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Report (Case Report)

Safe Co-Administration of Amenamevir with Calcineurin Inhibitors: Case Reports

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Although co-administration of amenamevir (a helicase–primase inhibitor) reportedly decreases exposure to midazolam, a CYP3A4 substrate, it remains unclear whether amenamevir induces the metabolism of calcineurin inhibitors (tacrolimus and cyclosporine) metabolized by CYP3A4. Herein, we illustrated two cases of induction of metabolism for calcineurin inhibitors by amenamevir. The concentration/dose normalized by body weight was defined as exposure to calcineurin inhibitors. The first case is a 63-year-old female (*CYP3A5*3/*3* in both the recipient and donor) who received sustained-release tacrolimus 1.0 mg × 1 after living-donor liver transplantation. Although she temporarily withdrew tacrolimus on days 1 and 2 (from the initiation of combination), the same dosage was restarted from day 3. There was no significant difference in the C/D ratio regardless of co-administration of amenamevir 400 mg × 1 for 4 days (day -16: 4.5 ng/mL, 277.2 ng/mL/mg/kg vs. day 5: 3.6 ng/mL, 221.8 ng/mL/mg/kg). The second case is a 71-year-old female who received an induction therapy of microemulsion cyclosporine 50 mg × 2 from day -2 for nephrotic syndrome. The genotype of *CYP3A5* was unknown. Blood cyclosporine concentrations at 2 h post-dose were 153.5 ng/mL (80.6 ng/mL/mg/kg) on day 2 and 166.8 ng/mL (87.6 ng/mL/mg/kg) on day 4 when administered amenamevir 400 mg × 1 for 5 days from day 0. After the discontinuation of amenamevir, blood cyclosporine concentration at 2 h post-dose on day 19 remained unchanged (170.4 ng/mL, 89.5 ng/mL/mg/kg). In conclusion, amenamevir co-administered for ≤5 days had less impact on the pharmacokinetics of tacrolimus and cyclosporine at low concentrations.

Key words amenamevir, calcineurin inhibitor, cytochrome P450 3A4, drug-drug interaction

INTRODUCTION

Amenamevir (a non-nucleoside compound) blocks helicase–primase, a key enzyme complex involved in varicella-zoster virus proliferation. Amenamevir 400 mg × 1 for 7 days is favorable in treating herpes zoster.[1] *In vitro* data suggest that 1.0 μM amenamevir potentially activates the drug-metabolizing enzyme CYP3A4/5 in human hepatocytes by 26.1% compared with rifampin (unpublished data; Maruho Co., Ltd.). Co-administration of amenamevir 400 mg for 10 days decreased exposure to midazolam (a CYP3A4 substrate) by approximately 50%.[2] Therefore, there is a concern that amenamevir may decrease the concentration of calcineurin inhibitors through CYP3A4 induction and diminish their immunosuppressive effects, however, the evidence for this topic is still lacking to the best of our knowledge. We illustrated two cases demonstrating the limited impact of amenamevir on the metabolism of calcineurin inhibitors at low concentrations.

Case presentation Written informed consent was obtained from the two patients for use in the study.

Case 1 A 63-year-old woman (61.6 kg and 27.8 kg/m^2) had undergone living-donor liver transplantation due to hepatocellular carcinoma on day -399. The genotype of both the recipient and donor was *CYP3A5*3/*3*. The immunosuppressive regimen was sustained-release tacrolimus (Graceptor Capsules, Astellas Pharma Inc.) 1.0 mg × 1. Amenamevir 400 mg was orally administered daily for 4 days because of herpes zoster (Fig. 1a, day 0), and tacrolimus was discontinued on days 1 and 2. As a flare of pain occurred on day 4, intravenous acyclovir (non-inducer of CYP3A4 and/or P-glycoprotein) 300 mg × 2 was administered for 4 days. Trough concentration (before morning dosing) at steady-state marginally decreased on day 5 (4.5 to 3.6 ng/mL, concentration/dose-normalized body weight [C/D]: 277.2 to 221.8 ng/mL/mg/kg). After discontinuing amenamevir, the trough concentration reached 4.3 ng/mL (C/D: 264.9 ng/mL/mg/kg) on day 33.

Case 2 A 71-year-old woman (52.5 kg and 21.9 kg/m^2) orally received microemulsion cyclosporine (Neoral Capsules, Novartis Pharma Co.) 25 mg × 2 against nephrotic syndrome (membranous nephropathy) from day -25. She received add-on treatment with prednisolone 30 mg × 1 orally (day -3) and titrated cyclosporine 50 mg × 2 (day -2). Subsequently, she started on amenamevir 400 mg × 1 for 5 days for herpes zoster (Fig. 1b, day 0). The cyclosporine concentration at

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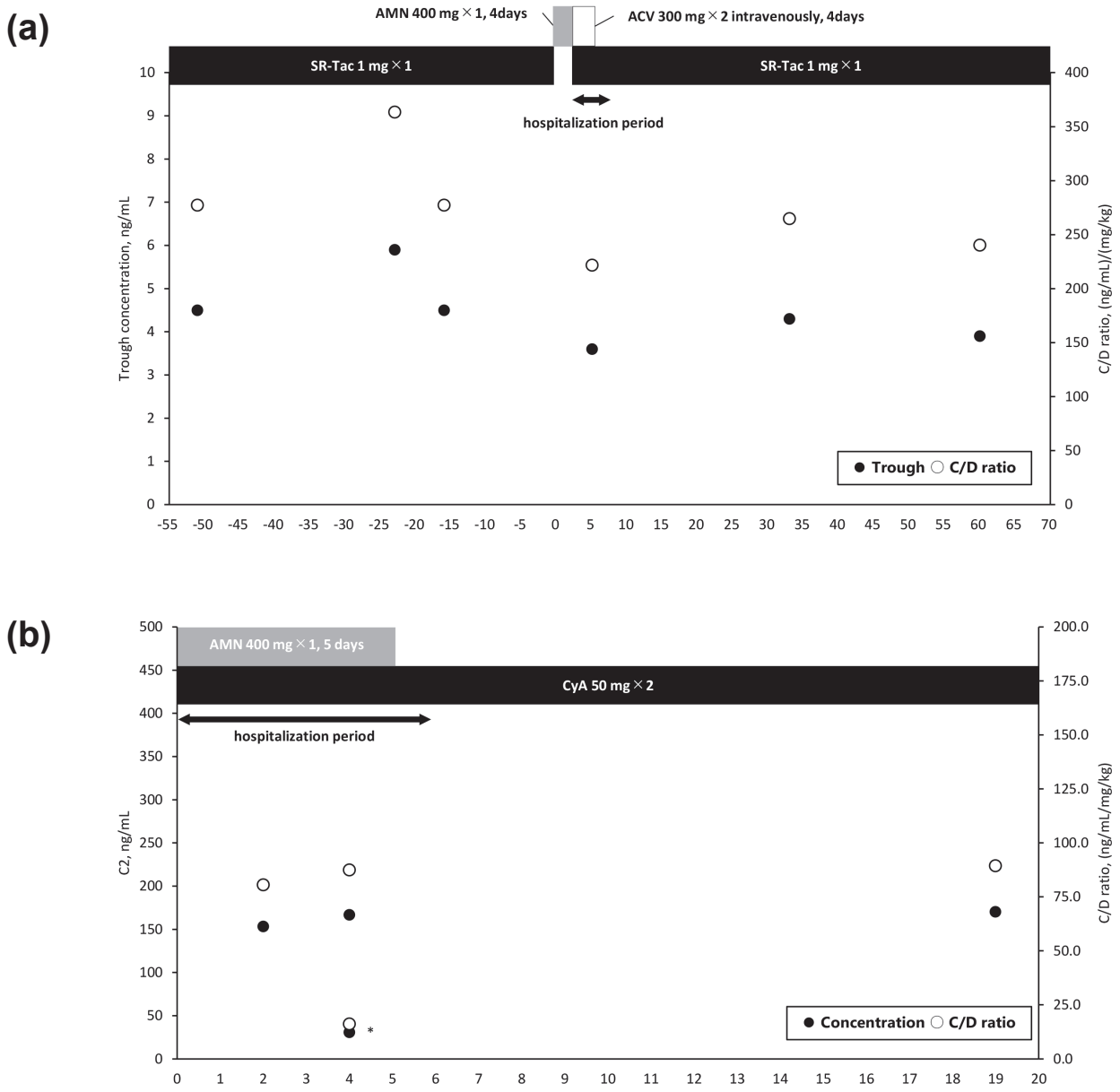

Fig. 1. Summary of the Co-Prescription of Amenamevir and Calcineurin Inhibitors

The X-axis represents the day, and the left and right Y-axes represent the concentration and the concentration/dose-normalized body weight, respectively. Day 0 is the date at which amenamevir was administered. The closed and opened circles represent the concentration (ng/mL) and the concentration/dose-normalized body weight (ng/mL/mg/kg), respectively.

(a). Influence of amenamevir on trough concentration and C/D ratio of tacrolimus in case 1.

A 63-year-old female, BW 61.6 kg, BMI 27.8 kg/m^2. Living-donor liver transplantation (hepatocellular carcinoma). CYP3A5 genotype (Recipient: *3/*3, Donor: *3/*3). The black and grey bars represent the administration of tacrolimus and amenamevir, respectively. The blood tacrolimus concentration was analyzed by the chemiluminescent immunoassay method (Abbott Japan LLC). The calibration range was from 0.0 to 30.0 ng/mL with a quantitation limit of 2.0 ng/mL. Abbreviations: BW; body weight, BMI; body mass index, C/D; concentration/dose-normalized body weight, SR-Tac; sustained-release tacrolimus, AMN; amenamevir, ACV; acyclovir.

(b). Influence of amenamevir on C2 and C/D ratio of cyclosporine in case 2.

A 71-year-old female, BW 52.5 kg, BMI 21.9 kg/m^2. Nephrotic syndrome (membranous nephropathy). CYP3A5 genotype: Unknown. The black and grey bars represent the administration of cyclosporine and amenamevir, respectively. The blood cyclosporine concentration was analyzed by the affinity chrome mediated Immunoassay (Siemens Healthineers Co., Ltd.). The calibration range was from 25.0 to 500.0 ng/mL with a quantitation limit of 25.0 ng/mL. *Trough concentration of CyA. Abbreviations: BW; body weight, BMI; body mass index, C2; concentration at 2 h post-dose, C/D; concentration/dose-normalized body weight, CyA; cyclosporine, AMN; amenamevir.

2 h post-dose (C2) while co-administrating amenamevir was 150-170 ng/mL, although on the way to steady-state. There was no change in the cyclosporine C2 level on day 19 after the discontinuation of amenamevir (170.4 ng/mL).

DISCUSSION

The short-term use of amenamevir can be co-administered with low concentrations of calcineurin inhibitors. The calculated gastrointestinal concentration of amenamevir is >3000 μM

(an oral dose of 400 mg with 250 mL water and molecular weight; 482.552), which is higher than a reported blood concentration (3.9 μM).[2] Conceptually, amenamevir can attain concentrations that induce CYP3A4/5; however, the induction of metabolism for calcineurin inhibitors was not observed. This finding is supported by physiologically-based pharmacokinetic simulation, which outputted that area under the plasma drug concentration-time curve ratio when given amenamevir at 400 mg × 1 was 0.890 (tacrolimus) and 0.843 (cyclosporine) based on the pharmacokinetic profile of amenamevir[3] (Appendix 1).

Tacrolimus is mainly metabolized by CYP3A4 in the loss of CYP3A5 function (case 1). Nonetheless, there was no significant change in tacrolimus pharmacokinetics. Amenamevir did not alter cyclosporine C2 (case 2), an alternative marker of the area under the plasma drug concentration-time curve for nephrotic syndrome.[4] Strong CYP3A4 inducers (e.g., rifampin) have been reported to increase the clearance of calcineurin inhibitors by ≥50% in the range of tacrolimus >5.0 ng/mL.[5,6] Additionally, the dosing period of amenamevir was shorter in our cases than in a drug-drug interaction study (4 or 5 days vs. 10 days).[2] Furthermore, there were no influential factors affecting CYP metabolism including inflammatory disorders and concomitant use of CYP3A4 and/or P-glycoprotein inhibitors (e.g., azole antifungals, grapefruit, and St John's wort) in the medical records from two cases. Notably, Adeloye *et al*. reported that co-administered amenamevir with cyclosporine decreases amenamevir exposure, and they hypothesized auto-induction by amenamevir, but this remains clarified.[2]

Consequently, our data indicated that amenamevir has a limited effect on the metabolism of calcineurin inhibitors at low concentrations.

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Conflict of interest The authors declare no conflict of interest.

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