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CASE REPORT

Coadministration of tenofovir decreased atazanavir plasma concentration after unilateral nephrectomy

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Abstract We report a case in which the atazanavir (ATV) concentration in the plasma decreased after unilateral nephrectomy in a patient receiving tenofovir (TDF). The patient was a 39-year-old man diagnosed with human immunodeficiency virus type 1 infection and was being treated with TDF/emtricitabine, ATV, and ritonavir. Before nephrectomy, ATV and TDF plasma trough concentrations were 810 and 65 ng/ml, respectively. At this time, estimated glomerular filtration rate (eGFR) was 111 ml/min/1.73 m^2. Approximately 5 months after starting antiretroviral therapy (ART), the patient underwent nephrectomy. Plasma concentrations were remeasured 18 weeks after the operation, and the TDF concentration had increased to 109 ng/ml, whereas the ATV concentration decreased to 290 ng/ml. His eGFR decreased to 50 ml/min/1.73 m^2 at the time of the second measurement. The decreased ATV plasma concentration suggested that interactions between ATV and TDF were exacerbated by an increase in TDF plasma concentration caused by renal dysfunction. This case report suggests that it is important to monitor the ATV plasma concentration to ensure that it is no less than the target trough concentration when renal function decline is observed in patients receiving ART including ATV and TDF.

Keywords Atazanavir · Tenofovir · Human immunodeficiency virus type 1 · Therapeutic drug monitoring · Drug interaction · Nephrectomy

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Introduction

Antiretroviral therapy (ART) has resulted in significant improvement in the survival of human immunodeficiency virus type 1 (HIV-1)-infected patients since the introduction of HIV-1 protease inhibitors (PIs) [1, 2]. ART usually consists of two nucleoside reverse transcriptase inhibitors (NRTIs), with a ritonavir (RTV)-boosted PI, non-NRTI, or integrase inhibitor [3]. Atazanavir (ATV) is a member of the PI class of antiretroviral (ARV) drugs, recommended as one of the preferred agents by the guidelines for the initiation of treatment when coadministered with the strong CYP3A4 inhibitor RTV [3]. Tenofovir (TDF) is grouped with the NRTI class of ARV drugs and is a preferred component of the first-line regimen in the guidelines.

Therapeutic drug monitoring (TDM), an important clinical technique in personalized medicine, is currently widely applied in medical treatments using antibiotics, immunosuppressive agents, antiepileptic agents, and other drugs [4–6]. In ART, TDM is recommended in specific clinical scenarios such as cases in which pathophysiological changes (e.g., renal dysfunction) or drug–drug interactions adversely affect pharmacokinetics [3]. However, TDM for ART is not recommended for routine use in the

clinical care of HIV-1-infected patients because of a lack of large prospective studies showing that TDM improves clinical or virological outcomes [3]. TDM is still not a generally accepted strategy in ART at clinical sites. By contrast, data from small studies showed that TDM for ART improves virological response and decreases the incidence of concentration-related drug toxicity [7, 8]. Nevertheless, although TDM may provide clinical utility to HIV-1-infected patients, further clinical evidence is needed to assess the usefulness of TDM in ART.

We report a case of changes in ATV plasma concentration before and after unilateral nephrectomy. Our report suggests that it is important to consider changes in ARV drug plasma concentrations caused by to drug–drug interactions and decline in renal function. Informed consent was obtained from the patient for publication of this report.

Case report

A 39-year-old Japanese man was admitted to our hospital with fever, coughing, and dyspnea. He was diagnosed with HIV-1 infection and pneumocystis pneumonia after admission. On day 2 after admission, blood laboratory results showed the following: $CD4^+$ T-cell count, 51 cells/μl, and HIV RNA, 2.5×10^5 copies/ml. He was initially treated with sulfamethoxazole-trimethoprim for 21 days. After completion of the treatment, we started ART with TDF/emtricitabine (FTC), ATV, and RTV.

On day 3 after starting ART, we performed a computed tomography scan for follow-up on pneumonia, and incidentally found a renal mass suggestive of renal cell carcinoma (RCC). The patient was diagnosed with suspected RCC (cT1aN0M0). On day 37 after starting ART, we measured plasma concentrations of ATV and TDF, as follows. Pre-dose blood samples were collected in heparinized tubes and centrifuged for 10 min at $3{,}000 \times g$; the resultant plasma was removed and stored at −20 °C until analysis. ATV plasma concentration was analyzed using liquid chromatography–tandem mass spectrometry, and TDF plasma concentration was analyzed by high-performance liquid chromatography. ATV and TDF plasma concentrations were 810 and 65 ng/ml, respectively. The ATV plasma concentration was higher than that of the target trough (150 ng/ml) specified in the American Department of Health and Human Services (DHHS) guidelines [3].

On day 149 after starting ART, the patient underwent radical nephrectomy of the right kidney; adjuvant chemotherapy was not performed. His serum creatinine was higher post-nephrectomy than pre-nephrectomy. We were concerned about further deterioration of renal function and, therefore, switched from TDF/FTC to abacavir/lamivudine (3TC). However, the patient's ART was changed again to TDF/FTC because of the appearance of persistent skin rash and itching sensation. We selected TDF/FTC because it has excellent efficacy, a favorable toxicity profile, and a convenient dosage schedule in comparison with those of zidovudine/3TC. On day 277 after starting ART, we anticipated that renal dysfunction after nephrectomy might affect the pharmacokinetics of ATV and TDF, and remeasured these plasma concentrations. We found that the TDF plasma concentration increased to 109 ng/ml; although the ATV plasma concentration was maintained at the target trough concentration, it decreased to 290 ng/ml. His viral load was undetectable (less than 40 copies/ml) on day 327 after starting ART.

At the time of both measurements of ARV drug plasma concentrations, the patient took ATV with food. In addition, the patient did not use medications that interact with ARV drugs. There was no significant difference in the time to blood sampling for TDM from the time that the patient took the ARV drugs. There were no appreciable signs of altered liver function, such as changes in plasma concentration of ATV (Table 1). Figure 1 outlines the clinical course of the patient.

Discussion

In this report, we focused on changes in plasma concentration of ARV drugs induced by decreased renal function after unilateral nephrectomy. TDF plasma concentration was increased, whereas ATV plasma concentration was decreased in our patient after the operation. Because low ATV concentration may lead to virological failure [10, 11], we believe that detailed analysis of the patient's course may help to prevent treatment failure with ART that includes ATV and TDF.

TDF is a renally eliminated drug excreted by glomerular filtration and active tubular secretion. Previous reports have documented increases in TDF concentration caused by decline in renal function [12]. Julien et al. [13] reported that serum creatinine level and creatinine clearance rate affected TDF clearance. Our patient also showed increased TDF plasma concentration after decline in renal function following nephrectomy, consistent with previous findings. ATV is eliminated primarily by the liver. The renal elimination of unchanged ATV was approximately 7 % of the administered dose [14]. The ATV minimum concentration was reportedly 96 % higher in subjects with severe renal impairment than in those with normal renal function [14]. In contrast, although the ATV plasma concentration in our case was above the target trough concentration before nephrectomy, its post-nephrectomy concentration fell to near the target trough concentration despite reduced renal function.