Journal of Pharmaceutical Health Care and Sciences

CASE REPORT

Open Access

Markedly elevated blood concentrations of everolimus during concomitant posaconazole therapy in a liver transplant recipient: a case report

Machiko Hirai[1], Keisuke Umemura[1], Yoshiki Katada[1*], Yusuke Kojima[1], Hiroki Ishimura[1], Yurie Katsube[1], Daiki Hira[1], Shoichi Kageyama[2], Masahiro Tsuda[1,3], Shunsaku Nakagawa[1], Etsuro Hatano[2] and Tomohiro Terada[1]

Abstract

Background Everolimus (EVL) is widely used as an immunosuppressive agent in combination with calcineurin inhibitors, including tacrolimus (TAC), after liver transplantation. Posaconazole (PSCZ) is a triazole antifungal agent used for the treatment and prophylaxis of invasive fungal infections. Because PSCZ is a potent inhibitor of cytochrome P450 (CYP) 3A4, clinically significant drug–drug interactions with CYP3A substrates may occur. Although both EVL and TAC are primarily metabolized by CYP3A4, quantitative clinical data regarding the relationship between EVL and PSCZ remain limited.

Case presentation We report the case of a living-donor liver transplant patient receiving EVL and TAC who was treated with PSCZ for suspected allergic bronchopulmonary mycosis. During PSCZ therapy, the concentration/dose (C/D) ratios of EVL and TAC increased by approximately 15-fold and 6-fold, respectively. The PSCZ trough concentration reached 8.8 μg/mL, and the serum potassium level decreased 2.5 mmol/L. Both the magnitude of increase in TAC exposure and increase in EVL exposure were more pronounced than those reported previously. Excessive PSCZ exposure may have augmented CYP3A inhibition, and the greater dependence of EVL metabolism on CYP3A compared to TAC likely contributed to the marked elevation in EVL exposure.

Conclusions This case suggests that the drug–drug interaction between EVL and PSCZ may be more pronounced than that between TAC and PSCZ in certain cases with high PSCZ concentrations. When PSCZ is co-administered with EVL, close monitoring of the EVL concentration is recommended. Therapeutic drug monitoring of PSCZ may also be considered in selected cases to optimize safety and avoid excessive exposure, particularly when adverse events are suspected or clinically significant drug–drug interactions are anticipated.

Keywords Everolimus, Posaconazole, Tacrolimus, Drug–drug interaction, Liver transplantation, CYP3A

*Correspondence:
Yoshiki Katada
katada@kuhp.kyoto-u.ac.jp
[1]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
[2]Division of Hepato-Biliary Pancreatic Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan
[3]Department of Pharmacy, University of Fukui Hospital, 23-3 Matsuoka-Shimoaizuki, Eiheiji-Cho, Yoshida-Gun, Fukui 910-1193, Japan

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

Everolimus (EVL) is a rapamycin derivative that inhibits the mammalian target of rapamycin (mTOR). EVL is used as an immunosuppressant in combination with calcineurin inhibitors (CNIs), including tacrolimus (TAC) and cyclosporine, in liver transplantation recipients [1]. Because liver transplant recipients require long-term immunosuppressive treatment, they are highly susceptible to invasive fungal diseases [2]. Posaconazole (PSCZ) is a triazole antifungal agent commonly used for the treatment and prophylaxis of invasive fungal infections [3] and functions as a potent inhibitor of cytochrome P450 (CYP) 3A4 [4]. Therefore, clinically significant drug–drug interactions may occur when PSCZ is co-administered with CYP3A substrates.

TAC is primarily metabolized by CYP3A4/5 and is a substrate of P-glycoprotein (P-gp). Consequently, the concomitant administration of PSCZ markedly increases TAC blood concentration in solid organ transplant patients, and various strategies for managing TAC concentration during PSCZ therapy have been extensively investigated [5, 6]. In these reports, the TAC trough concentration/dose (C/D) ratio elevated to 4.4-fold on average, and TAC dose reduction to approximately one-third has been suggested to maintain TAC therapeutic ranges. EVL is predominantly metabolized by CYP3A enzymes and is eliminated mainly via biliary excretion. In addition, EVL is also a substrate of P-gp [7]. Despite these pharmacokinetic similarities, quantitative clinical data regarding drug–drug interactions between EVL and PSCZ remain limited compared to those between TAC and PSCZ. Several studies have reported the interactions between EVL and other triazole antifungal agents with CYP3A-inhibitory properties. For example, with voriconazole, the mean C/D ratio of EVL increased approximately 8.7-fold during cotreatment therapy in lung transplant recipients, and EVL trough concentrations increased 7.5-fold in renal transplant recipients [8, 9]. Similarly, co-administration of itraconazole was associated with a 74% reduction in EVL clearance in renal transplant recipients [10]. A previous study demonstrated that the EVL trough C/D ratio was 3.5-fold higher during PSCZ co-administration than that without PSCZ in lung transplant recipients [11]. Another study revealed that a 3.8-fold increase in EVL trough concentration during PSCZ therapy in a renal transplant recipient [9]. Based on these previous reports, the drug–drug interaction between EVL and PSCZ might be expected to be of comparable magnitude to that between TAC and PSCZ. However, we observed a marked elevation in the EVL concentration induced by PSCZ in a liver transplant case.

The recommended EVL trough concentration range is 3–8 ng/mL for kidney, liver, and heart transplantation patients [12]. EVL trough concentrations exceeding 8 ng/mL have been associated with a higher incidence of adverse events, such as thrombocytopenia and hypertriglyceridemia, than concentrations within the 3–8 ng/mL range (thrombocytopenia: 3–9%, hypertriglyceridemia: 22–39%, respectively) [13]. Furthermore, Shihab et al. evaluated EVL-related adverse events across trough concentration categories (< 3, 3–6, 6–8, 8–12, and > 12 ng/mL) and reported that the lowest incidence of adverse events, including delayed wound healing, peripheral edema, dyslipidemia, and proteinuria, was observed in the 3–8 ng/mL group [14]. Therefore, maintaining blood concentrations of EVL within the therapeutic range is essential for minimizing exposure-dependent toxicities.

Here, we report the case of a liver transplant patient who received concomitant PSCZ and EVL therapy for allergic bronchopulmonary mycosis, resulting in a marked elevation of EVL blood concentrations. This report describes the clinically observed drug–drug interactions between PSCZ and EVL in a liver transplant case and discusses practical management strategies in transplant settings.

Case presentation

The patient was a woman in her sixties who had undergone living-donor liver transplantation at our institution, Kyoto University Hospital, for hepatitis B virus-induced cirrhosis and hepatorenal syndrome 8 years prior to 20XX (20XX-8). Table 1 represents the patient characteristics, baseline laboratory parameters, and prescribed medications. The patient was prescribed with EVL (Certican®) 1.5 mg/day and extended-release TAC (Graceptor®) 0.2 mg once every two days. The trough EVL level was well controlled at approximately 5 ng/mL (target trough value: approximately 5 ng/mL), and the trough TAC level was also well controlled at approximately 0.5 ng/mL (target trough value: 0.5–2 ng/mL). Her regular medications included EVL (0.75 mg twice daily), TAC (0.2 mg once every two days), mycophenolate mofetil (250 mg twice daily), prednisolone (1.5 mg once daily), and entecavir (0.5 mg once every two days). The genetic polymorphism of *CYP3A5* in this patient was **3/*3*. At our institution, *CYP3A5* genetic polymorphism is routinely assessed in liver transplant recipients receiving TAC, provided that informed consent is obtained, because it is known to significantly influence TAC pharmacokinetics and support individualized dose optimization.

The patient experienced cough and was treated by inhaled corticosteroid/long-acting β-agonists (mometasone furoate 80 μg/indacaterol 150 μg once daily) and carbocisteine (500 mg twice daily), but symptoms persisted. A chest computed tomography scan revealed residual opacity and sputum culture detected filamentous fungi. The patient was suspected to have allergic bronchopulmonary mycosis. The patient's primary surgeon

Table 1 Baseline characteristics, laboratory parameters, and medications and doses administered

Variable	
Characteristics	
Age (years)	60s
Sex	Female
Height (cm)	151.8
Weight (kg)	46.9
CYP3A5 genotype	**3/*3*
Laboratory parameters	
Aspartate aminotransferase (U/L)	22
Alanine aminotransferase (U/L)	17
Total bilirubin (mg/dL)	0.5
Albumin (g/dL)	4.2
Prothrombin time-international normalized ratio (PT-INR)	1.01
Platelet ($\times 10^9$/L)	157
Creatinine (mg/dL)	0.81
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2)	54.2
Potassium (mmol/L)	4.7
Type IV collagen 7 S (ng/mL)	3.8
Autotaxin (mg/L)	1.034
Mac2-binding protein glycosylation isomer (M2BPGi, cut-off index)	0.57
Medications	
Everolimus	1.5 mg/day
Tacrolimus (extended-release)	0.2 mg every two days
Mycophenolate mofetil	500 mg/day
Prednisolone	1.5 mg/day
Entecavir	0.5 mg every two days

and respiratory physician discussed the treatment, and oral PSCZ was prescribed (300 mg twice daily on day 0, followed by 300 mg once daily from day 1). Figure 1 summarizes the clinical course, including doses, TAC/EVL/PSCZ blood concentration levels, and serum creatinine and potassium levels. Considering possible drug–drug interactions, EVL was reduced to a half dosage (0.5 mg in the morning and 0.25 mg in the evening), and TAC was continued with the same dose (Fig. 1 (i)). The trough EVL and TAC levels 55 days prior to the start of PSCZ (day – 55) were 5.2 ng/mL and 0.6 ng/mL, respectively. Given the low baseline TAC concentration, the target levels were re-evaluated in consultation with the transplant physician, and a higher target concentration (up to approximately 2 ng/mL) was considered appropriate because TAC blood concentration of 0.6 ng/mL on day – 55 was low, and this fluctuation was within acceptable ranges. Accordingly, the TAC dose was maintained at the same dose. On day 6, the trough EVL level was high at 23.1 ng/mL and the trough TAC level was 2.2 ng/mL, but the patient did not develop any apparent adverse effects such as stomatitis or pancytopenia. In addition, the trough concentration of PSCZ was 7.3 μg/mL. McCreary et al. reported that toxicity threshold for PSCZ trough levels was above 3–3.75 μg/mL [15]; the trough PSCZ level was above the target range at the time of measurement. In Japan, therapeutic drug monitoring of PSCZ is not routinely performed in clinical practice, partly because it is not covered by the national health insurance system. Therefore, dose adjustment based on serum concentrations was not undertaken in this case, and treatment decisions were guided primarily by clinical assessment and tolerability.

The patient's serum potassium level decreased from 4.7 mmol/L (day – 55) to 3.4 mmol/L, which was attributed to an adverse effect of PSCZ administration. EVL was discontinued from the evening of day 6 up to day 8 (Fig. 1 (ii)) and resumed at 0.5 mg/day on day 9 (Fig. 1 (iii)). TAC and PSCZ were administered at the same doses. On day 14, the trough EVL level remained high at 20.7 ng/mL, the TAC level was 3.4 ng/mL, and the PSCZ level was 10.3 μg/mL. On the same day, the platelet count was 105×10^9/L, showing a decreasing trend (Table 2). Drug administration was suspended from the evening of day 6 to that of day 8 and then restarted at 0.5 mg/day. The subsequent blood EVL concentration was 20.7 ng/mL. Since this was approximately 4-times higher than the target trough concentration, reducing the dose by at least one quarter was necessary. Given the possibility that CYP3A inhibitory effects might be further enhanced after starting PSCZ, and that the next outpatient visit was scheduled after 1 week, discontinuation of the drug from the evening of day 14 to day 20 was decided.

EVL was again discontinued from the evening of day 14 to that of day 20 (Fig. 1 (iv)). During this period, TAC was reduced to 0.2 mg twice per week, while PSCZ was continued at the same dose. On day 21, the trough EVL level was 3.7 ng/mL, which was within the target range. The TAC level was 1.9 ng/mL, which was within the target range. EVL was resumed at 0.25 mg thrice per week, and TAC and PSCZ were continued at the same dose (Fig. 1 (v)). EVL was administered on Tuesdays, Thursdays, and Saturdays, and TAC was administered on Tuesdays and Fridays. Because EVL and TAC were administered following different dosing schedules, the days of a week were specified to facilitate medication adherence. The patient's adherence was consistently maintained. On day 28, the patient experienced leg edema with an increase in body weight of 2 kg. On day 41, her serum potassium level decreased to 2.4 mmol/L, and potassium chloride tablets (600 mg twice daily) were started. On day 49, her serum potassium level was 2.5 mmol/L, and the trough PSCZ level was 8.8 μg/mL. Her lung opacities improved, and PSCZ treatment was completed. Even after that, EVL (0.25 mg thrice a week) and TAC (0.2 mg twice a week) administration were continued at the same doses.

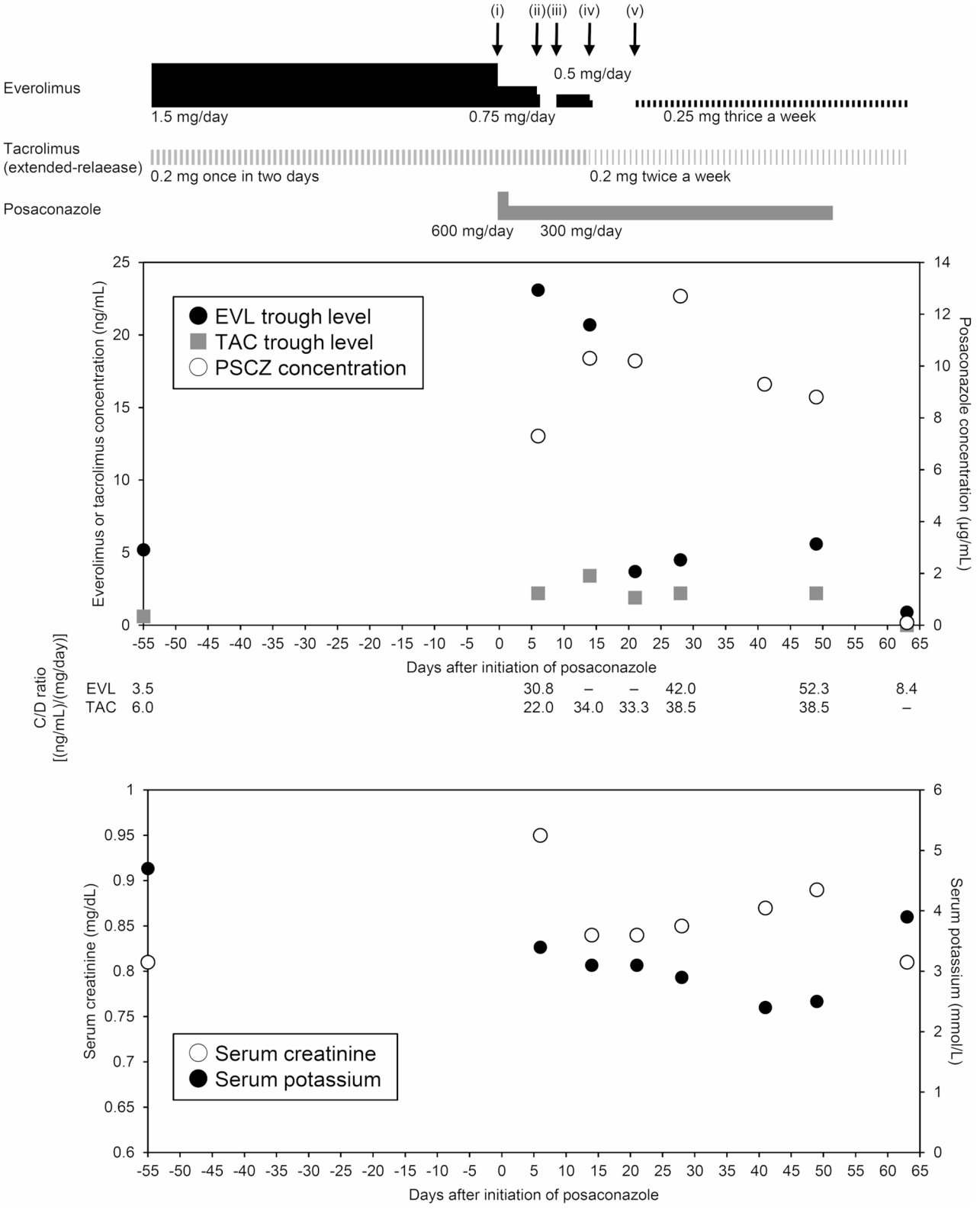


Fig. 1 The clinical course of the patient. EVL, TAC, and PSCZ doses, EVL and TAC trough levels, PSCZ concentrations, and laboratory parameters are shown. The C/D ratio was calculated as the drug concentration divided by the average daily dose over the last 7 days. For the C/D ratio, the daily dose was defined as the total dose administered over 7 days divided by 7. If a drug-free period was included, the daily dose could not be calculated and was denoted by a hyphen (–). If the concentration was below the limit of detection, the C/D ratio could not be calculated and was denoted by a hyphen (–). Panels (i) – (v) correspond to the intervention points described in the text. EVL, everolimus; TAC, tacrolimus; PSCZ, posaconazole; C/D, concentration/dose

Table 2 Results of laboratory tests regarding liver functions

Laboratory parameters	Day − 55	Day 6	Day 14	Day 21	Day 63
Aspartate aminotransferase (U/L)	22	20	18	19	17
Alanine aminotransferase (U/L)	17	15	13	14	13
Total bilirubin (mg/dL)	0.5	0.5	0.6	0.5	0.7
Albumin (g/dL)	4.2	3.8	3.3	3.3	3.4
Prothrombin time-international normalized ratio (PT-INR)	1.01	0.99	1.03	1.08	1.08
Platelet ($\times 10^9$/L)	157	151	105	121	182
Type IV collagen 7 S (ng/mL)	3.8	–	–	–	5.2
Autotaxin (mg/L)	1.034	–	–	–	0.881
Mac-2-binding protein glycosylation isomer (M2BPGi, cut-off index)	0.57	–	–	–	1.2

Post-transplant conditions of the patient were stable, and immunosuppressive agents comprised four medications (TAC, EVL, mycophenolate mofetil, and prednisolone); therefore, urgent increases of TAC and EVL doses were considered unnecessary. On day 63, her serum potassium level increased to 3.9 mmol/L, leg edema improved, and lung opacity did not worsen. Although the EVL and TAC trough levels decreased to 0.9 ng/mL and < 0.5 ng/mL respectively, her transaminases and bilirubin levels remained within the normal ranges (Table 2).

Discussion and conclusions

Administration of immunosuppressants after liver transplantation is necessary to prevent rejection. Because immunosuppressants generally have narrow therapeutic windows, careful attention must be paid to potential drug–drug interactions, particularly in transplant recipients who frequently require concomitant medications. In the present case, marked increases in the C/D ratios of EVL and TAC of approximately 15-fold and 6-fold, respectively, were observed during PSCZ therapy.

PSCZ is a potent inhibitor of CYP3A [4], and several studies have demonstrated that PSCZ significantly increases TAC exposure in patients undergoing solid organ transplantation [5, 6, 11]. In contrast, clinical data regarding drug–drug interactions between EVL and PSCZ remain limited. Chanoine et al. reported that the EVL trough C/D ratio was 3.5-fold higher during PSCZ co-administration than that without PSCZ in lung transplant recipients [11]. Similarly, Billaud et al. described a 3.8-fold increase in EVL trough concentration during PSCZ therapy in a renal transplant recipient [9]. However, to the best of our knowledge, no previous studies have described this interaction in liver transplant recipients. In the present report, we describe a liver transplant recipient in whom the concomitant administration of EVL and PSCZ resulted in a markedly greater increase in EVL exposure than previously reported. Although the liver function test results were almost within the normal range, given slightly elevated levels of type IV collagen and Mac-2-binding protein glycosylation isomer (M2BPGi), which are the markers of hepatic fibrosis, certain abnormalities in liver function after liver transplantation may have influenced EVL and/or PSCZ metabolism.

To explore the mechanism underlying this pronounced interaction, we applied the contribution ratio of the target metabolizing enzyme to the oral clearance of substrates and inhibition ratio of inhibitors (CR–IR method), which predicts the magnitude of drug–drug interactions based on the contribution of a metabolizing enzyme to the oral clearance of a substrate and the inhibitory potency of a co-administered drug [16]. Although systemic exposure is ideally assessed using the area under the concentration–time curve (AUC), its measurement is often impractical in routine clinical settings. Therefore, the C/D ratio was used as a surrogate marker in this study; however, it does not directly correspond to AUC and should be interpreted cautiously. In the CR–IR method, the contribution of CYP3A to oral clearance (CR_{CYP3A}) and the inhibition ratio of CYP3A (IR_{CYP3A}) were used to estimate the increase in the AUC according to the following equation:

$$\text{AUC increase} = 1/(1 - \text{CR}_{\text{CYP3A}} \times \text{IR}_{\text{CYP3A}}).$$

Based on previous reports, CR_{CYP3A} values for EVL and TAC were estimated to be 0.95 and 0.66, respectively, and the IR_{CYP3A} value for PSCZ was estimated to be 0.87 [7, 16–18]. Using these parameters, the predicted AUC increases for EVL and TAC during PSCZ co-administration were approximately 5.8-fold and 2.3-fold, respectively.

In contrast, in the present case, the observed increases in the C/D ratios of EVL and TAC after 49 days of PSCZ therapy were approximately 15-fold and 6.4-fold, respectively, which substantially exceeded the predicted values. The trough concentration of PSCZ reached 8.8 μg/mL, which was markedly higher than previously reported levels. McCreary et al. reported that the target PSCZ trough concentrations are ≥ 0.5–0.7 μg/mL for prophylaxis and ≥ 1–1.5 μg/mL for treatment, and trough concentrations exceeding 3–3.75 μg/mL are associated with an increased

risk of toxicity [15]. The observed concentration in this case substantially exceeded these thresholds. Relatively small body size and advanced age of the patient may have contributed to the elevated PSCZ exposure, as discussed later. Accordingly, this case may be more appropriately interpreted as a drug–drug interaction occurring under conditions of excessive PSCZ exposure, rather than typical co-administration. Such a high PSCZ concentration may have resulted in near-complete inhibition of CYP3A activity, thereby enhancing its interaction with EVL. Indeed, previous studies have demonstrated that high PSCZ concentrations significantly increase the mean trough levels of midazolam, a prototypical CYP3A substrate [17, 18]. In addition, co-administration of EVL and ketoconazole, a potent CYP3A inhibitor, increased EVL exposure by 11.2–17-fold [19]. Assuming an IR_{CYP3A} value of 0.99, the predicted AUC for EVL and TAC would be approximately 16.8-fold and 2.9-fold, respectively. This estimate closely approximates the observed increase in EVL exposure in the present case, although a discrepancy remains for TAC. As this is a single case report, the findings may not be generalizable to other patients. The PSCZ concentration in this case was markedly elevated compared with typical clinical settings, which may limit the applicability to other patients. Furthermore, the mechanistic interpretation based on the CR–IR method should be considered a plausible explanation, and other potential mechanisms cannot be excluded.

The greater increase in EVL exposure compared with TAC may be primarily explained by the higher dependence of EVL on CYP3A-mediated metabolism. In contrast, *CYP3A5* polymorphism may have contributed to interindividual variability in TAC exposure as a secondary factor. Notably, the patient harbored the *CYP3A5*3/*3* genotype, which is associated with the absence of CYP3A5 metabolic activity. This genetic background may further amplify the dependence of drug clearance on CYP3A4, potentially contributing to the unexpectedly large increase in EVL exposure. More detailed pharmacogenetic and pharmacokinetic analyses are required to fully elucidate the observed discrepancies, particularly for TAC.

The PSCZ trough concentrations in this study were consistent with the reported toxicity ranges. Several population pharmacokinetic studies identified factors associated with elevated PSCZ exposure. Kohl et al. reported that increasing age is associated with a decreased volume of distribution [20], whereas Vehreschild et al. demonstrated that higher body weight is correlated with a larger apparent volume of distribution [21]. In addition, AbuTarif et al. identified diarrhea, proton pump inhibitor use, and elevated serum bilirubin or gamma-glutamyl transferase levels as significant covariates affecting PSCZ exposure [22]. In the present case, there were no problematic issues with the patient's medication adherence or food intake, and no diarrhea was observed. The patient was in her sixties and had a body weight of 46.9 kg, with a BMI of 20.3, which was not indicative of underweight status but reflected a relatively small body size. Together, these findings suggest that patient-specific factors, including advanced age and relatively small body size, may have contributed to the elevated PSCZ concentration observed in this case. Although liver enzyme levels remained within normal ranges throughout the observation period, mild changes in synthetic function markers, such as albumin and platelet counts, and slight elevation of type IV collagen and M2BPGi levels were observed (Tables 1 and 2), suggesting that liver function may not have been entirely stable. These factors may also have influenced PSCZ exposure to some extent.

Hypokalemia has been reported as an adverse effect of PSCZ [23–25]. The underlying mechanism is thought to involve PSCZ-induced pseudohyperaldosteronism (PIPH), which is characterized by secondary hypertension, hypokalemia, and occasional metabolic alkalosis [26]. PIPH has been shown to be associated with elevated PSCZ blood concentrations [27]. Although renin–aldosterone levels were not measured, the temporal association with high PSCZ exposure suggests possible PIPH. Furthermore, in the present case, hypokalemia and leg edema developed concomitantly with high PSCZ exposure, suggesting that PIPH may have contributed to these symptoms. Hypokalemia due to PIPH is unlikely to be directly related to EVL, and is a recognized adverse effect associated with PSCZ.

Serum creatinine showed a slight increase from day 14 to day 49; however, the magnitude of change was small and therefore it was not considered clinically significant. A clear causal relationship with EVL, TAC, or PSCZ could not be established. This mild fluctuation may reflect variability related to clinical conditions or concomitant medications.

In conclusion, liver transplant recipients receiving long-term immunosuppressive therapy with CNI and mTOR inhibitors are at a high risk of clinically significant drug–drug interactions when triazole antifungal agents are prescribed. Our findings suggest that the interaction between EVL and PSCZ may be more pronounced than that between TAC and PSCZ, particularly in patients with high PSCZ exposure. When PSCZ is administered, especially to elderly or underweight patients, clinicians should be vigilant not only for PSCZ-related adverse effects, such as hypokalemia due to PIPH, but also for unexpectedly strong pharmacokinetic interactions with EVL. Therapeutic drug monitoring of immunosuppressants is essential, whereas monitoring of PSCZ concentrations may be considered in selected cases to optimize safety and avoid excessive exposure, particularly when

adverse events are suspected or clinically significant drug–drug interactions are anticipated. However, as measurement of PSCZ concentrations is not covered by insurance, routine monitoring may be challenging in some clinical settings and should therefore be reserved for selected clinical scenarios.

Abbreviations

AUC	Area under the concentration-time curve
C/D	Concentration/dose
CNIs	Calcineurin inhibitors
CR	Contribution ratio
CYP	Cytochrome P450
EVL	Everolimus
IR	Inhibition ratio
mTOR	Mammalian target of rapamycin
P-gp	P-glycoprotein
PIPH	Posaconazole-induced pseudohyperaldosteronism
PPI	Proton pump inhibitor
PSCZ	Posaconazole
TAC	Tacrolimus

Acknowledgements
We are grateful to the transplant surgeons, physicians, pharmacists, and nurses for their assistance with and care for the patient.

Author contributions
MH, KU, and Y Katada conceptualized and designed the study. MH, KU, and Y Katada drafted the manuscript. MH, KU, Y Katada, Y Kojima, and HI monitored the patient and acquired data. Y Katsube, DH, MT, SN, and TT critically reviewed the manuscript. SK and EH were the primary doctors who supervised the treatment. All authors contributed to the preparation of the final manuscript.

Funding
This study did not receive any specific grants from funding agencies in the public, commercial, or non-profit sectors.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This case report was prepared with full consideration of protecting personal information in compliance with the "Guidelines for the protection of patient privacy in medical papers including case reports and presentations at academic conferences." This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (R0545-2).

Consent for publication
The patient consented for publication of this report.

Competing interests
The authors declare no competing interests.

Received: 11 March 2026 / Accepted: 10 July 2026
Published online: 15 July 2026

References

1. Ganschow R, Pollok JM, Jankofsky M, Junge G. The role of everolimus in liver transplantation. Clin Exp Gastroenterol. 2014;7:329–43. https://doi.org/10.2147/CEG.S41780. eCollection.
2. Lum L, Lee A, Vu M, Strasser S, Davis R. Epidemiology and risk factors for invasive fungal disease in liver transplant recipients in a tertiary transplant center. Transpl Infect Dis. 2020;22:e13361. https://doi.org/10.1111/tid.13361. [EPub].
3. Torres HA, Hachem RY, Chemaly RF, Kontoyiannis DP, Raad II. Posaconazole: a broad-spectrum triazole antifungal. Lancet Infect Dis. 2005;5:775–85. https://doi.org/10.1016/S1473-3099(05)70297-8.
4. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharm Sci. 2004;21:645–53. https://doi.org/10.1016/j.ejps.2004.01.005.
5. Vanhove T, Bouwsma H, Hilbrands L, Swen JJ, Spriet I, Annaert P, et al. Determinants of the magnitude of interaction between tacrolimus and voriconazole/posaconazole in solid organ recipients. Am J Transpl. 2017;17:2372–80. https://doi.org/10.1111/ajt.14232. [EPub].
6. Berge M, Chevalier P, Benammar M, Guillemain R, Amrein C, Lefeuvre S, et al. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. Ther Drug Monit. 2009;31:396–9. https://doi.org/10.1097/FTD.0b013e31819de6fd.
7. Kovarik JM, Beyer D, Schmouder RL. Everolimus drug interactions: application of a classification system for clinical decision making. Biopharm Drug Dispos. 2006;27:421–6. https://doi.org/10.1002/bdd.524.
8. Outeda Macías M, Salvador Garrido P, Elberdín Pazos L, Martín Herranz MI. Management of everolimus and voriconazole interaction in lung transplant patients. Ther Drug Monit. 2016;38:305–12. https://doi.org/10.1097/FTD.0000000000000294.
9. Billaud EM, Antoine C, Berge M, Abboud I, Lefeuvre S, Benammar M, et al. Management of metabolic cytochrome P450 3A4 drug-drug interaction between everolimus and azole antifungals in a renal transplant patient. Clin Drug Investig. 2009;29:481–6. https://doi.org/10.2165/00044011-200929070-00006.
10. Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. Clin Pharmacol Ther. 2001;70:247–54. https://doi.org/10.1067/mcp.2001.118022.
11. Chanoine S, Gautier-Veyret E, Pluchart H, Tonini J, Fonrose X, Claustre J, et al. Tablets or oral suspension for posaconazole in lung transplant recipients? Consequences for trough concentrations of tacrolimus and everolimus. Br J Clin Pharmacol. 2021;87:427–35. https://doi.org/10.1111/bcp.14398. [EPub] 2020 Jun 22.
12. van Gelder T, Fischer L, Shihab F, Shipkova M. Optimizing everolimus exposure when combined with calcineurin inhibitors in solid organ transplantation. Transpl Rev (Orlando). 2017;31:151–7. https://doi.org/10.1016/j.trre.2017.02.007. [EPub].
13. Kovarik JM, Tedesco H, Pascual J, Civati G, Bizot MN, Geissler J, et al. Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. Ther Drug Monit. 2004;26:499–505. https://doi.org/10.1097/00007691-200410000-00007.
14. Shihab FS, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. Clin Transpl. 2013;27:217–26. https://doi.org/10.1111/ctr.12045. [EPub] 2012 Dec 12.
15. McCreary EK, Davis MR, Narayanan N, Andes DR, Cattaneo D, Christian R, et al. Utility of triazole antifungal therapeutic drug monitoring: insights from the Society of Infectious Diseases Pharmacists: endorsed by the Mycoses Study Group Education and Research Consortium. Pharmacotherapy. 2023;43:1043–50. https://doi.org/10.1002/phar.2850.
16. Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet. 2007;46:681–96. https://doi.org/10.2165/00003088-200746080-00005.
17. Krishna G, Moton A, Ma L, Savant I, Martinho M, Seiberling M, et al. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: a phase I, randomized, open-label, crossover study in healthy volunteers. Clin Ther. 2009;31:286–98. https://doi.org/10.1016/j.clinthera.2009.02.022.
18. Krishna G, Ma L, Prasad P, Moton A, Martinho M, O'Mara E. Effect of posaconazole on the pharmacokinetics of simvastatin and midazolam in healthy volunteers. Expert Opin Drug Metab Toxicol. 2012;8:1–10. https://doi.org/10.1517/17425255.2012.639360. [EPub] 2011 Dec 19.
19. Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Blood concentrations of everolimus are markedly increased by ketoconazole. J Clin Pharmacol. 2005;45:514–8. https://doi.org/10.1177/0091270005275368.
20. Kohl V, Müller C, Cornely OA, Abduljalil K, Fuhr U, Vehreschild JJ, et al. Factors influencing pharmacokinetics of prophylactic posaconazole in patients

undergoing allogeneic stem cell transplantation. Antimicrob Agents Chemother. 2010;54:207–12. https://doi.org/10.1128/AAC.01027-09.
21. Vehreschild JJ, Müller C, Farowski F, Vehreschild MJ, Cornely OA, Fuhr U, et al. Factors influencing the pharmacokinetics of prophylactic posaconazole oral suspension in patients with acute myeloid leukemia or myelodysplastic syndrome. Eur J Clin Pharmacol. 2012;68:987–95. https://doi.org/10.1007/s00228-012-1212-y.
22. AbuTarif MA, Krishna G, Statkevich P. Population pharmacokinetics of posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. Curr Med Res Opin. 2010;26:397–405. https://doi.org/10.1185/03007990903485056.
23. Martino J, Fisher BT, Bosse KR, Bagatell R. Suspected posaconazole toxicity in a pediatric oncology patient. Pediatr Blood Cancer. 2015;62:1682. https://doi.org/10.1002/pbc.25568.
24. Boughton C, Taylor D, Ghataore L, Taylor N, Whitelaw BC. Mineralocorticoid hypertension and hypokalaemia induced by posaconazole. Endocrinol Diabetes Metab Case Rep. 2018;2018:17–0157. https://doi.org/10.1530/EDM-17-0157. eCollection.
25. Mahmood M, Abu Saleh O, Sohail MR. Hypokalemia and hypertension associated with supratherapeutic posaconazole levels. Antimicrob Agents Chemother. 2017;61:e00019–17. https://doi.org/10.1128/AAC.00019-17. Print.
26. Kuriakose K, Nesbitt WJ, Greene M, Harris B. Posaconazole-induced pseudohyperaldosteronism. Antimicrob Agents Chemother. 2018;62:e02130–17. https://doi.org/10.1128/AAC.02130-17. Print.
27. Nguyen MH, Davis MR, Wittenberg R, Mchardy I, Baddley JW, Young BY, et al. Posaconazole serum drug levels associated with pseudohyperaldosteronism. Clin Infect Dis. 2020;70:2593–8. https://doi.org/10.1093/cid/ciz741.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.