also sampled, and the RAL concentrations were measured using high performance liquid chromatography.

**Results** : The RAL concentrations in plasma after the introduction of CAPD were reduced to about 1/4 the value before the introduction of CAPD. RAL was detected in the peritoneal dialysate at a concentration near that seen in the plasma after the introduction of CAPD. Nonetheless, the plasma HIV-1 RNA viral load after the introduction of CAPD was  $<4.0 \times 10^1$  copies/mL, and no reduction in CD4 was observed.

**Conclusion** : In this case, RAL exerted an antiviral effect when administered at the usual dosage, even after the introduction of CAPD.

**Key words** : raltegravir, continuous ambulatory peritoneal dialysis, removal, HIV, dialysis

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## Introduction

Raltegravir (RAL) is the first of a new class of HIV-1 drugs known as integrase inhibitors and is known to be metabolized by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Patients with decreased renal function or liver function can be treated with RAL without requiring dosage reduction. Although the antiviral activity of RAL is known to be retained upon its elimination by hemodialysis and continuous venovenous hemodiafiltration<sup>1,2)</sup>, the pharmacokinetics and therapeutic effects of RAL during continuous ambulatory peritoneal dialysis (CAPD) remain largely unknown. We investigated the RAL concentrations in the plasma and dialysate of a patient infected with HIV-1 who began undergoing CAPD treatment and evaluated the effect on the clinical

outcome.

## Case Report

This study was performed with the permission of the Jichi Medical University ethics committee. We performed the study after sufficiently explaining the contents of the study to the patient and obtaining his consent to participate in this study.

We report the case of a 38-year-old man who was diagnosed as having been infected with HIV-1 in addition to having diabetic nephropathy. HIV-1 RNA was detected during a medical examination that was conducted before the patient underwent laser treatment for diabetic proliferative retinopathy and vitreous hemorrhage. The HIV-1 RNA viral load was  $1.5 \times 10^5$  copies/mL, and the CD4 count was 86 cells/ $\mu$ L. The patient was treated once a day with each of the following drugs : abacavir (ABC, 600 mg), lamivudine (3TC, 150 mg), atazanavir (ATV, 300 mg), and ritonavir (RTV, 100 mg). In addition to receiving insulin therapy using Insulin lispro (Humalog<sup>®</sup>),

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the patient was treated with a calcium channel blocker (amlodipine besilate, 5 mg/day), a diuretic (furosemide, 40 mg/day), and sodium polystyrene sulfonate (15 g/day). The antiretroviral therapy (ART) regimen was modified from ATV and RTV to RAL (400 mg, twice daily) because of exacerbated hyperlipidemia. At this point, the HIV-1 RNA viral load was  $4.0 \times 10^1$  copies/mL and the CD4 count was 210 cells/ $\mu$ L. Because of the diabetic nephropathy, the patient was subsequently admitted for the initiation of CAPD. The patient's serum creatinine value was 11.76 mg/dL, and his creatinine clearance was 9 mL/min at the time of hospitalization.

CAPD was introduced on day 11 of hospitalization using the stepwise initiation of peritoneal dialysis according to the Moncrief and Popovich technique. The patient's condition was clinically stable, and 2 L of dialysate (MIDPELIQ® 135) was administered to the patient five times a day. The patient was discharged from our hospital 52 days after the initiation of CAPD without the development of peritonitis.

During his hospitalization, plasma and dialysate samples were collected and the RAL concentrations were assayed. RAL was administered to the patient twice daily at 7:00 am and 7:00 pm. The patient's blood was sampled before dosing (0 h) and at 3 h after dosing on hospital days 3 to 5 and days 57 to 59. The dialysate was sampled at the following time points : 7:00–11:00, 11:00–15:00, 15:00–19:00, 19:00–23:00, and overnight (23:00–7:00) on hospital day 57 (Fig. 1). The blood samples were centrifuged (3,000 rpm, 10 min), and the plasma samples (1 mL) were collected and stored at  $-20^\circ\text{C}$  until assayed. Five milliliters of the dialysate samples was collected and stored at  $-20^\circ\text{C}$  until assayed. All the samples were outsourced to BML Inc. (Tokyo, Japan) for the measurement of the RAL concentrations using high performance liquid chromatography.

The RAL concentrations in the plasma and dialysate

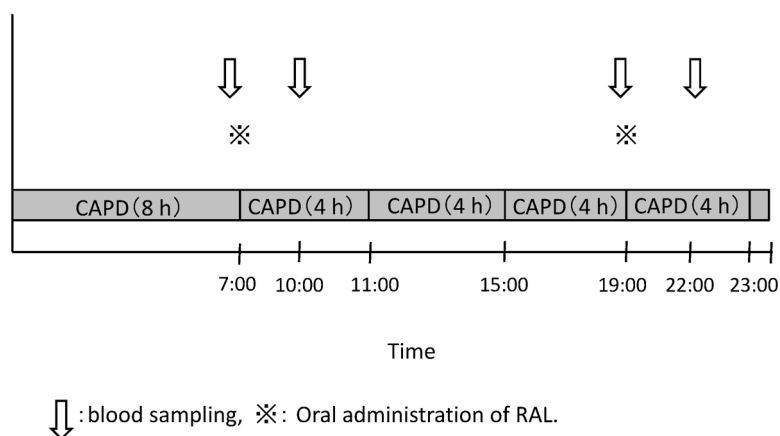
were presented using a box plot analysis ; significant differences were determined using the Welch *t*-test. Statistical significance was regarded as a *p* value  $<0.05$ . We did not adjust the dosage of RAL before or after the introduction of CAPD.

## Results

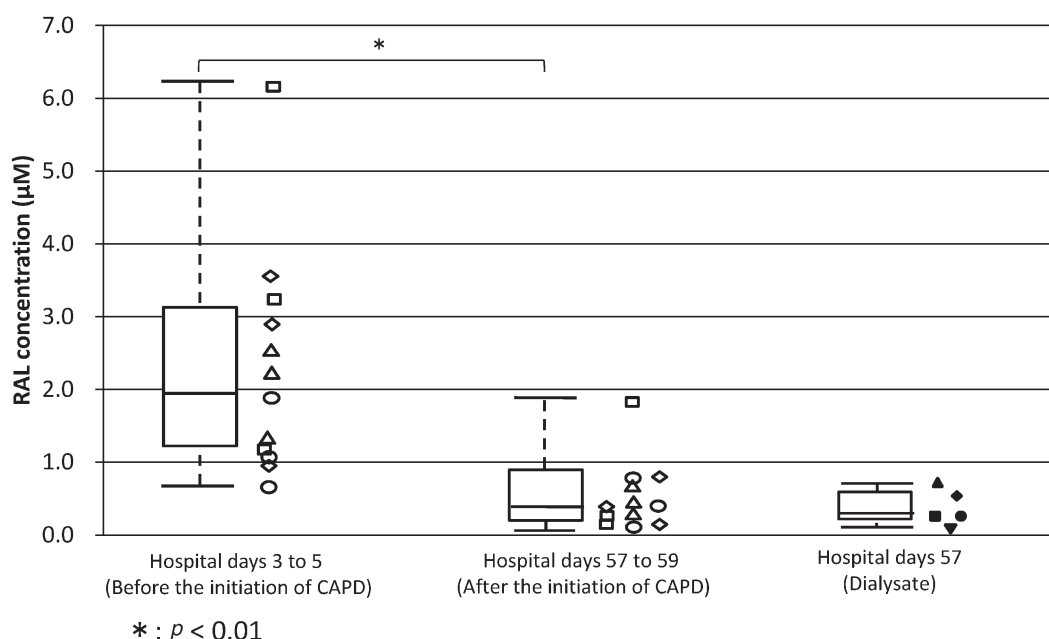
In the present case, the RAL plasma concentration on hospital days 57 to 59 (after the initiation of CAPD) (median : 0.45  $\mu$ M) showed an obvious decrease, compared with that on days 3 to 5 (before the initiation of CAPD) (median : 1.99  $\mu$ M) (Fig. 2). On the other hand, on hospital day 57, RAL was detected in the dialysate, and its concentration was 0.29  $\mu$ M (median) (Fig. 2). Two hundred days after the introduction of CAPD, the HIV-1 RNA viral load was under  $4.0 \times 10^1$  copies/mL and the CD4 count was 235 cells/ $\mu$ L. No decrease in the CD4 count was observed after the initiation of CAPD. Furthermore, 2 years after the introduction of CAPD, the HIV-1 RNA viral load was consistently undetectable.

## Discussion

While the recommended therapeutic dosage of RAL for hemodialysis patients is 800 mg/day with no dose taken before dialysis, the blood concentration during the introduction of CAPD was within the dosage recommended in the DHHS guidelines, which do not specify a dosage<sup>3)</sup>. As RAL is mainly metabolized by UGT1A1, the amount of medication does not need to be reduced, even if the renal function is low, because the drug metabolites are mainly excreted in the feces. When the RAL concentration in the plasma was compared before and after the introduction of CAPD in the present case, the RAL concentration had decreased by approximately 76% (Fig. 2). However, in our patient, the plasma HIV-1 RNA viral load did not increase and the CD4 count did not decrease, despite the absence of any increase in the dosage of RAL.



**Figure 1** Schematic representation of study



**Figure 2** RAL concentration in plasma and dialysate

RAL concentrations in plasma on hospital days 3 to 5 (before CAPD initiation) and days 57 to 59 (after CAPD initiation). ○, 7:00 ; □, 10:00 ; △, 19:00 ; ◇, 22:00.

RAL concentrations in dialysate on hospital day 57. ■, 7:00–11:00 ; ▲, 11:00–15:00 ; ●, 15:00–19:00 ; ▼, 19:00–23:00 ; ◆, 23:00–7:00.

The box plot shows the maximum, Q3 (75 percentile), median, Q1 (25 percentile), and minimum concentrations.

Furthermore, many CAPD patients have an increased large pore clearance with significant albumin loss through the peritoneum<sup>4)</sup>. The rate of albumin binding is 83% for free RAL in the blood<sup>5)</sup>, which may make it easier to migrate through the peritoneal membrane into the dialysate from the blood. However, the accumulation of a drug in the body is thought to depend on the route of excretion and metabolism. The *in vivo* antiviral concentration of RAL is thought to be 0.033  $\mu\text{M}$ <sup>6)</sup>. In the present case, the lowest plasma concentration was determined to be 0.153  $\mu\text{M}$  during the study period, but the plasma HIV-1 RNA viral load did not increase. The results of the present study suggest a need for the careful monitoring of HIV-RNA and CD4 counts, since the post-CAPD RAL concentration can be reduced to 1/4 of the pre-CAPD concentration. More data is needed to optimize RAL treatment in patients undergoing CAPD.

**Conflicts of interest** : None of the authors have any conflicts of interest to declare.

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## 腹膜透析による血中ラルテグラビルの推移

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**目的:** 血液透析患者のラルテグラビル (以下 RAL) 投与量は常用量より増量する必要はないが, 腹膜透析患者への適切な投与量は不明である。腹膜透析 (以下 CAPD) 導入患者の RAL 投与量と臨床効果を評価するために, われわれは血漿中と腹膜透析液中の RAL 濃度を調査した。

**方法:** 対象患者から RAL 血中濃度を測定するために, CAPD 導入前と導入後に内服前と内服後 3 時間後にそれぞれ採血をした。また透析液への RAL の移行を確認するために透析液を採集した。それぞれの検体の RAL 濃度は, 高速液体クロマトグラフィー法で測定した。

**結果:** CAPD 導入後の血漿中 RAL 濃度は CAPD 導入前に比べおよそ 1/4 に減少した。RAL は腹膜透析液からも検出され, CAPD 導入後の血漿中 RAL 濃度と近い濃度であった。それにもかかわらず血漿中の HIV-1 RNA 量は  $4.0 \times 10^1$  copies/mL 以下であり CD4 陽性リンパ球の減少は観察されなかった。

**結論:** 本症例では, RAL は CAPD 導入後も通常用量で抗ウイルス効果を示した。

**キーワード:** ラルテグラビル, 腹膜透析, 血中濃度, HIV, 透析