INTERNAL MEDICINE

Therapeutic Drug Monitoring of Anti-human Immunodeficiency Virus Drugs in a Patient with Short Bowel Syndrome

Motoko Ikuma[1], Dai Watanabe[1], Hiroki Yagura[2], Misa Ashida[1], Masaaki Takahashi[3], Masaaki Shibata[3], Tadafumi Asaoka[4], Munehiro Yoshino[2], Tomoko Uehira[1], Wataru Sugiura[5] and Takuma Shirasaka[1]

Abstract

An elderly woman with human immunodeficiency virus-1 infection developed short bowel syndrome as a result of extensive intestinal resection. Considering the possibility of poor absorption of antiretroviral drugs (ARVs), therapeutic drug monitoring (TDM) was performed. A single-dose test of 6 ARVs (darunavir, ritonavir, lopinavir, etravirine, maraviroc, and raltegravir) did not provide information on the appropriate ARV, and repeated TDM under continuous antiretroviral therapy resulted in viral suppression below 50 copies/mL, which was considered to be treatment success. These assessments suggest the importance of TDM in the steady state for the successful treatment of individuals with impaired gastrointestinal function using ARVs.

Key words: human immunodeficiency virus-1 infection, antiretroviral therapy, short bowel syndrome, therapeutic drug monitoring

Introduction

The combined use of multiple antiretroviral drugs (ARVs) in human immunodeficiency virus (HIV)-1 infected individuals has allowed the suppression of the proliferation of HIV-1 and the continuous maintenance of the plasma HIV-1 RNA level (VL) below the lower limit of detection. However, if the plasma ARV concentrations remain below the target concentrations, there is a risk of virological failure and emergence of ARV resistance (1). Target trough plasma concentrations (Cmin) have been determined for some ARVs (2), and for those without a target Cmin value, median Cmin values determined using clinical studies are provided in guidelines (2). Thus, it is clinically important to measure the plasma ARV concentrations. However, data on

whether routine use of drug monitoring improves clinical outcomes are limited, and the measurement of plasma ARV concentrations is not recommended in routine clinical practice (2).

Although the risk of vascular disorders, particularly ischemic heart disease, increases in HIV-1-infected individuals (3), a relationship between HIV-1 infection and non-occlusive mesenteric ischemia (NOMI) has not yet been determined. NOMI is a variation of acute ischemic enteritis not accompanied by arterial obstruction (4) caused by visceral ischemia, which is induced by a decrease in the circulating plasma volume or blood pressure. Because the symptoms are non-specific, it is difficult to diagnose the disease early after onset, and the mortality rate is high. It typically has a sudden onset with abdominal pain in individuals aged ≥50 years with underlying diseases, such as ischemic heart
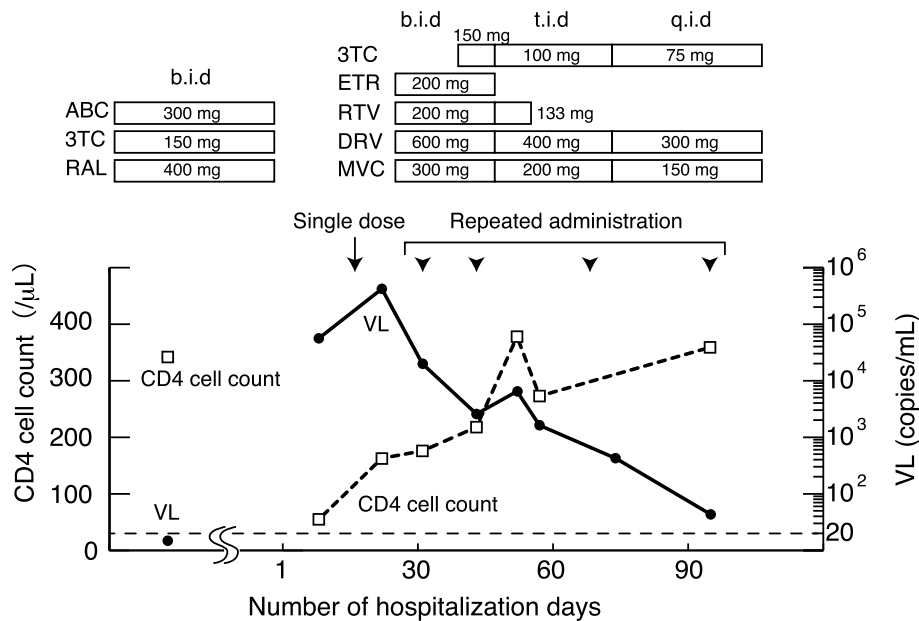
Figure. Course of antiretroviral drugs (ARVs) and serial changes in the CD4 cell count and HIV-1 RNA level (VL) in our patient with HIV-1. In the top table, the administered ARVs, administration periods, doses, and number of daily administrations are shown. In the bottom table, the VL and CD4 cell count are indicated by open squares and closed circles, respectively. Arrow and arrowheads indicate the timing of the determination of plasma drug concentrations after single-dose administration and repeated administrations, respectively. 3TC: lamivudine, ABC: abacavir, DRV: darunavir, ETR: etravirine, LPV: lopinavir, MVC: maraviroc, NOMI: non-occlusive mesenteric ischemia, RAL: raltegravir, RTV: ritonavir

disease and kidney disease. As anaerobic metabolism is promoted in ischemic organs, hyperlactacidemia has been reported (4).

The presence of serious absorptive impairments resulting from gastrointestinal diseases or surgical reconstruction of the gastrointestinal tract might be associated with poor ARV absorption, which could result in antiretroviral therapy (ART) failure. However, information on the plasma ARV concentrations in patients with impaired gastrointestinal function is very limited. We herein report the results of therapeutic drug monitoring (TDM) in an HIV-1-infected patient who developed short bowel syndrome after extensive intestinal resection due to NOMI.

Case Report

A 72-year-old woman with a history of treated diabetes, hypertension, and hyperlipidemia developed candidiasis in January 2011, and she was diagnosed with HIV-1. Her CD4+ T-lymphocyte count (CD4 cell count) was 32 cells/μL, and her VL was 16,600 copies/mL. Continuous ART with abacavir (ABC), lamivudine (3TC), and raltegravir (RAL) was initiated within the following month. In December 2012, the CD4 cell count recovered to 265 cells/μL, and the VL was controlled below the lower limit of detection.

In February 2013, she experienced abdominal pain and vomiting. Her level of consciousness decreased over a few hours, and she was transported for emergency treatment. Her

blood pressure was maintained at 102/58 mmHg. Tachycardia and labored polypnea were present, and her level of consciousness was rated at a Glasgow Coma Scale score of 13. A blood gas analysis revealed metabolic acidosis (pH 7.0) accompanied with hyperlactacidemia (199 mg/dL), and abdominal computed tomography showed gas in the superior mesenteric and intrahepatic portal veins in addition to intramural emphysema of the colon.

According to a diagnosis of intestinal ischemia, ART was suspended, and emergency laparotomy was performed. The intestine extending from the jejunum to the colon appeared black and necrosed; however, the color of the mesentery was normal with a satisfactory blood flow. Therefore, she was diagnosed with NOMI. Subtotal small bowel resection and jejunostomy were performed, and a 70 cm segment of the jejunum from the ligament of Treitz was preserved. Approximately 95 cm of the small intestine was preserved. Moreover, the large intestine was completely resected.

After surgery, lactic acidosis rapidly resolved, and intensive care was continued. On day 21 of hospitalization, her CD4 cell count was 163 cells/μL, and the VL was 49,600 copies/mL (Figure). The HIV-1 subtype was identified as B. Additionally, no drug-resistant mutation was noted on drug-resistance testing, and a viral tropism assay indicated R5 tropism.

Due to concerns regarding poor ARV absorption because of short bowel syndrome, tests were performed with single-dose administration of select ARVs to determine the most

Table 1. Plasma Antiretroviral Drug Concentrations after Single-dose Administration in Our Patient with Short Bowel Syndrome.

	DRV	RTV	LPV	ETR	MVC	RAL
Dose (mg)	400	100	400	100	150	400
C1 (μg/mL)	0.350	<0.01	<0.01	0.550	0.243	0.307
C2 (μg/mL)	1.590	<0.01	<0.01	1.110	0.580	0.566
C3 (μg/mL)	2.180	<0.01	<0.01	2.090	0.452	0.312
C5 (μg/mL)	1.690	<0.01	<0.01	1.630	0.389	0.114

DRV: darunavir, RTV: ritonavir, LPV: lopinavir, ETR: etravirine, MVC: maraviroc, RAL: raltegravir, C1, C2, C3, and C5: the plasma antiretroviral drug concentrations at 1, 2, 3, and 5 hours, respectively, after the single-dose administration.

Table 2. Plasma Antiretroviral Drug Concentrations under Repeated Administrations in Our Patient with Short Bowel Syndrome.

	DRV	RTV	ETR	MVC	3TC
Dose (mg, b.i.d)	600	200	200	300	150
Cmin (μg/mL)	<0.01	<0.01	<0.01	0.128	N.A.
C2 (μg/mL)	0.94	<0.01	<0.01	0.476	N.A.
C3 (μg/mL)	1.1	<0.01	<0.01	0.43	N.A.
C6 (μg/mL)	0.82	<0.01	<0.01	0.26	N.A.

DRV: darunavir, RTV: ritonavir, LPV: lopinavir, ETR: etravirine, MVC: maraviroc, 3TC: lamivudine, N.A.: not assessed, Cmin: the plasma antiretroviral drug concentration just before the next dose, C2, C3, and C6: the plasma antiretroviral drug concentrations at 2, 3, and 6 hours, respectively, after administration.

appropriate ARV combination. Darunavir (DRV, 400 mg), ritonavir (RTV, 100 mg), lopinavir (LPV, 400 mg), etravirine (ETR, 100 mg), maraviroc (MVC, 150 mg), and RAL (400 mg) were simultaneously administered via a transnasal gastric tube. DRV, MVC, and RAL tablets were pulverized before administration. The ETR tablet was dissolved by immersion in water at 55℃ for 10 minutes. Liquid preparations of LPV and RTV were used. Among the co-administered drugs, omeprazole was the only drug predicted to affect the plasma concentrations of ARVs (2). This agent increased the gastrointestinal pH, which resulted in an increase in the solubility of RAL. The plasma drug concentrations were determined, as previously reported (5-9), using plasma collected at 1, 2, 3, and 5 hours after drug administration. The peak concentration (Cmax) for each drug was recorded (Table 1). The Cmax values of LPV and RTV were below the lower limit of detection (0.01 μg/mL). The Cmax values of MVC (0.580 μg/mL) and RAL (0.566 μg/mL) were observed 2 hours after administration, and those of DRV (2.18 μg/mL) and ETR (2.09 μg/mL) were observed 3 hours after administration. These values were compared with the median Cmax values of previous single-dose tests in healthy adults (10-14). The Cmax of RAL was markedly lower in our patient than in individuals from the previous clinical trials (1.496 μg/mL). However, the values of DRV, ETR, and MVC were similar between our patient and the patients from the previous clinical trials (DRV 600 mg, 5.96 μg/mL; ETR 200 mg, 0.500 μg/mL; and MVC 300 mg, 0.736 μg/mL). According to these results, continuous ART was resumed on day 25 of hospitalization with DRV (600 mg), RTV (200 mg), ETR (200 mg), and MVC (300 mg) administration every 12 hours. Although the Cmax of RTV was below the lower limit of detection, it was administered with the expectation of a booster effect on DRV and MVC.

The plasma ARV concentrations were measured under repeated administrations. Six days after the resumption of ART (on day 31 of hospitalization), the patient's blood was sampled immediately before ARV administration, and the plasma concentration of each agent was determined (Cmin). The Cmin of MVC and DRV was 0.45 μg/mL and 1.72 μg/mL, respectively. However, unlike the results of the single-dose test, the Cmin of ETR was below the lower limit of

detection (0.01 μg/mL). Therefore, 3TC (150 mg) was also administered every 12 hours for 14 days after the resumption of ART (on day 39 of hospitalization). Tube feeding was initiated from day 32 of hospitalization.

The Cmin and Cmax values were determined again 18 days after the resumption of ART (on day 43 of hospitalization) (Table 2). All the concentrations of ETR and RTV were below the lower limits of detection. The Cmin of MVC was above the target trough recommended by the guidelines (0.05 μg/mL). The Cmax of DRV was 1.1 μg/mL, however, the Cmin was below the lower limit of detection (0.01 μg/mL). These results suggested a high rate of DRV elimination, indicating that the booster effect expected by RTV was inadequate. Therefore, ETR and RTV administration was discontinued, and the dosing intervals of the other ARVs (3TC, DRV, and MVC) were changed while maintaining the total daily dose. With 8-hour intervals (t.i.d.), the Cmin values of DRV and MVC were below the lower limit of detection and 0.093 μg/mL, respectively, and with 6-hour intervals (q.i.d.), they were 0.210 μg/mL and 0.039 μg/mL, respectively. These values were lower than the plasma DRV concentrations identified in previous clinical trials (median: 3.3 μg/mL) or the target plasma concentration of MVC (0.05 μg/mL). However, the VL decreased to 32 copies/mL at 71 days after the resumption of ART (on day 96 of hospitalization), indicating an initial antiretroviral effect. Unfortunately, 82 days after the resumption of ART (on day 107 of hospitalization), the patient developed catecholamine-resistant sepsis due to a catheter-related bloodstream infection and died.

Discussion

In our patient with HIV-1 infection, short bowel syndrome developed because of extensive intestinal resection for NOMI. The postoperative ART regimen was determined according to the measurement of the plasma drug concentrations. The antiviral effects of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are dependent on the intracellular concentrations of their metabolites (15); therefore, the effectiveness of measuring their plasma concentrations is unclear. Furthermore, a method to measure the plasma NRTI

concentrations was not available, except for tenofovir; therefore, we chose to exclude NRTIs from the choice of administered drugs.

Regarding lactic acidosis, NRTIs are known to inhibit mitochondrial DNA synthesis and induce mitochondrial disorders and lactic acidosis (16). In our patient, marked lactic acidosis was observed at the onset of NOMI, but it rapidly resolved after resection of the ischemic intestine. Although NRTIs could have contributed to lactic acidosis, it is more likely that NOMI played a greater role than NRTIs in our patient. We eventually administered 3TC because the plasma concentrations of only two ARVs could be maintained in a measurable range and the mitochondrial toxicity of 3TC is weaker than that of other NRTIs (17).

We performed a single-dose test to select the appropriate ARVs. However, there was a risk that ARV resistance could have developed after single doses of the ARVs. In addition, the single-dose test could not predict the plasma concentrations of ARVs under repeated administrations, indicating that a single-dose test was less helpful than TDM under continuous ART. In our patient, the plasma concentrations of many ARVs decreased over time. For instance, ETR was detected in the plasma in the single-dose test but not in the steady state on repeated administrations. Additionally, the Cmin of MVC in the steady state tended to decrease over time, despite an increased frequency of administration. Possible explanations for these decreases over time include short intestinal transit times related to alleviated intestinal paralysis by intensive treatment; drug interactions; the induction of the expression of drug-metabolizing enzymes, such as cytochrome P450 3A4 (CYP3A4), and drug transporters, such as P-glycoprotein; and the initiation of tube feeding. Tube feeding may improve the absorption of DRV and ETR because the plasma concentrations of these drugs were higher when they were taken with food than when they were taken without food (10, 13). On the other hand, suboptimal tube feeding can result in malabsorption of the drugs by inducing diarrhea or high output from the stoma. However, we were unable to determine the specific cause of the decreases in our patient. As our patient was continuously hospitalized after the onset of NOMI, poor adherence to the ART regimen was unlikely to be the cause of the decreased plasma ARV concentrations.

Although RTV was not detected in the plasma, it might have been involved in the increased plasma concentrations of MVC and DRV. RTV inhibits not only CYP3A4 in the liver, but also CYP3A4 and p-glycoprotein in the epithelial cells of the small intestine (18), which reportedly promotes the absorption of concomitantly used ARVs (19). While the degree of involvement of the inhibitory actions of RTV in the liver and small intestine is unknown, the decrease in the Cmin of MVC after RTV administration was discontinued might suggest its booster effect.

It should be noted that the pharmacokinetic profiles of DRV and MVC were superior to the profiles of other ARVs tested in this case. In patients with short bowel syndrome, many factors, such as a short residual intestine, accelerated gastrointestinal transit, and presence of gastrointestinal disease, are associated with drug malabsorption, and the absorption of drugs with low bioavailability is especially influenced by these factors. On the other hand, successful oral anticoagulation with warfarin was previously noted in some cases with short bowel syndrome (20), which might be explained by the rapid and extensive absorption of warfarin through the stomach and proximal small intestine and its nearly complete bioavailability in individuals with normal gastrointestinal function. Other drugs, showing good absorption in patients with short bowel syndrome, have characteristics similar to those of warfarin (20). Although detailed information was lacking, DRV and MVC may have these characteristics.

We herein reported the results of ARV TDM in an HIV-1-infected patient with short bowel syndrome due to extensive intestinal resection for NOMI. We detected decreased plasma concentrations of all of the ARVs that were measured. However, repeated TDM over 10 weeks resulted in successful treatment in this case. To the best of our knowledge, this is the first report on ARV TDM in a patient with short bowel syndrome. While there is generally little need to routinely monitor ARV concentrations, TDM is considered to be important to maintain the plasma ARV concentrations in individuals with impaired gastrointestinal function, as it can be difficult to predict the temporal change in the plasma ARV concentrations in these individuals.

Author's disclosure of potential Conflicts of Interest (COI).
Wataru Sugiura: Employment, GlaxoSmithKline.

References

1. Fabbiani M, Di Giambenedetto S, Bracciale L, et al. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. J Antimicrob Chemother **64**: 109-117, 2009.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services [Internet]. [cited 2015 Apr. 19]. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf
3. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J **35**: 1373-1381, 2014.
4. Trompeter M, Brazda T, Remy CT, Vestring T, Reimer P. Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. Eur Radiol **12**: 1179-1187, 2002.
5. Takahashi M, Hirano A, Okubo N, Kinoshita E, Nomura T, Kaneda T. Development and application of a simple LC-MS method for the determination of plasma maraviroc concentrations. J Med Invest **57**: 245-250, 2010.
6. Hirano A, Takahashi M, Kinoshita E, et al. High performance liquid chromatography using UV detection for the simultaneous quantification of the new non-nucleoside reverse transcriptase in-

hibitor etravirine (TMC-125), and 4 protease inhibitors in human plasma. Biol Pharm Bull 33: 1426-1429, 2010.

7. Takahashi M, Kudaka Y, Okumura N, Hirano A, Banno K, Kaneda T. Pharmacokinetic parameters of lopinavir determined by moment analysis in Japanese HIV type 1-infected patients. AIDS Res Hum Retroviruses 24: 114-115, 2008.

8. Takahashi M, Konishi M, Kudaka Y, et al. A conventional LC-MS method developed for the determination of plasma raltegravir concentrations. Biol Pharm Bull 31: 1601-1604, 2008.

9. Takahashi M, Kudaka Y, Okumura N, Hirano A, Banno K, Kaneda T. The validation of plasma darunavir concentrations determined by the HPLC method for protease inhibitors. Biol Pharm Bull 30: 1947-1949, 2007.

10. Pharmaceuticals and Medical Devices Agency. Interview form of Prezista® (darunavir) [Internet]. 13th ed. Available from: http://www.info.pmda.go.jp/go/interview/1/800155_6250030F1027_1_007_1 F. 2013 (in Japanese).

11. Pharmaceuticals and Medical Devices Agency. Interview form of Celcentri® (maraviroc) [Internet]. 6th ed. Available from: http://www.info.pmda.go.jp/go/interview/2/166272_6250034F1025_6_CLT_1F. 2013 (in Japanese).

12. Pharmaceuticals and Medical Devices Agency. Interview form of Isentress® (raltegravir) [Internet]. 14th ed. Available from: http://www.info.pmda.go.jp/go/interview/2/170050_6250032F1026_2_012_1F. 2013 (in Japanese).

13. Pharmaceuticals and Medical Devices Agency. Interview form of Intelence® (etravirine) [Internet]. 6th ed. Available from: http://www.info.pmda.go.jp/go/interview/1/800155_6250033F1020_1_003_1 F. 2013 (in Japanese).

14. Pharmaceuticals and Medical Devices Agency. Interview form of Kaletra® (lopinavir/ritonavir) [Internet]. 1st ed. Available from: http://www.abbvie.co.jp/content/dam/abbviecorp/japan/docs/if_kaletra_j.pdf. 2013 (in Japanese).

15. Fletcher CV, Kawle SP, Kakuda TN, et al. Zidovudine triphosphate and lamivudine triphosphate concentration-response relationships in HIV-infected persons. AIDS 14: 2137-2144, 2000.

16. Arenas-Pinto A, Grant AD, Edwards S, Weller IV. Lactic acidosis in HIV infected patients: a systematic review of published cases. Sex Transm Infect 79: 340-343, 2003.

17. McComsey G, Lonergan JT. Mitochondrial dysfunction: patient monitoring and toxicity management. J Acquir Immune Defic Syndr 37 Suppl 1: S30-S35, 2004.

18. Profit L, Eagling VA, Back DJ. Modulation of P-glycoprotein function in human lymphocytes and Caco-2 cell monolayers by HIV-1 protease inhibitors. AIDS 13: 1623-1627, 1999.

19. Holmstock N, Mols R, Annaert P, Augustijns P. In situ intestinal perfusion in knockout mice demonstrates inhibition of intestinal p-glycoprotein by ritonavir causing increased darunavir absorption. Drug Metab Dispos 38: 1407-1410, 2010.

20. Ward N. The impact of intestinal failure on oral drug absorption: a review. J Gastrointest Surg 14: 1045-1051, 2010.