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

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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

(Intern Med 55: 3059-3063, 2016)
(DOI: 10.2169/internalmedicine.55.6777)

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...
January 2011, and she was diagnosed with HIV-1. Her CD4 count recovered to 265 cells/μL, and the VL was controlled below the lower limit of detection.

Additionally, no drug-resistant mutation was noted on drug-resistance testing. The HIV-1 subtype was identified as B.

After surgery, lactic acidosis rapidly resolved, and intensive care was continued. On day 21 of hospitalization, 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. Apically, the large intestine was completely resected. Moreover, the large intestine was completely resected. The 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.

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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.

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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. Continuous ART with adefovir, lamivudine, ABC: abacavir, DRV: darunavir, ETR: etravirine, LPV: lopinavir, MVC: maraviroc, NOMI: non-occlusive mesenteric ischemia, RAL: raltegravir, RTV: ritonavir.
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°C 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). 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 Cmax values of DRV and MVC were below the lower limit of detection and 0.93 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

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

<table>
<thead>
<tr>
<th>Dose (mg, b.i.d)</th>
<th>DRV</th>
<th>RTV</th>
<th>LPV</th>
<th>ETR</th>
<th>MVC</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>400</td>
<td>100</td>
<td>400</td>
<td>100</td>
<td>150</td>
<td>400</td>
</tr>
<tr>
<td>C1 (μg/mL)</td>
<td>0.350</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.550</td>
<td>0.243</td>
<td>0.307</td>
</tr>
<tr>
<td>C2 (μg/mL)</td>
<td>1.590</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>1.110</td>
<td>0.580</td>
<td>0.566</td>
</tr>
<tr>
<td>C3 (μg/mL)</td>
<td>2.180</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>2.900</td>
<td>0.452</td>
<td>0.312</td>
</tr>
<tr>
<td>C4 (μg/mL)</td>
<td>1.690</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>1.630</td>
<td>0.389</td>
<td>0.114</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose (mg, b.i.d)</th>
<th>DRV</th>
<th>RTV</th>
<th>LPV</th>
<th>ETR</th>
<th>MVC</th>
<th>3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>600</td>
<td>200</td>
<td>200</td>
<td>300</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>Cmin (μg/mL)</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.128</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>C2 (μg/mL)</td>
<td>0.94</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.476</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>C3 (μg/mL)</td>
<td>1.1</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.43</td>
<td>N.A.</td>
<td></td>
</tr>
<tr>
<td>C4 (μg/mL)</td>
<td>0.82</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.26</td>
<td>N.A.</td>
<td></td>
</tr>
</tbody>
</table>

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.
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.

The results of this report have been presented in part at the 27th annual conference of The Japanese Society for AIDS Research (November 2013), Kumamoto, Japan.

Author’s disclosure of potential Conflicts of Interest (COI).

Wataru Sugiura: Employment, GlaxoSmithKline.

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