Influence of azole antifungal drugs on blood tacrolimus levels after switching from intravenous tacrolimus to once-daily modified release tacrolimus in patients receiving allogeneic hematopoietic stem cell transplantation

Short title: Differential effects of VRCZ and FLCZ on variation in pharmacokinetics of Tac-MR

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CONFLICT OF INTEREST

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Summary

What is known and objective: Azole antifungal drugs are often co-administered with tacrolimus after allogeneic hematopoietic stem cell transplantation (HSCT). However, the influence of azole antifungal drugs on variation in tacrolimus pharmacokinetics when switching from intravenous tacrolimus (Tac-iv) to once-daily modified release tacrolimus (Tac-MR) remains to be elucidated. This study was performed to evaluate the effects of oral azole antifungal drugs on variation in tacrolimus pharmacokinetics after conversion to Tac-MR in HSCT patients.

Methods: Patients concomitantly receiving fluconazole (FLCZ) or voriconazole (VRCZ) along with tacrolimus were evaluated retrospectively. Blood tacrolimus concentrations before and after changing to oral administration were compared between FLCZ and VRCZ groups.

Results and discussion: A total of 52 patients (34 FLCZ and 18 VRCZ) were included in the analysis. There were no significant differences in the most recent daily dose (D_{iv}) and blood level (C_{iv}) of Tac-iv, C_{iv}/D_{iv}, and ratio of daily dose of tacrolimus on the first to second day after changing to Tac-MR ($D_{po1\text{-}2}$) to D_{iv} between FLCZ and VRCZ groups ($P > .2$). The trough levels of tacrolimus on the first to second day after switching to Tac-MR ($C_{po1\text{-}2}$) and on the third to fifth day after the switch ($C_{po3\text{-}5}$) were significantly higher in the VRCZ group than the FLCZ group ($P < .05$). The values of $(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$ and $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ in the VRCZ group were significantly lower compared with those in the FLCZ group ($P < .05$). Furthermore, individual values of $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ in the FLCZ group varied widely.

What is new and conclusion: VRCZ increased blood tacrolimus level more markedly than FLCZ after switching to Tac-MR, while FLCZ caused a large variation in tacrolimus blood level. These results suggest that therapeutic monitoring of tacrolimus after the switch may need to be performed carefully considering that orally co-administered VRCZ and FLCZ exhibit different change in blood tacrolimus level just after the switch.

1 WHAT IS KNOWN AND OBJECTIVE

Tacrolimus is an immunosuppressive drug that is widely used in patients undergoing transplantation and in those with autoimmune diseases. In allogeneic hematopoietic stem cell transplantation (HSCT), tacrolimus is effective for the prophylaxis of graft-versus-host disease.[1-3] As the pharmacokinetics of tacrolimus show large inter- and intra-individual variabilities, therapeutic monitoring of this drug is required to reduce the side effects and increase its effectiveness. Tacrolimus is predominantly metabolized by cytochrome P450 3A4 (CYP3A4) and CYP3A5 in the liver and small intestine.[4-6] Azole antifungal drugs are frequently used during the administration of tacrolimus to prevent fungal infections after HSCT. Azole antifungal drugs inhibit CYP3A activity and therefore increase the blood level of tacrolimus.[6-8] In addition, the degree of CYP3A inhibition is known to vary among azole antifungal drugs.[9] Therefore, the extent of blood tacrolimus concentration elevation in HSCT patients is considered to be dependent on the co-administered azole antifungal drugs.

Treatment with tacrolimus is commonly begun by continuous infusion the day before HSCT. When oral intake becomes possible following HSCT, tacrolimus is switched to oral administration. Oral administration of tacrolimus was first developed as a twice-daily formulation (Prograf®). Recently, once-daily modified release tacrolimus (Tac-MR; Graceptor® in Japan, Astagraf XL® in the US, and Advagraf® in Europe) has been developed to improve patient adherence.[10,11] A previous study showed that blood tacrolimus levels in HSCT patients were decreased by conversion from intravenous tacrolimus (Tac-iv) to Tac-MR.[12] This change in tacrolimus blood level when tacrolimus formulation is changed

from Tac-iv to Tac-MR should be investigated. In addition, tacrolimus blood levels were reported to vary depending on co-administered azole antifungal drugs when the route of administration of tacrolimus is changed from continuous intravenous infusion to twice-daily oral formulation.[13] In fact, it is difficult to control the blood concentrations of tacrolimus just after changing from Tac-iv to oral formulation and hence dose adjustment of tacrolimus is required in many cases. However, there have been no clinical reports regarding the influence of azole antifungal drugs on variability in tacrolimus pharmacokinetics after switching from Tac-iv to Tac-MR in HSCT patients. As the pharmacokinetics of Tac-MR differ from the conventional twice-daily formulation,[14] it is clinically important to elucidate the characteristics of the interactions between Tac-MR and azole antifungal drugs.

In this study, we evaluated the effects of oral azole antifungal drugs on variation in tacrolimus pharmacokinetics when changing route of administration from Tac-iv to Tac-MR in HSCT patients.

2 METHODS

2.1 Study design, setting, and patient population

This retrospective study was conducted at Shinshu University Hospital. The study population consisted of 57 patients who received HSCT at our hospital and were discharged between January 2009 and December 2015, were ≥ 20 years old, switched from Tac-iv to Tac-MR, and concomitantly received oral azole antifungal drugs on switching the tacrolimus administration route. Patients who received drugs that would affect the pharmacokinetics of tacrolimus (four

patients receiving certain calcium channel blocker), in whom the dose of azole antifungal drug changed 1 to 5 day(s) after switching the route of tacrolimus, and those with period from transplantation to switching the administration route > 90 days (one patient) were excluded from this study. Therefore, the analyses were performed in 52 patients. The affecting drugs were defined as those causing CYP3A-mediated drug interactions described in the contraindications and precautions for co-administration in the Japanese Ethical Drug Package Insert of Graceptor®.[15]

The study was approved by the Ethics Committee of Shinshu University School of Medicine.

2.2 HSCT regimen and measurement of blood tacrolimus concentrations

Patients underwent conditioning chemotherapy with or without total body irradiation 7 to 2 days before HSCT. At the beginning of conditioning chemotherapy, the patients also started to receive oral azole antifungal drugs for the prophylaxis of fungal infections. The patients received Tac-iv by continuous infusion 1 day before HSCT. When oral administration of tacrolimus was enabled at the discretion of the attending physician, patients switched from Tac-iv to Tac-MR. The daily dose of tacrolimus was adjusted to maintain blood levels between 10 and 20 ng/mL in the continuous infusion period. After the switch to Tac-MR, the daily dose was adjusted to maintain blood trough levels between 5 and 10 ng/mL. Whole blood tacrolimus concentrations were measured by chemiluminescent immunoassay (CLIA) with the ARCHITECT i1000 System (Abbott Japan Co., Matsudo, Japan). The day on which

the route of tacrolimus administration was changed was defined as day 0.

2.3 Data collection and calculation

The following data were collected from the electronic medical records: sex, age, height, body weight, type of transplantation, period from transplantation to switch in route of tacrolimus administration, clinical laboratory parameters measured most recently before the switch (creatinine, total bilirubin, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, white blood cells, red blood cells, hemoglobin, hematocrit, platelet), the most recent daily dose (D_{iv}) and blood concentration (C_{iv}) of tacrolimus during continuous intravenous infusion, and drugs administered concomitantly when switching to Tac-MR. In addition, the daily dose of Tac-MR (D_{po}) and trough blood concentration of tacrolimus (C_{po}) at 1 to 5 day(s) after changing to Tac-MR were also collected.

2.4 Statistical analyses

The concentration to dose ratio (C/D ratio, ng/mL per mg/kg) of tacrolimus was calculated from its blood concentrations and daily doses during continuous intravenous infusion and oral administration. As the influence of continuous intravenous infusion persisted just after switching to oral administration, C_{po} was divided into C_{po} on the first to second day after the switch ($C_{po1\text{-}2}$) and C_{po} on the third to fifth day after the switch ($C_{po3\text{-}5}$). Furthermore, these C_{po} values were expressed as mean values due to missing data.

Continuous variables were expressed as the median and interquartile range and were compared using Wilcoxon's rank-sum test. Categorical variables were compared using Fisher's exact test or chi-square test. Correlations between factors were evaluated using Spearman's rank-correlation coefficient. All statistical calculations were carried out using the JMP® 11 (SAS Institute Inc., Cary, NC). In all analyses, $P < 0.05$ was taken to indicate statistical significance.

3 RESULTS

3.1 Patients characteristics

Baseline demographic characteristics of the patients are shown in Table 1. Of 52 patients, 34 and 18 received oral fluconazole (FLCZ) and voriconazole (VRCZ), respectively, when the route of tacrolimus was changed from continuous intravenous infusion to oral administration. Azole antifungal drugs other than FLCZ and VRCZ were not used in this population. There were no significant differences in sex, age, height, body weight, type of transplantation, days from transplantation to switch of the route of tacrolimus administration, creatinine, or hematological parameters between FLCZ and VRCZ groups. Laboratory liver function parameters, total bilirubin (0.5 mg/dL vs 0.4 mg/dL; $P = .0035$), aspartate aminotransferase (23.5 IU/L vs 18.0 IU/L; $P = .0093$), and alanine aminotransferase (26.0 IU/L vs 12.0 IU/L; $P = .0020$), were significantly higher in the FLCZ group than the VRCZ group. The frequencies of corticosteroids and mycophenolate mofetil, co-administered immunosuppressants, showed no significant differences between FLCZ and VRCZ groups. A similar result was also

observed with regard to proton pump inhibitors (labeprazole for 40 patients, esomeprazole for one patient).

3.2 Outcomes

Blood tacrolimus levels before and after conversion to oral administration were compared between FLCZ and VRCZ groups. There were no significant differences between FLCZ and VRCZ groups in the values of C_{iv}, D_{iv}, and C_{iv}/D_{iv} (Table 2). Furthermore, the ratio of conversion from intravenous to oral administration of tacrolimus, $D_{po1\text{-}2}/D_{iv}$, was similar between the two groups (3.8 vs 3.8; $P = .9309$). However, $C_{po1\text{-}2}$ and $C_{po3\text{-}5}$ were significantly higher in the VRCZ group than the FLCZ group (10.1 ng/mL vs 9.3 ng/mL; $P = .0360$, 8.8 ng/mL vs 7.5 ng/mL; $P = .0339$, respectively). The ratios of $C_{po1\text{-}2}/D_{po1\text{-}2}$ and $C_{po3\text{-}5}/D_{po3\text{-}5}$ in the VRCZ group tended to be higher than those in the FLCZ group [246.4 (ng/mL)/(mg/kg) vs 175.1 (ng/mL)/(mg/kg); $P = .0581$, 292.9 (ng/mL)/(mg/kg) vs 173.4 (ng/mL)/(mg/kg); $P = .0901$, respectively]. The ratio of C_{iv}/D_{iv} to C_{po}/D_{po}, an index of variation in blood tacrolimus concentration after conversion from intravenous to oral administration, was next compared between FLCZ and VRCZ groups. The ratio of $(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$ in the VRCZ group was significantly lower than that in the FLCZ group (4.1 vs 4.9; $P = .0108$; Figure 1A), indicating that VRCZ more markedly increased blood tacrolimus concentration than FLCZ. A similar result was observed for the ratio of $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ (3.3 for VRCZ vs 4.5 for FLCZ; $P = .0298$; Figure 1B), although the individual values in the FLCZ group varied widely [range (1.1 to 14.7) and interquartile range (3.2 to 7.9) for FLCZ, range

(0.9 to 6.6) and interquartile range (2.5 to 5.9) for VRCZ]. For two patients of the VRCZ group, the administration of Tac-MR was stopped temporarily on the first or second day after switching to Tac-MR due to the high blood level of tacrolimus. These patients had the two lowest values of $(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$ ratio among all of the patients analyzed. Therefore, the data on the third to fifth days after the switch in these two patients of the VRCZ group were not available.

Total bilirubin, aspartate aminotransferase, and alanine aminotransferase showed significant differences between FLCZ and VRCZ groups (Table 1). It is possible that the variations in these liver function parameters influenced the ratios of $(C_{iv}/D_{iv})/(C_{po}/D_{po})$. Therefore, we examined correlations between $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratios and liver function parameters. The $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratios were not significantly correlated with total bilirubin, aspartate aminotransferase, or alanine aminotransferase in all patients, as shown in Table 3 (all $P > .05$). Furthermore, these trends were unaltered even when stratified by the azole antifungal drugs (all $P > .05$).

4 DISCUSSION

This is the first study to evaluate the effects of azole antifungal drugs on blood tacrolimus levels after conversion from Tac-iv to Tac-MR in HSCT patients. The subjects included in this study concomitantly received either oral FLCZ or VRCZ along with tacrolimus. FLCZ is commonly used during the administration of tacrolimus to prevent fungal infections except for aspergillus infection after HSCT. On the other hand, VRCZ is administered primarily to

the patients with suspected or confirmed aspergillus infection. The selection of these azole antifungal drugs is determined according to guidelines established by the Japan Society for Hematopoietic Cell Transplantation. The FLCZ group showed significantly higher levels of total bilirubin, aspartate aminotransferase, and alanine aminotransferase compared with the VRCZ group. However, the median values of these liver function parameters were within the respective normal ranges. Furthermore, there were no significant correlations of these liver function parameters with $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratios in either group. Therefore, it was suggested that the differences in these liver function parameters between FLCZ and VRCZ groups may not affect the variations in blood tacrolimus levels.

Metabolic interactions between tacrolimus and azole antifungal drugs are well known. It has been reported that FLCZ and VRCZ elevate blood tacrolimus levels.[6-8] Our data regarding $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratios indicated that VRCZ increased blood tacrolimus concentrations more remarkably than FLCZ after conversion from intravenous to oral administration of tacrolimus. A previous study with a twice-daily formulation of tacrolimus indicated that the ratio of $(C_{po3\text{-}5}/D_{po3\text{-}5})/(C_{iv}/D_{iv})$ in the group with itraconazole or VRCZ co-administration was significantly higher than that in the FLCZ group, although this study included only a small number of patients receiving VRCZ ($n = 4$).[13] In addition, an *in vitro* study showed that VRCZ more potently inhibited CYP3A-mediated tacrolimus oxidation than FLCZ.[9] These findings suggested that marked elevation of blood tacrolimus concentration by VRCZ after changing to Tac-MR may be due to the stronger inhibitory effect of VRCZ on CYP3A activity as compared with FLCZ. When the route of tacrolimus administration is

changed from intravenous to oral administration, tacrolimus is metabolized not only in the liver but also in the small intestine. Thus, the intestinal metabolism of tacrolimus is inhibited by orally co-administered azole antifungal drugs. As Tac-MR is long retained in the intestinal tract due to the sustained-release formulation, drug interactions of tacrolimus with azole antifungal drugs in the small intestine may be long-lasting. In this study, two patients receiving VRCZ discontinued the administration of Tac-MR at first or second day after changing to Tac-MR, because of the high blood levels of tacrolimus. Therefore, care is required regarding marked elevation of tacrolimus blood levels in patients orally receiving VRCZ just after switching to Tac-MR.

The variability of the $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ ratio in the FLCZ group was greater than that in the VRCZ group. As medication management for the inpatients included in this study was operated under the supervision by medical staffs, the effect of medication adherence on the variation in tacrolimus concentrations may be negligible. Tacrolimus is metabolized by CYP3A4 and CYP3A5. A previous *in vitro* study showed that VRCZ inhibits the catalytic activities of CYP3A4 and CYP3A5 to a similar extent.[16] On the other hand, it has been reported that the inhibitory effect of FLCZ on CYP3A4 is approximately nine times stronger than that on CYP3A5.[17] Moreover, CYP3A5 is known to exhibit polymorphic expression that is mainly accounted for by the *CYP3A5*3* allele, which results in expression deficiency.[18] In the case of HSCT patients expressing CYP3A5, tacrolimus is metabolized by both CYP3A4 and CYP3A5. When CYP3A5-expressing patients concomitantly receive FLCZ, the potent inhibition of tacrolimus metabolism by FLCZ would be avoided, because

the metabolism of tacrolimus by CYP3A5 is less or weakly inhibited by FLCZ. On the other hand, tacrolimus is metabolized exclusively by CYP3A4 in CYP3A5 non-expressing patients. When these patients take FLCZ together with tacrolimus, the potent inhibition of tacrolimus metabolism by FLCZ would occur due to lack of CYP3A5-mediated tacrolimus metabolism. In fact, it has been reported that the blood concentration of tacrolimus (Tac-MR) after co-administration of FLCZ is significantly higher in CYP3A5 non-expressing patients than in those expressing CYP3A5.[19] These findings suggest that the variation in $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ ratio in the FLCZ group may be attributable to the isoform selectivity of FLCZ-mediated CYP3A inhibition and interindividual differences in CYP3A5 expression. No such variation was observed in the $(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$ ratio. This may have been because the influence of tacrolimus during continuous intravenous infusion may remain on the first to second day after switching to oral administration. Even if the tacrolimus blood level is stable for 1 – 2 days after the switch, this concentration may change after 3 – 5 days. When FLCZ is co-administered with tacrolimus, attention should be paid to altered blood levels of tacrolimus for several days after changing the route of administration from Tac-iv to Tac-MR.

There were some limitations in this medical record-based retrospective study. First, there were missing data regarding tacrolimus blood concentrations. It was preferable that $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratios on the same day after switching to Tac-MR were compared between FLCZ and VRCZ groups. However, we were not able to separate $C_{po1\text{-}2}$ and $C_{po3\text{-}5}$ into a single day C_{po} due to missing data and then evaluate these ratios on the same day after the

switch. Second, the *CYP3A5* genotypes were not taken into account in this study. The rate of CYP3A5 non-expression is estimated to be 60.5% in the Japanese population.[20] The *CYP3A5* genotype is an important factor affecting the variation in tacrolimus pharmacokinetics. It has been reported that *CYP3A5* genetic polymorphism has a greater influence on the pharmacokinetics of Tac-MR than twice-daily tacrolimus formulation.[21,22] However, the *CYP3A5* genotypes of the subjects included in this study were unknown due to the retrospective nature of this study based on medical records. Last, we were not able to evaluate the variation in bioavailability of tacrolimus because of our study design, although its bioavailability as well as drug interactions with azole antifungal drugs is one of the factors influencing the variation in tacrolimus blood levels after switching to Tac-MR.

5 WHAT IS NEW AND CONCLUSION

Our results indicated that the degree of change in blood tacrolimus level when switching route of administration from Tac-iv to Tac-MR after HSCT was different between VRCZ and FLCZ. VRCZ elevated tacrolimus blood level more remarkably than FLCZ after the switch to Tac-MR. On the other hand, FLCZ caused a large variation in tacrolimus blood level. This study suggests that therapeutic monitoring of tacrolimus after switching from Tac-iv to Tac-MR may need to be performed carefully considering that orally co-administered VRCZ and FLCZ exhibit different change in blood tacrolimus level just after the switch.

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TABLE 1 Baseline demographic characteristics of HSCT patients receiving FLCZ and VRCZ

Variables	FLCZ group (n = 34)		VRCZ group (n = 18)		*P* Value
Sex, male, n (%)	17	(50.0)	10	(55.6)	.7029
Age, median (IQR), years	55.5	(23.5-63.0)	40.5	(30.3-61.5)	.2986
Height, median (IQR), cm	162.2	(155.1-172.3)	160.6	(153.1-170.6)	.6443
Body weight, median (IQR), kg	55.6	(48.5-62.3)	51.1	(45.6-59.0)	.2484
Body mass index, median (IQR)	20.5	(18.3-23.1)	19.9	(18.4-22.2)	.3711
Type of transplantation					.2067
BMT, n (%)	25	(73.5)	11	(61.1)	
CBT, n (%)	8	(23.5)	4	(22.2)	
PBSCT, n (%)	1	(3.0)	3	(16.7)	
Period from transplantation to switching the route of tacrolimus administration, median (IQR), days	31.5	(27.8-35.8)	28.0	(25.8-34.0)	.2284
Creatinine, median (IQR), mg/dL	0.8	(0.7-1.0)	0.7	(0.5-1.0)	.1214
Total bilirubin, median (IQR), mg/dL	0.5	(0.4-0.7)	0.4	(0.3-0.5)	.0035
Lactate dehydrogenase, median (IQR), IU/L	241.0	(195.5-319.3)	228.5	(176.5-283.3)	.6237
Aspartate aminotransferase, median (IQR), IU/L	23.5	(19.8-32.5)	18.0	(13.5-23.0)	.0093
Alanine aminotransferase, median (IQR), IU/L	26.0	(17.8-49.0)	12.0	(9.5-22.8)	.0020
Alkaline phosphatase, median (IQR), IU/L	284.5	(236.5-319.0)	254.0	(173.3-300.8)	.1690
White blood cell, median (IQR), $\times 10^3/\mu L$	3.2	(2.5-4.3)	4.3	(2.0-6.1)	.2901
Red blood cell, median (IQR), $\times 10^6/\mu L$	2.8	(2.6-3.1)	2.9	(2.7-3.2)	.4474
Hemoglobin, median (IQR), g/dL	8.9	(8.3-9.9)	9.5	(8.2-9.8)	.6166
Hematocrit, median (IQR), %	25.9	(24.5-28.3)	27.6	(25.2-29.0)	.2406
Platelet, median (IQR), $\times 10^4/\mu L$	4.0	(2.8-8.9)	6.5	(2.7-11.1)	.2645
Corticosteroids, n (%)	13	(38.2)	7	(38.9)	.9632
Mycophenolate mofetil, n (%)	5	(15.2)	4	(22.2)	.7029[a]
Proton pump inhibitors, n (%)	26	(76.5)	15	(83.3)	.7275[a]
FLCZ dose					
100 mg/day, n (%)	2	(5.9)	0	(0)	-[b]
200 mg/day, n (%)	31	(91.1)	0	(0)	-[b]
400 mg/day, n (%)	1	(2.9)	0	(0)	-[b]
VRCZ dose					
200 mg/day, n (%)	0	(0)	1	(5.6)	-[b]
400 mg/day, n (%)	0	(0)	17	(94.4)	-[b]

Abbreviations: FLCZ, fluconazole; VRCZ, voriconazole; IQR, interquartile range; BMT, bone marrow transplantation; CBT, cord blood transplantation; PBSCT, peripheral blood stem cell transplantation.

[a] Fisher's exact test.

[b] Not analyzed.

TABLE 2 Comparison of blood concentrations and daily doses of tacrolimus before and after conversion to oral administration between FLCZ and VRCZ groups

Variables	FLCZ group (n = 34)		VRCZ group (n = 18)		*P* Value
C_{iv}, median (IQR), ng/mL	12.0	(10.6-13.3)	12.6	(11.4-13.5)	.6169
D_{iv}, median (IQR), mg/kg/day	0.014	(0.010-0.018)	0.013	(0.009-0.015)	.2407
C_{iv}/D_{iv}, median (IQR), (ng/mL)/(mg/kg)	838.5	(704.1-1114.3)	957.4	(805.6-1229.4)	.2368
$C_{po1\text{-}2}$, median (IQR), ng/mL	9.3	(6.9-10.3)	10.1	(8.2-12.5)	.0360
$D_{po1\text{-}2}$, median (IQR), mg/kg/day	0.051	(0.041-0.062)	0.043	(0.036-0.061)	.1877
$C_{po1\text{-}2}/D_{po1\text{-}2}$, median (IQR), (ng/mL)/(mg/kg)	175.1	(102.7-265.2)	246.4	(160.4-355.1)	.0581
$D_{po1\text{-}2}/D_{iv}$, median (IQR)	3.8	(3.5-3.9)	3.8	(3.4-4.0)	.9309
$C_{po3\text{-}5}$, median (IQR), ng/mL	7.5	(6.2-9.0)	8.8	(7.1-12.1)[a]	.0339
$D_{po3\text{-}5}$, median (IQR), mg/kg/day	0.047	(0.026-0.069)	0.032	(0.026-0.052)[a]	.1731
$C_{po3\text{-}5}/D_{po3\text{-}5}$, median (IQR), (ng/mL)/(mg/kg)	173.4	(87.5-326.3)	292.9	(135.0-431.1)[a]	.0901
$D_{po3\text{-}5}/D_{iv}$, median (IQR)	3.1	(2.5-4.1)	2.9	(2.1-3.5)[a]	.0861

Abbreviations: C_{iv}, blood concentration of tacrolimus during the continuous intravenous infusion. D_{iv}, daily dose of tacrolimus during the continuous intravenous infusion; C_{po}, trough blood concentration of tacrolimus during the oral administration; D_{po}, daily dose of tacrolimus during the oral administration; po1-2, days 1 – 2 after conversion to oral administration; po3-5, days 3 – 5 after conversion to oral administration.

[a]n = 16.

TABLE 3 Correlation of $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ ratio with significantly different baseline characteristics between FLCZ and VRCZ groups

	$(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$		$(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$	
Variables	ρ[a]	*P* Value	ρ[a]	*P* Value
All patients (n = 52)				
Total bilirubin	0.1783	.2061	-0.0426[b]	.7690
Aspartate aminotransferase	0.0551	.6982	-0.0561[b]	.6986
Alanine aminotransferase	0.1950	.1660	0.0961[b]	.5069
FLCZ group (n = 34)				
Total bilirubin	-0.1205	.4971	-0.2559	.1441
Aspartate aminotransferase	-0.1668	.3457	-0.1915	.2780
Alanine aminotransferase	0.0142	.9364	0.0235	.8948
VRCZ group (n = 18)				
Total bilirubin	0.4165	.0855	-0.0590[c]	.8283
Aspartate aminotransferase	0.1293	.6090	-0.2096[c]	.4359
Alanine aminotransferase	0.1100	.6639	-0.3114[c]	.2403

Abbreviations: C_{iv}, blood concentration of tacrolimus during the continuous intravenous infusion. D_{iv}, daily dose of tacrolimus during the continuous intravenous infusion; C_{po}, trough blood concentration of tacrolimus during the oral administration; D_{po}, daily dose of tacrolimus during the oral administration; po1-2, days 1 – 2 after conversion to oral administration; po3-5, days 3 – 5 after conversion to oral administration.

[a]Spearman's rank-correlation coefficient.

[b]n = 50.

[c]n = 16.

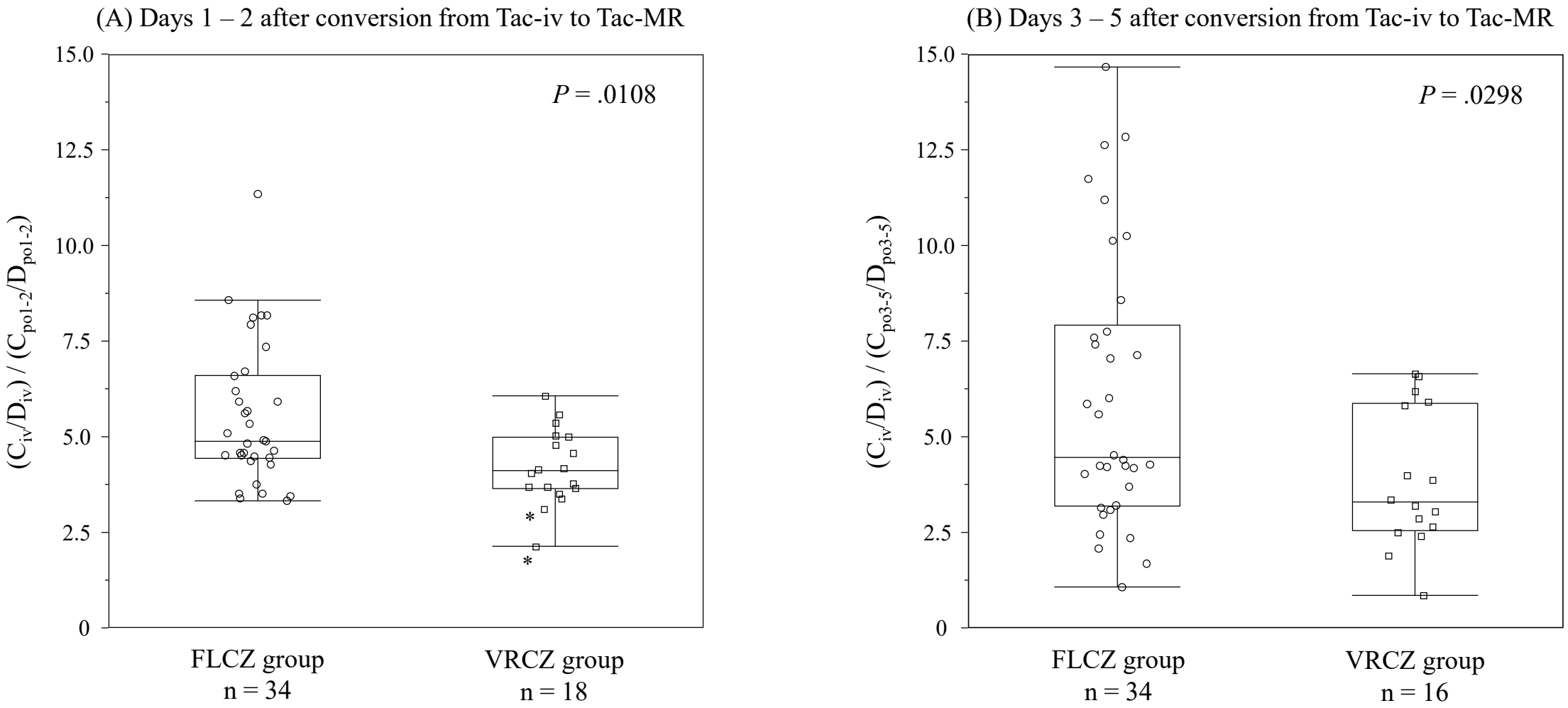
Figure legends

FIGURE 1 Comparison of $(C_{iv}/D_{iv})/(C_{po}/D_{po})$ between FLCZ and VRCZ groups.

(A) Data points show the $(C_{iv}/D_{iv})/(C_{po1\text{-}2}/D_{po1\text{-}2})$ ratios in individual HSCT patients receiving FLCZ (circles) and VRCZ (squares). *The administration of Tac-MR was discontinued due to the high blood level of tacrolimus. (B) Data points indicate the $(C_{iv}/D_{iv})/(C_{po3\text{-}5}/D_{po3\text{-}5})$ ratios in individual HSCT patients receiving FLCZ (circles) and VRCZ (squares).

Abbreviations: Tac-iv, intravenous tacrolimus; Tac-MR, once-daily modified release tacrolimus; C_{iv}, blood concentration of tacrolimus during continuous intravenous infusion. D_{iv}, daily dose of Tac-iv; C_{po}, trough blood concentration of tacrolimus after oral administration; D_{po}, daily dose of Tac-MR; 1-2, days 1 – 2 after conversion from Tac-iv to Tac-MR; 3-5, days 3 – 5 after conversion from Tac-iv to Tac-MR; FLCZ, fluconazole; VRCZ, voriconazole.

Figure 1


(A) Days 1 – 2 after conversion from Tac-iv to Tac-MR
P = .0108
(Civ/Div) / (Cpo1-2/Dpo1-2)
15.0
12.5
10.0
7.5
5.0
2.5
0
FLCZ group
n = 34
VRCZ group
n = 18
(B) Days 3 – 5 after conversion from Tac-iv to Tac-MR
P = .0298
(Civ/Div) / (Cpo3-5/Dpo3-5)
15.0
12.5
10.0
7.5
5.0
2.5
0
FLCZ group
n = 34
VRCZ group
n = 16