Current Therapeutic Research 102 (2025) 100775

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Effect of Hematopoietic Stem Cell Transplantation Regimen on Tacrolimus Pharmacokinetics

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ARTICLE INFO

Article history:
Received 31 July 2024
Accepted 23 December 2024

Key words:
hematopoietic stem cell transplantation
population pharmacokinetics
tacrolimus
therapeutic drug monitoring

ABSTRACT

Objectives: Treatment with tacrolimus requires strict control of the whole-blood concentration in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). In patients undergoing cord blood transplantation (CBT), there is a negative correlation between volume of distribution of tacrolimus and hemoglobin levels, which reflect the red blood cell (RBC) count. In this study, we evaluated the influence of the conditioning regimen (myeloablative and reduced-intensity conditioning) or donor source (cord blood, bone marrow, and peripheral blood stem cells) on the pharmacokinetics of tacrolimus in patients undergoing HSCT, including those undergoing CBT. We also examined applicability of dosing strategy of tacrolimus considering the RBC count.

Methods: We retrospectively analyzed clinical data—including whole-blood tacrolimus concentrations—from patients with HSCT. The observation period spanned from first continuous intravenous infusions until switch to oral medication, transfer to another hospital, relapse, or death. Population pharmacokinetic analysis was performed on whole-blood tacrolimus concentrations obtained from therapeutic drug monitoring during the observation period. Patient characteristics and laboratory data were evaluated as covariates.

Results: We enrolled 91 patients undergoing HSCT (CBT: $n = 56$; bone marrow transplantation: $n = 22$; and peripheral blood stem cell transplantation: $n = 13$); 58 and 33 patients received myeloablative conditioning and reduced-intensity conditioning, respectively. Whole-blood tacrolimus concentrations were accurately captured ($n = 1{,}658$ measurements) using a one-compartment and additive error model. The conditioning regimen and donor source did not have an impact on the pharmacokinetics of tacrolimus. Therefore, these factors were not considered when forming the dosing strategy. Nevertheless, a negative correlation between volume of distribution and hemoglobin level was confirmed, indicating that monitoring the RBC count is useful in assessing the dosing strategy.

Conclusions: A tacrolimus dosing strategy that considers the variability in hemoglobin levels applies to all patients undergoing HSCT.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for various hematologic malignancies, involving a conditioning regimen followed by rigorous postoperative management. Conditioning regimens, encompassing chemotherapy, and total-body irradiation prevent graft rejection through immunosuppression and reduce tumor cell numbers.[1] These regimens include myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC), chosen based on individual patient conditions. The type of HSCT, such as cord blood transplantation (CBT), bone marrow transplantation (BMT), or peripheral blood stem cell transplantation (PBSCT), is selected based on human leukocyte antigen

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https://doi.org/10.1016/j.curtheres.2024.100775

(HLA) compatibility between donor and recipient.[2] During postoperative management, immunosuppressants prevent graft-versus-host disease (GVHD), a leading cause of nonrelapse mortality in HSCT patients.[3] Precise dosage control of these immunosuppressants is crucial as insufficient or excessive immunosuppression can increase the risk of GVHD or infection.

Tacrolimus, a commonly used immunosuppressant for preventing GVHD in HSCT patients,[4,5] has a narrow therapeutic index concentration range in whole blood (10–20 ng/mL) and exhibits significant intra- and interindividual variability in pharmacokinetics. Therefore, therapeutic drug monitoring is essential for adjusting tacrolimus doses.[6,7] Our previous study involved a population pharmacokinetic (PPK) analysis of tacrolimus in patients with CBT (a type of HSCT) to enhance whole-blood tacrolimus concentration control. This study's results revealed a negative correlation between hemoglobin levels (reflecting RBC count) and tacrolimus volume of distribution (V_d) in patients with CBT, suggesting that monitoring hemoglobin levels can improve tacrolimus concentration control.[8]

In patients with HSCT, RBC counts decline due to bone marrow damage during conditioning regimens, and the number of days until engraftment also differ depending on the donor source (CBT, BMT, or PBSCT).[9,10] In our institution, patients with CBT relatively retain hematopoietic function, as milder conditioning regimens are often used than other donor sources. In our previous study, we revealed that RBC count is a factor affecting tacrolimus pharmacokinetics in patients with CBT; however, we could not confirm the effect of conditioning regimen types on tacrolimus pharmacokinetics. By contrast, the outcome of patients with HSCT (i.e., engraftment rate) reportedly differs depending on the donor source; thus, we hypothesized that a reason may be the different tacrolimus exposure of different donor sources. BMT and PBSCT are often treated with intensive chemotherapy and total-body irradiation (conditioning regimen), whereas CBT may be milder than this regimen for BMT and PBSCT. Furthermore, CBT has a relatively low risk of GVHD, whereas BMT and PBSCT have a higher risk of GVHD and require postoperative management, including infection prevention and immunosuppression. Thus, the three have different characteristics and require different pre- and postoperative management protocols. That is, the pharmacokinetics of tacrolimus could change owing to differences in patients' condition, procedures, and the type of concomitant medications used at each donor source. Recent studies have reported that different donor sources differently correlate with RBC counts and whole-blood tacrolimus concentrations and that donor source is an indicator of the amount of tacrolimus distributed in RBC.[11] Therefore, conditioning regimens and donor sources may considerably influence the rate and duration of the decreased RBC count. However, studies investigating the impact of conditioning regimens or donor sources on tacrolimus pharmacokinetics are limited.

We assessed the influence of conditioning regimens and donor sources on tacrolimus pharmacokinetics in patients with HSCT, including recipients with CBT.

Patients and Methods

Patients and study design

We retrospectively analyzed clinical data—including whole-blood tacrolimus concentrations—from patients with HSCT treated at Kobe City Medical Center General Hospital and the Institute of Biomedical Research and Innovation Hospital between February 2011 and February 2019. This study was approved by the Ethics Committees of both hospitals (approval numbers: zu161210 and k171221, respectively) and was conducted in accordance with the Declaration of Helsinki.

We collected data on the patients' characteristics, including sex, age, total-body weight (TBW), donor source (CBT, BMT, or PBSCT), and conditioning regimen (MAC or RIC). We also collected the patients' laboratory data, including hemoglobin levels.

Basic HSCT protocol

All patients underwent HSCT and postoperative management under the supervision of a single medical team, following an identical protocol at both hospitals. The conditioning regimen included anticancer agents and total-body irradiation. Tacrolimus was administered as an intravenous continuous infusion (0.02 mg/kg/day [initial dose]) 1 day before HSCT. Dose adjustments were incorporated based on whole-blood tacrolimus concentration to maintain the target range of 10–20 ng/mL during the observation period. Tacrolimus levels were measured using a chemiluminescent immunoassay on an ARCHITECT i1000 SR analyzer (Abbott Japan Co., Ltd., Japan), with a 2-ng/mL detection limit. Selected patients were also administered other immunosuppressants such as methotrexate or mycophenolate mofetil in conjunction with tacrolimus. Infection prophylaxis included the use of antimicrobial, antiviral, or antifungal agents. RBC transfusions were administered according to clinical guidelines.[12] The observation period extended from the initiation of continuous intravenous infusions until patients transitioned to oral medication, were transferred to another medical institution, experienced disease relapse, or died.

Tacrolimus PPK analysis

We conducted a PPK analysis using a nonlinear mixed-effects model in Phoenix® NLME version 8.3 (Certara, St. Louis, MO, USA). The parameters were estimated employing the first-order conditional estimate-extended least squares (FOCE-ELS) method.

The pharmacokinetics of tacrolimus were described using a one-compartment model with first-order elimination.

Interindividual variability for all pharmacokinetic parameters was characterized using the following exponential error model Eq. (1):

$$P_i = \theta_p \times \exp(\eta_i) \quad (1)$$

where P_i is the pharmacokinetic parameter for the i^{th} individual, θ_p is the population mean value of the parameters, and η_i is the random effect following a normal distribution with mean 0 and variance ω^2.

The residual variability in the measurements was described by the following additive error model Eq. (2):

$$Obs_{ij} = Pred_{ij} + \varepsilon \quad (2)$$

where Obs_{ij} and $Pred_{ij}$ represent the j^{th} observed and predicted concentrations in the i^{th} patient, respectively, and ε is the random effect following a normal distribution with mean 0 and variance σ^2.

Covariate analysis and final PPK model development

In the univariate analysis, candidate covariates were individually introduced into the base model. Continuous variables (age, TBW, hemoglobin) were applied using a power model Eq. (3):

$$P_i = \theta_p \times \left(\frac{COV_i}{COV_{median}}\right)^{\theta_{COV}} \quad (3)$$

where P_i is the pharmacokinetic parameter for the i^{th} individual, θ_p is the population mean value of the parameters, COV_i is the i^{th} individual covariate, COV_{median} is the median value of the covariate, and θ_{COV} is the effect of the covariate on the pharmacokinetic

parameter. Categorical variables (sex, conditioning regimen, donor source, onset of engraftment, types of concomitant immunosuppressants, and types of azole antifungal agents) were introduced using an exponential category model Eq. (4):

$$P_i = \theta_p \times \theta_{COV}{}^{COV_i} \quad (4)$$

The significance of covariates influencing the pharmacokinetic parameters was determined using the objective function value (OFV). The difference in OFV (ΔOFV) from the base model was tested with the chi-squared test, with the number of degrees of freedom equal to the difference in parameters between the two models. Covariate selection followed a stepwise forward inclusion ($P < 0.01$) and backward elimination ($P < 0.001$) processes. Model validation methods are provided in the Supplementary Methods.

Effect of donor source or conditioning regimen on the random effects of each pharmacokinetic parameter

Each pharmacokinetic parameter's random effects (ηV_d and ηK_e) in individual patients were estimated using the Bayesian method with the final PPK model. These random effects were compared between donor sources (CBT, BMT, and PBSCT) and between conditioning regimens (MAC and RIC). Donor sources were compared using the Kruskal–Wallis test, whereas conditioning regimens were compared using the Mann–Whitney U test.

Statistical analysis

For categorical data, we used Fisher's exact test. Nonparametric tests were applied to continuous variable data: the Mann–Whitney U test used for two-group comparisons and the Kruskal –Wallis test for three-group comparisons. All tests were 2-sided, and $P < 0.05$ was considered to indicate statistical significance. All static statistical analyses were performed using R Version 4.3.1 software (The R Foundation for Statistical Computing).

Results

Patients' characteristics

Table 1 and Supplementary Table 1 present the patients' characteristics. We included 91 patients with HSCT, including 56 CBT, 22 BMT, and 13 PBSCT. Additionally, 58 and 33 patients received MAC and RIC, respectively. No statistically significant differences were found in the number of patients receiving each conditioning regimen (Fisher's exact test; $P = 0.494$). The days required for engraftment in patients undergoing CBT, BMT, and PBSCT were 22, 17, and 15, respectively. The CBT was associated with significantly longer engraftment periods than the other donor sources (Kruskal–Wallis test; $P = 0.00051$). Median hemoglobin levels were 8.6 g/dL (interquartile range: 8.1–9.1 g/dL), significantly lower than normal values. No statistically significant differences in hemoglobin levels were observed among patients who underwent CBT, BMT, and PBSCT. Renal function (serum creatinine) and hepatic function (aspartate transaminase and alanine transaminase) were normal in all patients. The median age of RIC and MAC patients was 58 and 44.5 years, respectively, indicating that patients receiving RIC were significantly older (Mann–Whitney U test; $P = 0.00023$).

Figure 1 depicts scatter plots of whole-blood tacrolimus concentration time, comprising 1,658 measurements from 91 patients. The median concentration was 13.2 ng/mL (2.8–29.9 ng/mL), with notable measurement variations.

Covariate analysis and PPK model development

In Table 2, the univariate analysis indicated that V_d was significantly associated with hemoglobin levels, TBW, and the type of conditioning regimen. However, the donor source type did not impact V_d or the elimination rate constant (K_e) due to the low ΔOFV and θ_{COV} close to 1.

The results of stepwise selection identified hemoglobin levels as a covariate for Vd (Table 3). Other factors did not exhibit statistical or clinical significance; thus, they were not considered covariates in the PPK model. Consequently, we incorporated hemoglobin levels and TBW as covariates for V_d in the final PPK model (model 12, Table 3).

Model validation

The final PPK model's GOF plots are presented in Supplementary Figure 1. The Obs versus PRED and Obs versus IPRED plots displayed symmetrical distributions, closely aligning with the identity line ($Y = X$) (Supplementary Figure 1A and B). This alignment indicates strong predictive performance. Furthermore, the CWRES versus PRED and CWRES versus time after dosing (i.e., elapsed time when each dose time is set to 0) plots did not exhibit any

Table 1
Characteristics of patients who underwent hematopoietic stem cell transplantation.

	Total ($n = 91$)	CBT ($n = 56$)	BMT ($n = 22$)	PBSCT ($n = 13$)
Demographic data				
Male/Female	53/38	33/23	10/12	10/3
Age (years), median (range)	51 (16–72)	56 (16–72)	46.5 (16–68)	51 (19–63)
Total-body weight (kg), median (range)	54.5 (34.5–146.8)	56.7 (38.4–83.8)	53.5 (37.0–75.8)	63 (53.5–146.8)
Conditioning, N (%)				
Myeloablative conditioning	58 (64)	35 (63)	16 (73)	7 (54)
Reduced-intensity conditioning	33 (36)	21 (38)	6 (27)	6 (46)
Engraftment, N (%)	80 (88)	47 (83)	21 (95)	12 (92)
Days to engraftment, median (range)	20 (11–100)	22 (13–100)	17 (12–100)	15 (11–100)
aGVHD (%), N (%)	18 (20)	12 (21)	3 (14)	3 (23)
Grade 2/3/4	11/6/1	9/2/1	2/1/0	0/3/0
Laboratory data[a], median (range)				
Hemoglobin (g/dL)	8.6 (6.9–12.5)	8.5 (7.0–12.2)	9.4 (7.2–11.8)	9.1 (6.9–12.5)
Aspartate aminotransferase (IU/L)	19 (7–136)	17 (7–136)	19 (9–34)	28 (7–82)
Alanine aminotransferase (IU/L)	20 (4–266)	21 (6–266)	19 (4–65)	35 (7–100)
Albumin (g/dL)	3.5 (0.4–4.8)	3.5 (2.3–4.3)	3.8 (0.4–4.8)	3.4 (2.2–4.0)
Serum creatinine (mg/dL)	0.54 (0.26–1.17)	0.55 (0.26–1.17)	0.48 (0.29–0.89)	0.54 (0.40–1.01)

CBT = cord blood transplantation; BMT = bone marrow transplantation; PBSCT = peripheral blood stem cell transplantation; GVHD = graft-versus-disease; aGVHD = acute graft-versus-disease.
[a] : Initial data after transplantation.

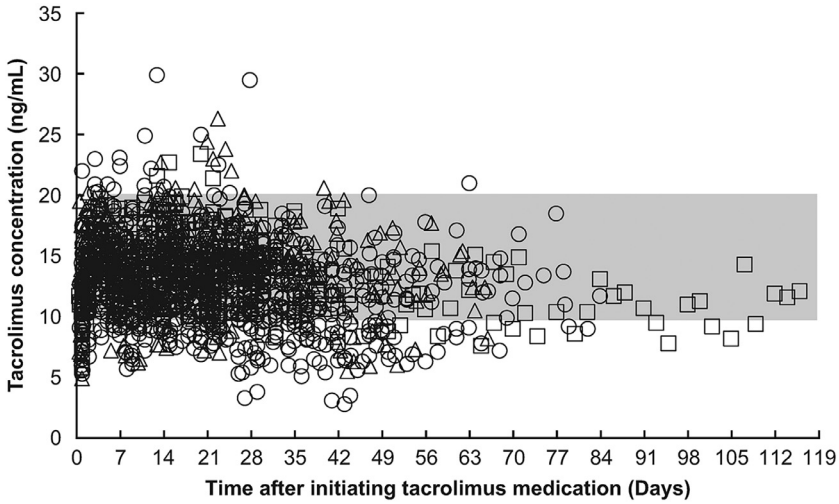

Figure 1. Profile of tacrolimus whole-blood concentration versus time. Tacrolimus concentrations ($n = 1{,}658$) were obtained from 91 patients who underwent HSCT. ○, patients who undewent CBT; △, patients who underwent BMT; and □, patients who underwent PBSCT. The shaded area shows the target therapeutic concentration range for tacrolimus. BMT, bone marrow transplantation; CBT, cord blood transplantation; HSCT, hematopoietic stem cell transplantation; PBSCT, peripheral blood stem cell transplantation.

Table 2
Univariate analysis.

Covariate	ΔOFV	df	Covariate type	θ_{COV1}	θ_{COV2}	RSE (%)
Hb on V_d	−325.07***	1	Power	−1.09	-	7.8
Hb on K_e	−287.07***	1	Power	−1.25	-	8.9
TBW on V_d	−9.48**	1	Power	0.47	-	17
Condition on V_d	−9.18**	1	Category	0.81	-	7.8
Condition on K_e	−3.47	1	Category	0.87	-	6.7
Donor source on V_d	−4.10	2	Category	1.01	1.22	9.9, 8.4
Donor source on K_e	−2.49	2	Category	1.12	1.12	8.6, 7.9

OFV = objective function value; ΔOFV = difference in OFV; df (degrees of freedom) = difference in the number of parameters from basic model; θ_{COV} = effect of the covariate on the pharmacokinetic parameter; RSE = relative standard error; V_d = volume of distribution; K_e = elimination rate constant; Hb = hemoglobin; TBW = total-body weight; Condition = conditioning regimen (0: MAC, 1: RIC); Donor source (0: CBT, 1: BMT, 2: PBSCT); MAC = myeloablative conditioning; RIC = reduced-intensity conditioning; CBT = cord blood transplantation; BMT = bone marrow transplantation; PBSCT = peripheral blood stem cell transplantation.
** : $P < 0.01$.
*** : $P < 0.001$.

Table 3
Covariate selection as factors affecting the pharmacokinetics of tacrolimus.

	Model number	Model	Covariate type	ΔOFV
Basic model	#1	No covariate		-
Forward addition first step	#2	#1 + Hb on V_d	Power	−325.07
	#3	#1 + Hb on K_e	Power	−287.07
	#4	#1 + TBW on V_d	Power	−9.48
	#5	#1 + Condition on V_d	Category	−9.18
Second step	#6	#2 + TBW on V_d	Power	−17.59
	#7	#2 + Condition on V_d	Category	−11.31
	#8	#2 + Hb on K_e	Power	−0.053
Third step	#9 (full model)	#6 + Condition on V_d	Category	−8.00
Backward elimination	#10	#9 − Hb on V_d	Power	334.68
	#11	#9 − TBW on V_d	Power	14.25
	#12 (final model)	#9 − Condition on V_d	Category	7.98

ΔOFV = difference in objective function value; V_d = volume of distribution; K_e = elimination rate constant; Hb = hemoglobin; TBW = total-body weight; Condition = conditioning regimen.

discernible trends; instead, data points were randomly dispersed around the X-axis ($Y = 0$) (Supplementary Figure 1A and B). These findings affirm the appropriateness of the error model for this study's population.

The prediction-corrected visual predictive check (pcVPC) plot depicted in Supplementary Figure 2 reveals that approximately 95% of observed values fell within 5th and 95th percentiles. The final PPK model demonstrated robust predictive accuracy, particularly during the critical period from transplantation to engraftment. However, prediction accuracy noticeably declined after approximately day 49.

Final PPK model

Table 4 displays the estimates derived from the final PPK model and bootstrap validation results. The typical values for V_d and K_e were 100.4 L and 0.027 h^{-1}, respectively. The relative standard error was minimal, signifying strong prediction accuracy. The

Table 4
Tacrolimus population pharmacokinetics parameters of the final model and bootstrap validation.

Parameter	Final model		Bootstrap data		Bias (%)
	Estimate	RSE (%)	Median	95th CI	
Structure parameters					
V_d (L) = $\theta_1 \times$ (Hb/8.6) ^ $\theta_2 \times$ (TBW/54.5) ^ θ_3					
θ_1	100.4	6.1	96.3	[83.2, 111.7]	4.08
θ_2	−1.10	7.2	−1.10	[−1.28, −0.93]	0.00
θ_3	0.57	11.1	0.56	[0.30, 0.90]	1.75
K_e (1/h) = θ_4	0.027	6.5	0.027	[0.023, 0.032]	0.00
Interindividual variability					
V_d (%)	16.5	18.1	16.1	[3.64, 29.8]	2.42
K_e (%)	24.7	22.6	24.8	[17.1, 39.6]	−0.40
Residual variability					
σ (ng/mL)	3.11	5.1	3.09	[2.77, 3.42]	0.64

RSE = relative standard error; 95th CI = lower and upper limits of the 95% confidence; V_d = volume of distribution; Hb = hemoglobin; TBW = total-body weight; K_e = elimination rate constant.
Residual (%) = (population mean estimate=bootstrap validation median)/population mean estimate × 100.

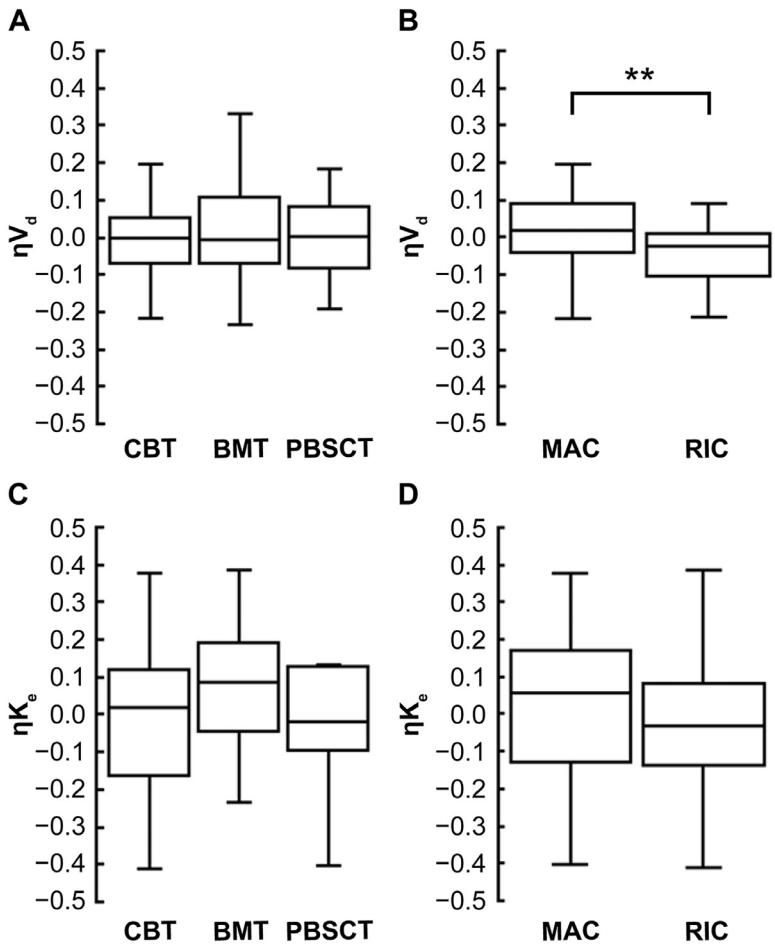

Figure 2. Effect of the conditioning regimen or donor source on the random effects of each pharmacokinetic parameter. (A) Eta V_d versus donor source. (B) Eta V_d versus conditioning regimen. (C) Eta K_e versus donor source. (D) Eta K_e versus conditioning regimen. For (A) and (C), statistical analysis was conducted using the Kruskal–Wallis test. For (B) and (D), statistical analysis was conducted using the Mann–Whitney U test. $^{**}P < 0.01$. BMT, bone marrow transplantation; CBT, cord blood transplantation; K_e, elimination rate constant; MAC, myeloablative conditioning; PBSCT, peripheral blood stem cell transplantation; RIC, reduced-intensity conditioning; V_d, volume of distribution.

PPK parameter estimates obtained from the original dataset fell within the 95th CI of the parameter estimates obtained from bootstrap validation ($n = 1{,}000$; 98.8% success rate) and closely aligned with the median. This alignment underscores the robustness and accuracy of the parameter estimates derived from the final model.

Effect of conditioning regimen or donor source on the random effects of each pharmacokinetic parameter

Figure 2 illustrates the random effects of each pharmacokinetic parameter and their comparison between donor sources and a comparison of random effects between conditioning regimens. No-

tably, the donor source did not affect either ηV_d or ηK_e. Conversely, a statistically significant difference was observed in the random effect of V_d between MAC and RIC. However, the median difference was merely 0.04, and when expressed as the MAC-to-RIC ratio, this difference was minimal (1.04).

Discussion

We investigated the impact of conditioning regimens and donor sources on tacrolimus pharmacokinetics in patients with HSCT. Consequently, even when expanding the population to include all patients with HSCT, the primary source of variation remains the RBC count, with conditioning regimens and donor sources failing to introduce substantial variability.

Frequent measurements (approximately every 2 days) and, if necessary, dose adjustments help maintain the target concentration of tacrolimus in whole blood (10–20 ng/mL). However, the success rates for achieving and maintaining the target range in the steady state were 77% (CBT), 89% (BMT), and 88% (PBSCT), with whole-blood tacrolimus concentrations exhibiting significant variability (ranging from 2.8 to 29.9 ng/mL) (Figure 1). These findings highlight the substantial challenge of maintaining the desired tacrolimus concentration range in these patients.

Table 1 demonstrates that several biochemical parameters derived from RBC, including hemoglobin, fell below the normal range. Furthermore, substantial individual variation was observed in hemoglobin levels throughout the observation period. Notably, there were no significant differences in physiological functions, including renal and hepatic functions, across donor sources. These results suggest that the extensive variability in whole-blood tacrolimus concentrations observed in patients with HSCT may be attributed to the wide range of hemoglobin levels, consistent with the results of our previous study. These results emphasize the importance of considering RBC count variation when devising a tacrolimus dosing strategy for patients with HSCT.

The selection of a donor source for HSCT is contingent on HLA compatibility. While BMT and PBSCT favor HLA-matched donors to mitigate GVHD risk, CBT can be pursued even with low HLA compatibility.[13,14] CBT requires a longer time for engraftment than other donor sources, as corroborated in this study (Table 1). The number of transfusions increases with the time required to restore bone marrow function. Consequently, differences in donor sources may influence RBC count variability. In a recent study on various donor sources, a correlation was reported between whole-blood tacrolimus concentration and RBC count in patients, not only with CBT but also with other donor sources.[11]

Regarding conditioning regimens, MAC involves intensive chemotherapy and total-body irradiation, causing rapid and persistent depletion of blood cells, including RBCs. Conversely, RIC results in a comparatively gradual decline in blood cell counts due to mild bone marrow destruction. These findings suggest that MAC may lead to a more extensive decrease in RBC counts than RIC.[15,16] Conditioning regimens and donor sources are typically selected based on patient-specific factors. Therefore, the degree of RBC count variation may vary among patients. Based on these observations, we hypothesized that the conditioning regimen and donor source influence tacrolimus pharmacokinetics. There was no difference in the proportion of patients receiving MAC or RIC based on donor source (Table 1). These data suggested that the conditioning regimen and donor source are independent factors potentially impacting the pharmacokinetics of tacrolimus.

Consistent with our previous studies, we incorporated hemoglobin levels and TBW as covariates for V_d in this study. However, the conditioning regimen and donor source were excluded as covariates. Moreover, there were no notable differences in the random effects (ηV_d and ηK_e) related to the conditioning regimen and donor source (Figure 2). Hence, the available evidence suggests that the type of conditioning regimen and donor source should not be considered factors that significantly influence the pharmacokinetics of tacrolimus. We consider that one of the reasons why the type of conditioning regimen did not affect tacrolimus pharmacokinetics is owing to the small effect of chemotherapy and total-body irradiation used in the conditioning regimen on RBC count (median hemoglobin values for MAC and RIC are 8.55 and 8.6 g/dL, respectively). Although the details are unknown, we consider that the difference in conditioning regimen had a small effect on the degree of RBC count variation and could not be a covariate for tacrolimus pharmacokinetics as RBC count is maintained during and after the conditioning regimen with RBC transfusions and hematopoietic growth factor, such as erythropoietin, to avoid anemia. Consequently, even when expanding the population to include all patients with HSCT, the primary source of variation remains the RBC count, with conditioning regimens and donor sources failing to introduce substantial variability. Previous studies have reported that hematocrit level, rather than hemoglobin level, an indicator of RBC count, is a factor that affects the pharmacokinetics of tacrolimus.[17–19] By contrast, hemoglobin levels are considered important at our institution because a hemoglobin level <7 g/dL is an indicator of RBC transfusion. Hematocrit levels are also measured at our institution, but with less number of data than hemoglobin levels. Therefore, we considered hemoglobin levels a desirable indicator of RBC count, a variable factor of tacrolimus pharmacokinetics in patients with HSCT. Furthermore, we obtained a positive correlation between hemoglobin and hematocrit levels. Accordingly, the hemoglobin level was used as an indicator of RBC count in this study.

The typical values for V_d and K_e were 100.4 L and 0.027 h^{-1}, respectively (compared with 91.4 L and 0.028 h^{-1} in our prior study). The coefficient θ_2, representing the impact of hemoglobin levels on V_d, was -1.10 in this study and -1.07 in the previous study, indicating a consistent effect. Furthermore, a previous study reported V_d and K_e of tacrolimus in patients with HSCT of 1.67 ± 1.02 L/kg (adjusted by weight in our subjects was 91 L) and 0.043 h^{-1}, respectively.[20] These parameters agree with the PPK parameters in this study, supporting our results. The validation of the PPK model, as demonstrated through bootstrap validation and GOF plots (Supplementary Figure 1, Table 4), revealed high prediction accuracy. The pcVPC plot (Supplementary Figure 2) also illustrated excellent prediction accuracy during the critical period from transplantation to engraftment. These results underscore the model's robustness and firmly support that RBC count is the primary variable governing tacrolimus pharmacokinetics, whereas conditioning regimen and donor source do not contribute to variability.

By contrast, the abovementioned reports on patients with renal transplant and pediatric HSCT[17–19] differ from the patient population in this study. Patients with HSCT have lower and more variable RBC counts than patients with renal transplant owing to the intense conditioning regimen required to destroy hematopoietic function to achieve graft engraftment and post-transplant RBC transfusions. Therefore, whole-blood tacrolimus concentrations may be more variable in patients with HSCT than in patients with renal transplant, and that tacrolimus dosing design should be more considerate of RBC count in patients with HSCT. By contrast, a study in patients with pediatric HSCT reported a decrease and variation in RBC counts and a negative correlation between volume of distribution and RBC counts,[17] similar to our results. Therefore, the previous report supports the results of this study in adults. However, a population including children needs to be investigated in the future.

Data from the 56 patients undergoing CBT was previously published. The percentage of donor sources for CBT at our institution is the highest, hence $>50\%$ of our data was obtained from patients

with CBT. However, as shown in Table 2, when introducing the influence of the donor source into V_d and K_e, the parameters representing the influence of the donor source were estimated with excellent accuracy; thus, we consider that the power to detect the donor source is not an issue. In the future, data from other populations other than CBT will be collected and discussed.

Conclusions

Our results indicate that neither the conditioning regimen nor the donor source influences tacrolimus pharmacokinetics. Consequently, we conclude that a tacrolimus dosing strategy considering variations in hemoglobin levels (reflecting RBC count) universally applies to all patients with HSCT rather than being limited to those undergoing CBT.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (C) [grant number 19K07180]. The authors thank Enago (www.enago.jp) for the English language review.

Declaration of Generative AI in Scientific Writing

none

Funding

This work was supported by the Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (C) [grant number 19K07180].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2024.100775.

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