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Optimal dose of everolimus administered with tacrolimus in living donor kidney transplantation

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ABSTRACT

Everolimus (EVR) is often administered with cyclosporine A (CsA), according to an established protocol. Although the administration protocol of EVR with tacrolimus (TAC) has not been established, it has been clinically demonstrated that a higher dose of EVR is necessary when used in combination with TAC than with CsA. In this study, we aimed to determine the optimal dose of EVR administered with TAC to maintain a similar EVR level in the blood to that observed when EVR is administered with CsA. Between June 2009 and January 2016, 22 patients who underwent living donor kidney transplantation were enrolled in this study. Among them, 12 patients were administered steroids, basiliximab, CsA, and EVR (CsA + EVR group) and 10 were administered steroids, basiliximab, TAC, and EVR (TAC + EVR group). Blood samples were collected at different time points from patients in both CsA + EVR and TAC + EVR groups, after drug administration. The trough EVR level in both groups was maintained within 3–8 ng/mL during the perioperative period. The optimal EVR doses for both groups were estimated by using a population pharmacokinetic analysis. Overall, the optimal dose of EVR for the TAC + EVR group was 3.59-fold higher than that for the CsA + EVR group to maintain a similar trough level to that of the latter group. Thus, administration of a higher EVR dose is recommended when provided in combination with TAC than with CsA to prevent adverse events caused by under immunosuppression, that could lead to acute kidney rejection.

1. Introduction

The concomitant use of calcineurin inhibitor (CNI) with mycophenolate mofetil (MMF) in kidney transplantation decreases the incidence of graft loss due to acute rejection, and thus significantly improves short-term graft survival [1] However, long-term graft survival does not improve with the administration of these immunosuppressants [2,3]; therefore, strategies to prevent organ failure for a prolonged time has become the focus of recent studies. A previous study investigated the pathological changes in graft biopsy specimens after 10 years of transplantation [3]. The study demonstrated that chronic allograft nephropathy was exacerbated due to the nephrotoxicity of CNI. Although concomitant intake of CNI and MMF improved short-term graft survival [4], CNI induced adverse nephrotoxicity. To avoid the adverse effects of CNI, mammalian target of rapamycin, sirolimus, and everolimus (EVR) have been used. In the ZEUS study [5], a CNI avoidance regimen, in which EVR was administered instead of CNI at 4–5 months after kidney transplantation, was investigated, and the results showed a significant improvement in the glomerular filtration rate (GFR). Furthermore, the CNI avoidance regimen increased the incidence of acute rejection compared with that of the CNI and MMF regimen, but the 5-year follow-up demonstrated no significant difference in the cumulative incidence of biopsy-proven acute rejection between the regimens [5,6]. On the contrary, concomitant administration of EVR and reduced-dose CNI presented results comparable to those of the conventional CNI and MMF regimen in terms of graft function, incidence of acute rejection, and de novo donor-specific antibody production [7,8]. The efficacy of the EVR and reduced-dose CNI regimen has been demonstrated by the low incidence of cytomegalovirus and BK virus infections, and skin cancer [7,9–11]. Therefore, the simultaneous use of EVR and a reduced

Abbreviations: AUC, area under curve; C_0 level, trough level; CD ratio, concentration/dose ratio; CNI, calcineurin inhibitor; CsA, cyclosporine A; EVR, everolimus; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; PPK, population pharmacokinetics; TAC, tacrolimus; TACER, extended-release tacrolimus

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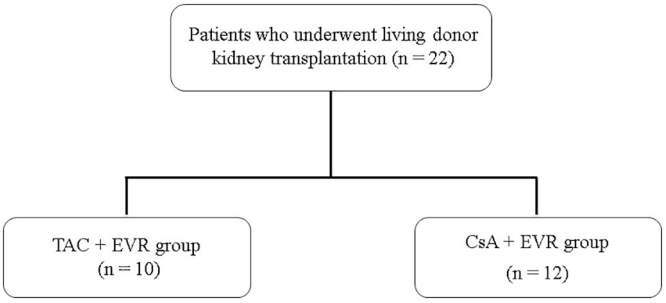

Fig. 1. Flow chart of patients enrolled in this study.
EVR: everolimus, TAC: tacrolimus, CsA: cyclosporine A.

CNI dose has become the standard regimen. However, adverse effects of EVR administration, such as lymphocele, delayed wound healing, dyslipidemia, and proteinuria, have been reported [5,10–13]. Dyslipidemia and proteinuria can be ameliorated with the intake of statin and angiotensin II receptor blocker [7]. These EVR effects have been mainly demonstrated by studies evaluating the concomitant administration of cyclosporine A (CsA) and EVR in kidney transplantation [1,5–7,9,11]. Recently, reports on the simultaneous intake of tacrolimus (TAC) and EVR during kidney transplantation have increased in number [8,10,14–16]. The efficacy of the TAC and EVR regimen was also evaluated in the TRANSFORM study [10]. In clinical practice, the dose of EVR administered with TAC is 2–3-fold higher than that with CsA [17]. However, there are only a few reports on the optimal dose of EVR administered with different CNIs in kidney transplantation [17]. Moreover, the optimal dose of EVR administered with TAC has not been established. Determining the optimal dose of EVR is important, because the dose and blood level of CNIs when provided with EVR are considerably lower than those of CNIs administered with MMF; insufficient dose and level of EVR in the blood might lead to acute cellular rejection [16,18–21]. In this study, we aimed to determine the optimal dose of EVR when used with TAC to maintain the level of EVR in the blood similar to that observed when EVR is administered with CsA using a population pharmacokinetic (PPK) analysis.

2. Methods

2.1. Ethics review

This study was approved by the Institutional Review Board of the Nagoya Daini Red Cross Hospital (Aichi, Japan) (Approval number 1250) and was conducted in accordance with the Declaration of Helsinki. Living donor kidney transplantation was performed in accordance with the Declaration of Istanbul.

2.2. Study design and participants

This retrospective cohort study was conducted according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. Between June 2009 and January 2016, 22 patients, who underwent living donor kidney transplantation in our hospital, were enrolled in the study. Among them, 12 patients were administered steroids, basiliximab, CsA, and EVR (CsA + EVR group) and 10 patients were administered steroids, basiliximab, TAC, and EVR (TAC + EVR group), as described in Fig. 1. This study was performed during the perioperative period. The relevant data were retrospectively collected from the patients' charts and analyzed anonymously. Therefore, the need for informed consent was waived by the relevant institutional review board.

2.3. Measurement of TAC, CsA, and EVR levels in the blood

Blood samples were collected after the administration of EVR and TAC, or EVR and CsA to determine the level of EVR in the blood. The levels of TAC and CsA in the blood were measured using a chemiluminescent immunoassay kit (ARCHITECT®; Abbott Japan, Chiba, Japan), according to the manufacturer's instruction. On the contrary, the level of EVR in the blood was determined using a latex agglutination turbidimetric immunoassay kit (Nanopia®; SEKISUI, Tokyo, Japan), according to the manufacturer's instruction.

2.4. Statistical analysis

Statistical analyses of patient characteristics were performed using the *t*-test and Mann-Whitney *U* test for continuous variables, and the Fisher's exact test for categorical variables. The results with P value < 0.05 were considered statistically significant.

PPK analysis was performed, by using the level of EVR in the blood, to obtain the model formula and pharmacokinetic parameters, which were then subsequently used for estimating the doses of EVR with TAC and with CsA. The EVR level in serum–time curves were fitted to PPK models, using the NLMIXED procedure of SAS (version 9.2; SAS Institute Inc., Cary, NC, U.S.A.). The model was parameterized to express the apparent clearance (CL), absorption rate constant (k_a), and elimination rate constant (k_e). These parameters were defined by the following equations:

$$CL = \mathrm{BW} \times \exp(\theta_1 + \eta_{cl})$$

$$k_a = \exp(\theta_2 + \eta_{ka})$$

$$k_e = \exp(\theta_3)$$

where, BW is the body weight of each patient, η_{cl} and η_{ka} are random variables normally distributed with means of zero, and covariances of ω_{cl}^2, ω_{ka}^2, and $\omega_{cl,\ ka}^2$. $\theta_{1,\ 2,\ 3}$ are fixed values.

These parameters were used to plot the level of a drug in the serum

Table 1
Patient characteristics.

	TAC + EVR group	CsA + EVR group	*P* value	Odds ratio	95% CI	
	10	12				
Age (y.o., SD)	43.0 (12.4)	44.5 (9.3)	0.748		−11.118	8.118
Male (%)	40	83.3	0.074	7.500	1.039	54.116
BMI (kg/m^2, SD)	25.4 (4.9)	23.3 (4.6)	0.318		−2.154	6.302
Preoperative serum AST (U/L, SD)	13.6 (4.4)	16.3 (6.6)	0.456			
Preoperative serum ALT (U/L, SD)	14.3 (4.2)	19.9 (16.1)	0.999			
Preoperative serum ChE (U/L, SD)	278.4 (62.1)	274.0 (77.0)	0.886		−58.693	67.493
Preoperative serum γGTP (U/L, SD)	22.6 (24.3)	20.8 (19.3)	0.771			
Preoperative serum total bilirubin (U/L, SD)	0.32 (0.09)	0.42 (0.16)	0.077		−0.224	0.012

TAC: tacrolimus; CsA: cyclosporine A; EVR: everolimus; BMI: body mass index.

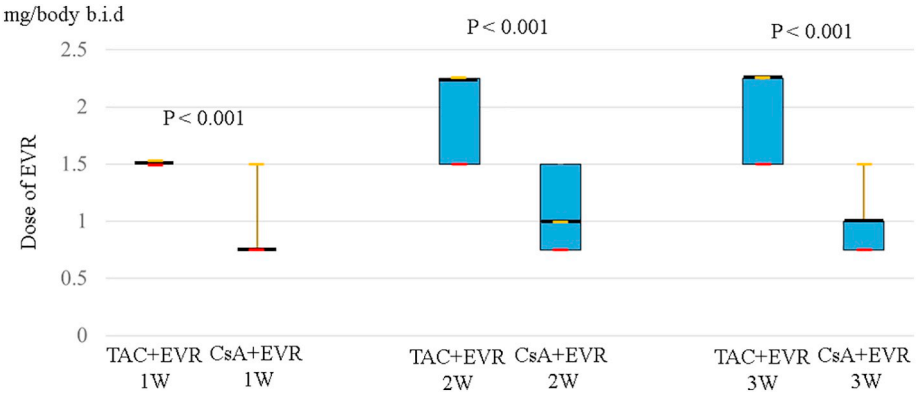

Fig. 2. Dose of everolimus administered with tacrolimus or cyclosporine A during the perioperative period.
The dose of EVR was significantly higher in the TAC + EVR group, compared to that in the CsA + EVR group at 1, 2, and 3 weeks after transplantation.
EVR: everolimus, TAC: tacrolimus, CsA: cyclosporine A.

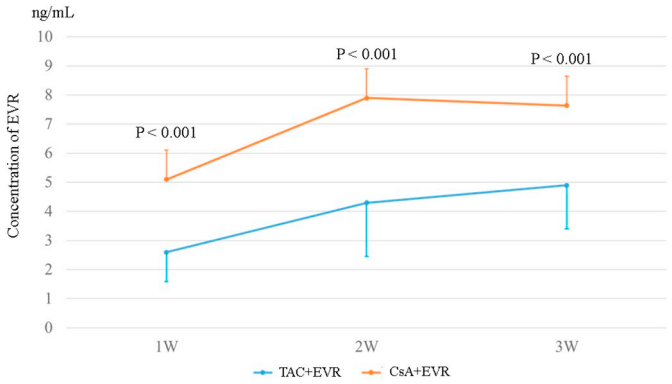

Fig. 3. Mean trough levels of everolimus administered with tacrolimus (blue) or cyclosporine A (red) during the perioperative period.
The trough level of EVR was significantly lower in the TAC + EVR group, compared to that in the CsA + EVR group at 1, 2, and 3 weeks after transplantation.
EVR: everolimus, TAC: tacrolimus, CsA: cyclosporine A. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

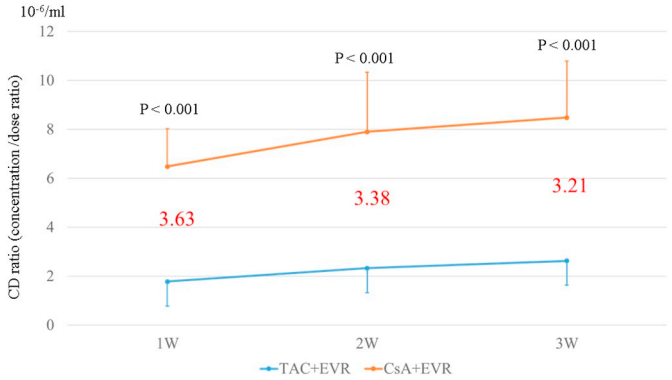

Fig. 4. The CD ratio (concentration/dose ratio) of the everolimus in TAC + EVR (blue) and CsA + EVR (red) groups.
The CD-ratio$_{(TAC+EVR\ group)}$ mean was significantly lower than that of CD-ratio$_{(CsA+EVR\ group)}$ at 1, 2, and 3 weeks after transplantation. The CD-ratio$_{(CsA+EVR\ group)}$/CD-ratio$_{(TAC+EVR\ group)}$ values for each week are shown in red numbers.
CD ratio: concentration/dose ratio, EVR: everolimus, TAC: tacrolimus, CsA: cyclosporine A. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

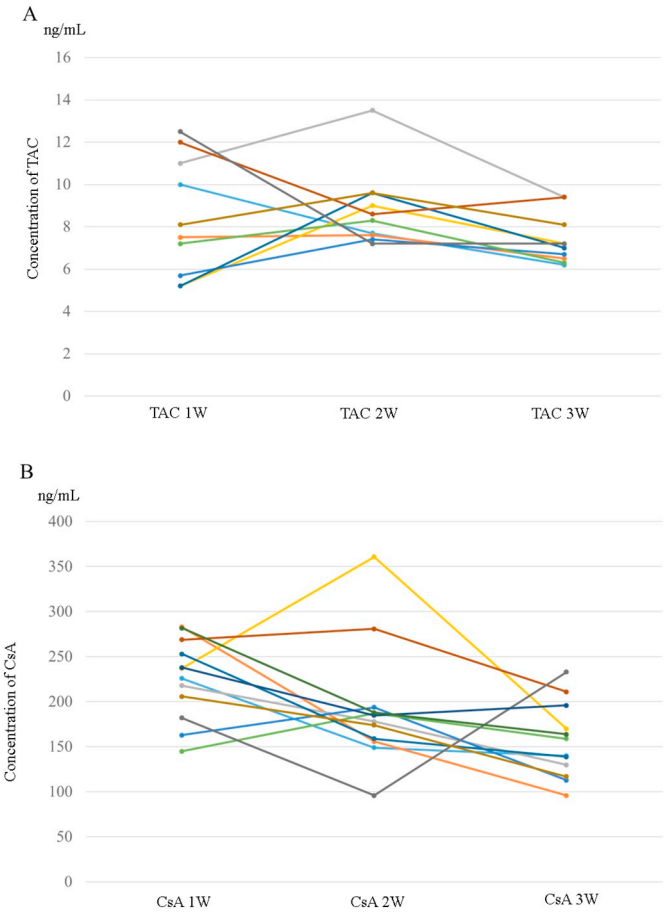

Fig. 5. A. C_0 (trough) levels of tacrolimus during the perioperative period.
B. Trough levels of cyclosporine A during the perioperative period.
Although the C_0 levels of TAC and CsA at 1 week after transplantation were higher than those of the target range, the levels gradually reached the target range at 3 weeks after transplantation.
CsA: cyclosporine A, TAC: tacrolimus.

versus time curves of the *i*th patient using the following equations. The PPK model (one-compartment model) was developed as follows:

$$C_{ij} = \frac{D_i k_{a_i} k_{e_i}}{CL_i (k_{a_i} - k_{e_i})} \{[\exp(-k_{e_i}(t_j)) - \exp(-k_{a_i}(t_j))] + [\exp(-k_{e_i}(12 + t_j)) - \exp(-k_{a_i}(12 + t_j))]\} + \varepsilon_{ij}$$

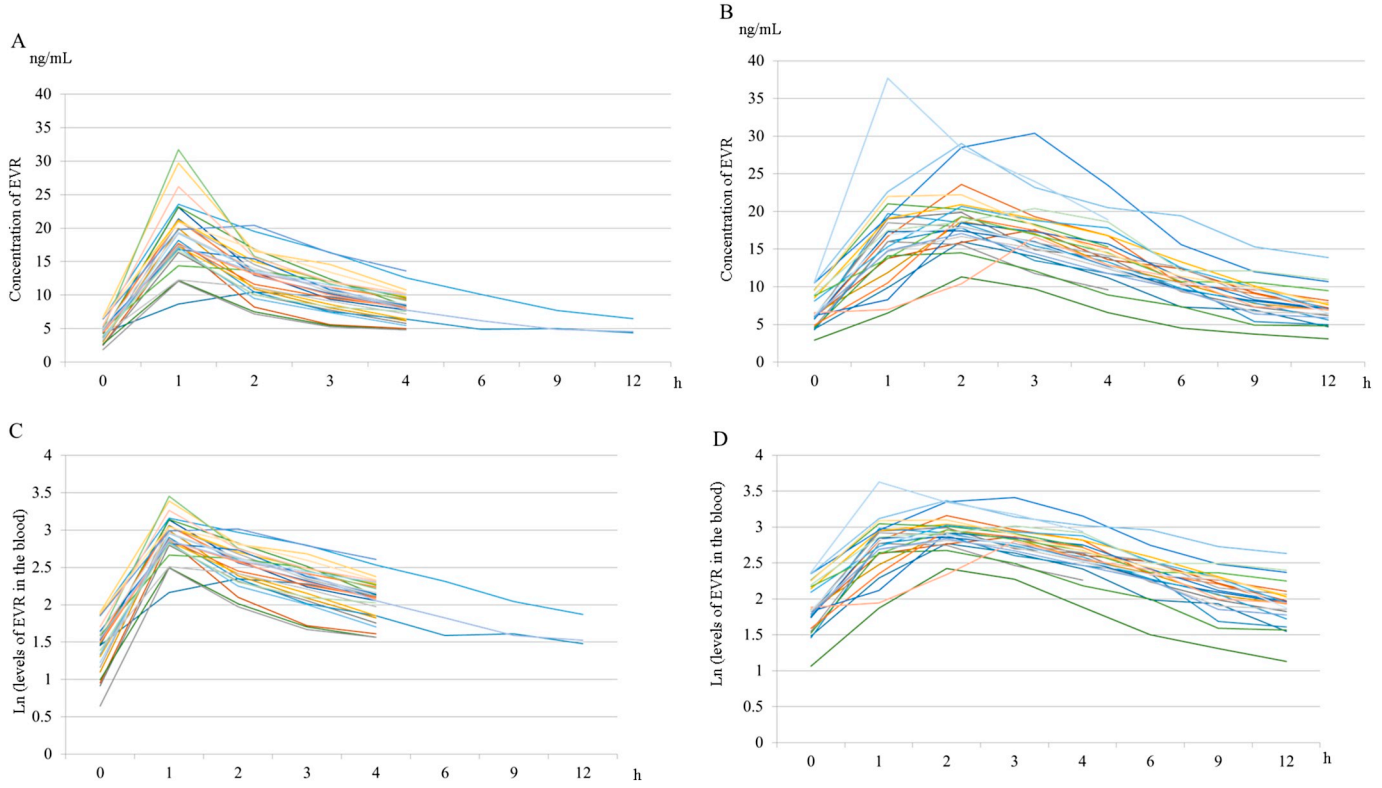

Fig. 6. A. Levels of everolimus in the blood after its administration to patients in the tacrolimus + everolimus group.
B. Levels of everolimus in the blood after its administration to patients in the cyclosporine A + everolimus group.
C. Natural logarithm of everolimus levels in the blood after its administration to patients in the tacrolimus + everolimus group.
D. Natural logarithm of everolimus levels in the blood after its administration to patients in the cyclosporine A + everolimus group.
The serum levels of EVR at each sampling time point were plotted as shown in panels A and B. The natural logarithms of EVR level in the blood after the administration of drugs in both groups are shown in panels C and D. For each group, the blood level of EVR almost linearly decreased after reaching the peak level.
Ln: Natural logarithm, EVR: everolimus.

where, C_{ij} is the jth observed level of a drug in the serum of the ith patient, D_i is dose, t_j is the jth observed time, and ε_{ij} is the random effect variable (additive measurement error due to intra-individual variation in serum levels, which was defined according to the normal distribution with a mean of zero and variance of σ).

To verify the predicted EVR value from (level of a drug in the serum) vs time curves, regression lines and correlation coefficients were calculated using SAS software (version 9.2; SAS Institute Inc., Cary, NC, U.S.A.). In addition, the minimum concentration during a dose interval at steady state ($C_{ss,\ min}$) was defined as follows:

$$C_{ss,min} = \frac{Dk_a k_e}{CL\ (k_a - k_e)}\left(\frac{e^{-k_e\tau}}{1 - e^{-k_e\tau}}\right)$$

where, τ is the dose interval. Using the above equation, the dose/BW at which the $C_{ss,\ min}$ was 3–8 ng/mL was calculated.

3. Results

3.1. Blood levels of EVR, TAC, and CsA during the perioperative period

In both groups, the blood C_0 level of EVR was adjusted within 3–8 ng/mL range. In the EVR + TAC group, the C_0 level of TAC was maintained at 4–7 ng/mL. Meanwhile, in the EVR + CsA group, the C_0 level of CsA was sustained at 100–150 ng/mL.

3.2. Participants

As mentioned in the Materials and Methods section, we grouped the enrolled patients into two groups: CsA + EVR group, which was administered steroids, basiliximab, CsA, and EVR, and TAC + EVR group, which was administered steroids, basiliximab, TAC, and EVR (Fig. 1). Blood samples were obtained at 175 (46 blood samples were obtained before the drug administration (C0), and 30, 30, 30, 30, 3, 3, and 3 blood samples were obtained 1, 2, 3, 4, 6, 9, and 12 h after the administration) and 252 (72 blood samples were obtained before the drug administration (C0), 27, 27, 27, 27, 24, 24, and 24 were obtained 1, 2, 3, 4, 6, 9, and 12 h after the administration) time points from patients in the TAC + EVR and CsA + EVR groups, respectively, during the perioperative period. Patient characteristics, including age, gender, BMI, and preoperative serum levels of AST, ALT, ChE, γGTP, and total bilirubin, indicative of liver functions, are shown in Table 1. Statistical comparisons of those parameters between both groups did not show a significant difference.

3.3. Pharmacokinetics of CsA, TAC, and EVR

3.3.1. The dose and C_0 level of EVR

The dose and C_0 level of EVR were significantly higher and lower, respectively, in the TAC + EVR group, compared to those in the CsA + EVR group at 1, 2, and 3 weeks after transplantation ($P < 0.001$; Figs. 2 and 3).The comparison between mean trough levels of EVR for CsA + EVR and TAC + EVR groups at 1, 2, and 3 weeks after transplantation were the following: 95% CI -3.316 to −1.541 ($P < 0.001$), 95% CI -4.902 to −2.251 ($P < 0.001$), and 95% CI -3.976 to −1.447 ($P < 0.001$), respectively (Fig. 3). The target C_0 level (3–8 ng/mL) was achieved in 2 weeks after transplantation.

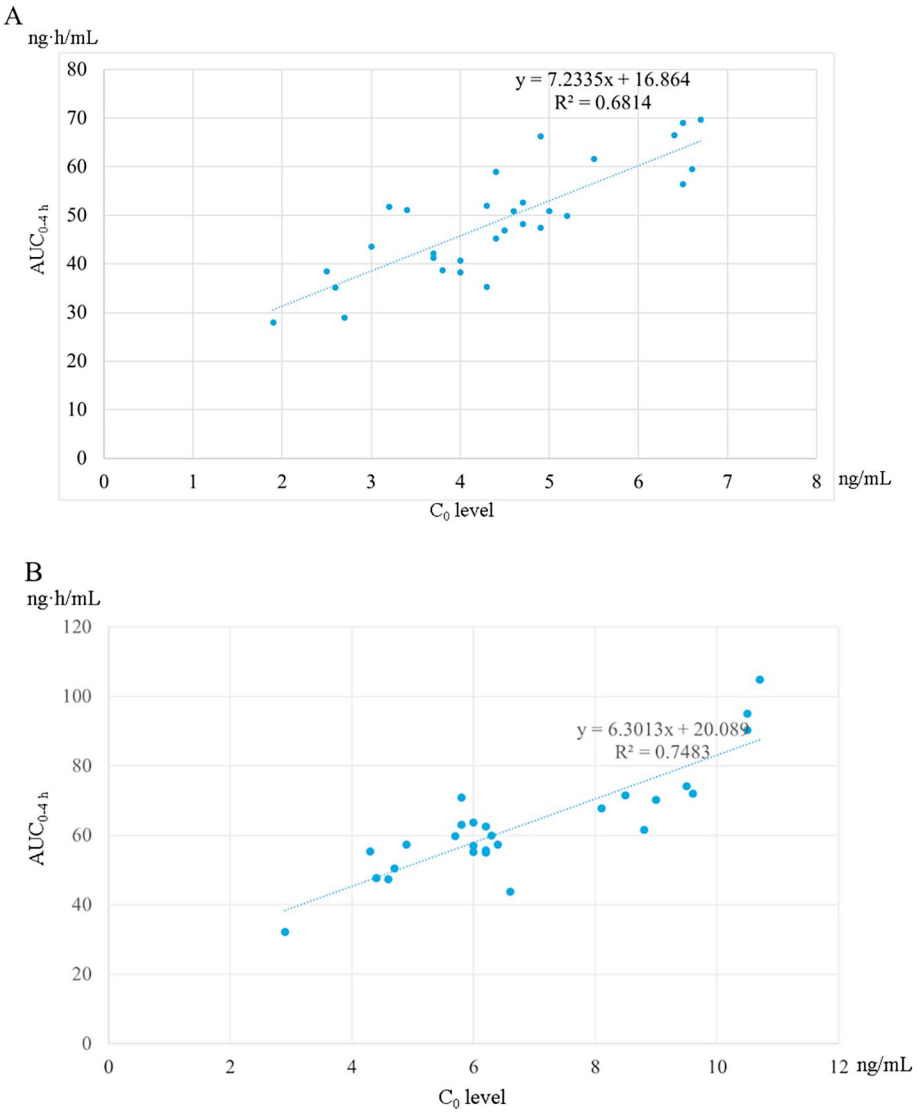

Fig. 7. A. Correlation between the C_0 level and area under curve of everolimus administered with tacrolimus. B. Correlation between the C_0 level and area under curve of everolimus administered with cyclosporine A. The R^2 of the TAC + EVR and CsA + EVR groups showed a good correlation between the C_0 level and AUC. AUC: area under curve, C_0 level: trough level, R^2 coefficient of determination.

Table 2
Pharmacokinetic parameters.

	TAC + EVR group	CsA + EVR group
	10	12
Measurement points	175	252
CL	BW*0.247	BW*0.088
k_a	6.050	1.662
k_e	0.123	0.094
ω_{cl}	0.510	0.136
$\omega_{cl,\ ka}$	0.428	0.064
ω_{ka}	0.359	0.399
Σ	2.107	2.435

PPK: population pharmacokinetics; TAC: tacrolimus; CsA: cyclosporine A; EVR: everolimus; CL: clearance; ka: absorption rate constant; ke: elimination rate constant; ωcl, ωcl, ka, and ωka: covariances; σ: variance; BW: body weight.

3.3.2. Concentration (C_0)/dose ratio of EVR in both groups

The concentration (C_0)/dose ratio of EVR, called CD ratio, in both groups at 1, 2, and 3 weeks after transplantation are plotted as shown in Fig. 4. The CD-ratio$_{(CsA+EVR\ group)}$/CD-ratio$_{(TAC+EVR\ group)}$ at 1, 2, and 3 weeks after transplantation were 3.63, 3.38, and 3.21, respectively. The mean CD-ratio$_{(TAC+EVR\ group)}$ was significantly lower than that of CD-ratio$_{(CsA+EVR\ group)}$ at 1, 2, and 3 weeks after transplantation: 95%CI –5.614 to −3.085 ($P < 0.001$), 95%CI –6.772 to −3.591 ($P < 0.001$, 95%CI –7.027 to −3.792 ($P < 0.001$), respectively.

3.3.3. C_0 levels of TAC and CsA in the perioperative period

The C_0 levels of TAC and CsA at 1, 2, and 3 weeks after transplantation were plotted as shown in Fig. 5A and B. Although the C_0 levels of TAC and CsA at 1 week after transplantation were higher than the target range in both groups, the levels gradually reached the target range at 3 weeks after transplantation.

3.3.4. PPK analysis of EVR

The serum levels of EVR at each sampling time point were plotted as shown in Fig. 6A and B. The natural logarithms of EVR level in the blood after the administration of drugs in both groups are shown in Fig. 6C and D. For each group, the blood level of EVR linearly decreased after reaching the peak level. This linearly tendency enabled to estimate the level of EVR in the blood by using a one compartment model in the

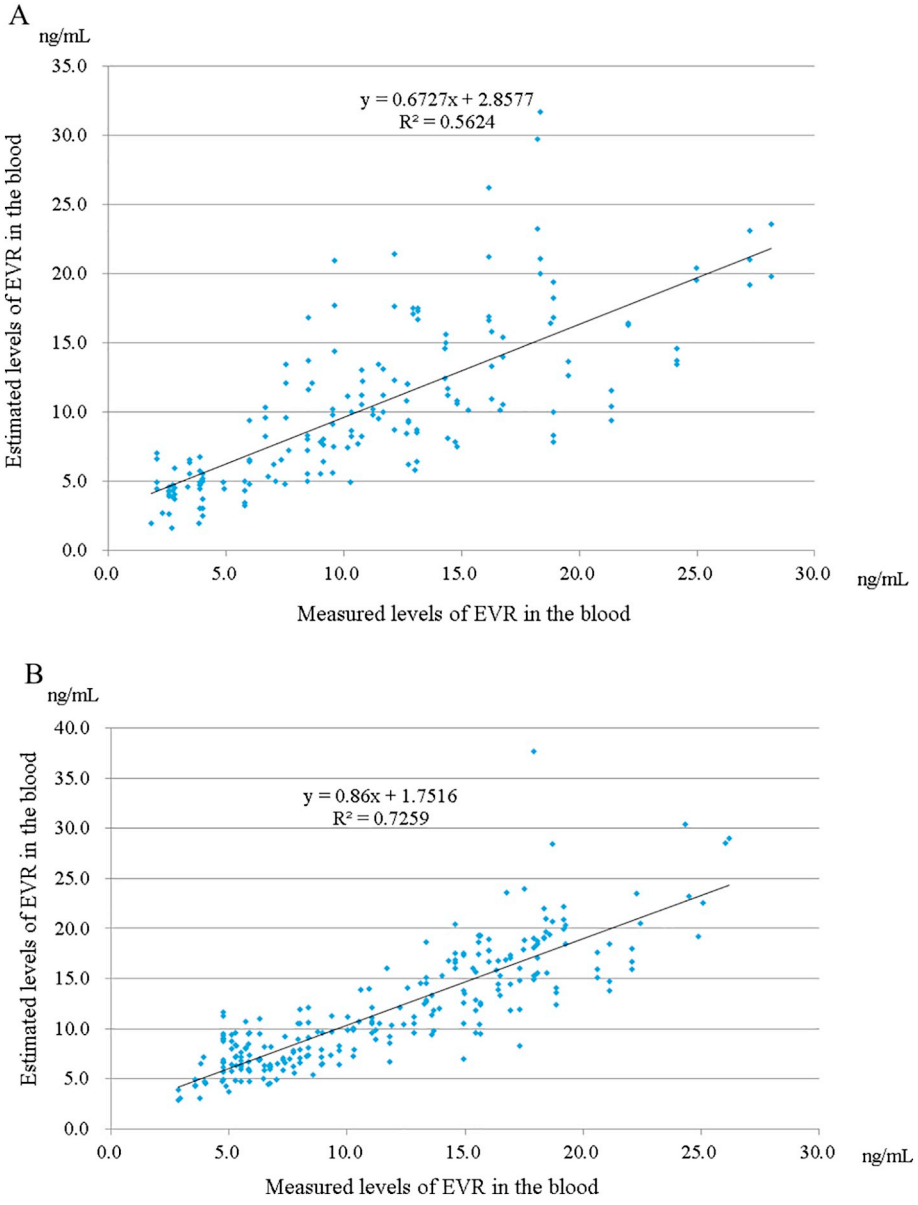

Fig. 8. A. Correlation between estimated and measured levels of everolimus in the blood in the tacrolimus + everolimus group.
B. Correlation between estimated and measured levels of everolimus in the blood in the cyclosporine A + everolimus group.
The relationship between the estimated level of EVR in the blood from the PPK model and the measured blood level is indicated by regression lines.
EVR: everolimus.

PPK analysis.

The relationship between the C_0 level and area under curve $(AUC)_{0-4h}$ is shown in Fig. 7A and B. The regression line equations were as follows:

TAC + EVR group: y

= 7.2335x + 16.864; R^2 (coefficient of determination) = 0.6814

CsA + EVR group: y = 6.3013x + 20.089; R^2 = 0.7483

The R^2 of the TAC + EVR and CsA + EVR groups showed a good correlation between the C_0 level and AUC.

3.3.5. PPK analysis

The parameters obtained using the PPK analysis are shown in Table 2. The relationship between the estimated level of EVR in the blood from the PPK model and the measured blood level is indicated by regression lines in Fig. 8A and B. The regression line equations were as follows:

TAC + EVR group: y = 0.6727x + 2.8577; R^2 = 0.5624

CsA + EVR group: y = 0.8600x + 1.7516; R^2 = 0.7259

3.3.6. Minimum concentration during a dose interval at steady state

The dose of EVR required to maintain the target C_0 level of EVR was calculated using the line equation obtained in Fig. 9A. The rates of EVR dose ($EVR_{TAC+EVR\ group}/EVR_{CsA+EVR\ group}$) to maintain the C_0 level of EVR of 3.0 ng/mL and 8.0 ng/mL were 3.589 and 3.587, respectively (Fig. 9B).

4. Discussion

The target range of EVR C_0 level was calculated based on previous clinical studies [22,23]. The lower exposure threshold of EVR (> 3 ng/mL) was defined according to the incidence of biopsy-proven acute

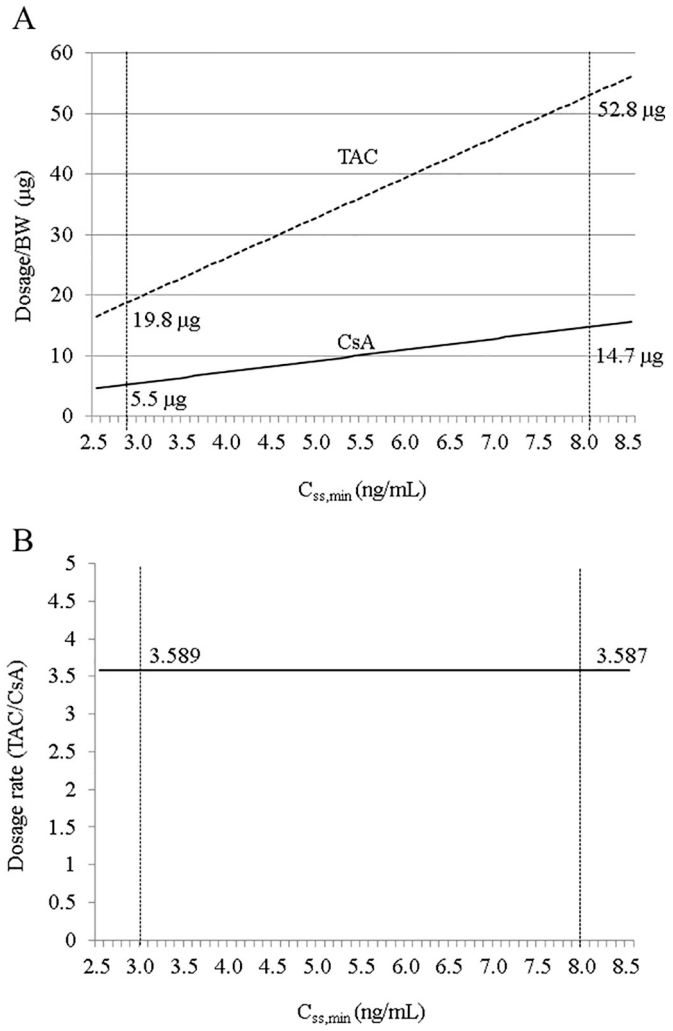

Fig. 9. Panel A. Optimal dose of everolimus in the tacrolimus + everolimus and cyclosporine A + everolimus groups, calculated from the formula of minimum concentration during a dose interval at steady state.
B. Rates of everolimus dose ($EVR_{TAC+EVR\ group}/EVR_{CsA+EVR\ group}$).
The dose of EVR required to maintain the target C_0 level of EVR was calculated using the line equation obtained in panel A. The rates of EVR dose ($EVR_{TAC+EVR\ group}/EVR_{CsA+EVR\ group}$) to maintain the C_0 level of EVR of 3.0 ng/mL and 8.0 ng/mL were 3.589 and 3.587, respectively.
BW: body weight, C_0 level: trough level, $C_{ss,\ min}$: minimum concentration during a dose interval at steady state, EVR: everolimus, TAC: tacrolimus, CsA: cyclosporine A.

rejection. Meanwhile, the upper exposure threshold of EVR (< 8 ng/mL) was determined according to the incidence of adverse events, such as dyslipidemia, thrombocytopenia, proteinuria, delayed wound healing, and peripheral edema, and the use of statin, or discontinuation of EVR due to the adverse events [22,23]. According to these studies [22,23], the target range of EVR C_0 level was determined as 3–8 ng/mL.

The pharmacokinetics of EVR was affected by liver function, P-glycoprotein and cytochrome CYP3A4 levels, drug–drug interactions, and fatty food intake, according to previous studies [24–26]. Cyclosporine A and TAC are metabolized by cytochrome CYP3A4 and are substrates of P-glycoprotein [26,27]. Although CsA and TAC block the efflux of EVR to a similar degree from the intestinal cells and through P-glycoprotein [22], CsA can reduce EVR clearance via the inhibition of cytochrome CYP3A4, thus, causing more EVR exposure to the patients than that by TAC [22]. In fact, in the present study, the mean dose and C_0 level of EVR administered with TAC were significantly higher and lower, respectively, than those of EVR with CsA. These results led to significant differences in the CD-ratio$_{(CsA+EVR\ group)}$/CD-ratio$_{(TAC+EVR\ group)}$ at 1, 2, and 3 weeks after transplantation. The simple comparison of the CD-ratio$_{(CsA+EVR\ group)}$/CD-ratio$_{(TAC+EVR\ group)}$ at 1, 2, and 3 weeks were > 3.0. This result implied that a higher dose of EVR is necessary when administered with TAC than with CsA. However, the optimal dose of EVR when provided with TAC to maintain the target EVR range has not been investigated and pharmacologically demonstrated. In this study, the PPK analysis was used to obtain the pharmacokinetic parameters for the model formula, considering intra- and inter-patient pharmacokinetics. The PPK analysis is convenient because repeated blood sampling from a patient is not necessary. Furthermore, blood samples from different patients enable to elucidate the pharmacokinetics and the effects of concomitant use of the drugs. A one compartment model was chosen for the model formula and PPK parameters, because the decrease of EVR level in the blood after reaching the peak levels was almost linear in both groups. Additionally, in the present study, there was no significant difference in the preoperative liver function of the patients between the TAC + EVR and CsA + EVR groups, even though other studies showed that the metabolism of EVR was affected by liver function [25,27]. The C_0 levels correlated well with AUC in both experimental groups, according to this and a previous study [20]. Therefore, the total exposure of EVR to patients might be represented by the C0 levels or AUC. Because C_0 is an easier parameter to calculate, we continued our studies determining C_0 levels, rather than AUC values. Therefore, in this study, we investigated the dose of EVR required to maintain the C_0 level of EVR within 3–8 ng/mL, when administered with TAC or CsA. The C_0 level of TAC and CsA gradually reached the target range of EVR at 3 weeks after transplantation.

The estimated level of EVR in the blood, according to the PPK model, correlated well with the measured level of EVR in the blood for each experimental group, TAC + EVR and CsA + EVR. With these established coefficients and model, the dose of EVR to maintain its minimum level in the steady state (3–8 ng/mL) with repeated administrations of EVR every 12 h was 3.59-fold higher in the TAC + EVR group than in the CsA + EVR group. The results indicated that the same dose of EVR administered with TAC and with CsA might not result in the same C_0 level of EVR after kidney transplantation. Furthermore, the TAC dose when provided with EVR was considerably less than that administered with MMF, and this condition might easily cause acute rejection [16,18–21]. A history of acute rejection has been reported to increase the incidence of chronic antibody-mediated rejection and lead to early graft loss [28,29]. Although the purpose of co-administering EVR with a reduced CNI dose is to prolong long-term graft survival by reducing CNI toxicity, adverse outcomes like acute rejection can occur under insufficient immunosuppression. According to this result, the optimal dose of EVR administered with TAC should be more than that used with CsA. Although the number of enrolled patients in this study was limited, and the blood samples were collected only during perioperative periods, the PPK study allowed us to predict the optimal dose of EVR when administered with TAC or CsA. The results obtained from this research indicated that the optimal dose of EVR when combined with TAC should be higher than the one used with CsA; therefore, the dose of EVR should be carefully assessed when combined with TAC during the treatment of patients undergoing kidney transplantation, or when patients are required to switch from concomitant use of EVR with CsA to TAC or use of MMF to EVR with TAC during maintenance period. Acute rejection, which could easily occur under insufficient administration of EVR and thus insufficient immunosuppression, may result in the de novo donor-specific anti-HLA antibody production and consequently, in graft loss due to chronic antibody-mediated rejection [28,29]. Administering the optimal dose of EVR from the beginning when used with TAC could reduce the frequency of graft loss and increase the long-term graft survival. Recently, TACER has been increasingly used instead of TAC. The incidence of all-cause mortality, transplant failure, acute rejection, and safety in hematological and biochemistry analyses, hepatic profile, and estimated GFR were similar

when compared between TACER and TAC [30,31]. The efficacy of concomitant administration of TACER and a similar mammalian target of rapamycin, sirolimus, has been investigated. Similarly, the incidence of biopsy-proven acute rejection, estimated GFR, and adverse events were similar to those observed with the combined administration of TACER and MMF [32]. In the future, studies of the simultaneous use of TACER and EVR should be conducted. As the pharmacokinetics of TACER and the coefficients and model obtained from a PPK analysis might be different from those of TAC, the optimal dose of EVR administered with TACER should be determined.

A limitation of this study is its retrospective design; therefore, randomized clinical studies of the optimized dose of EVR administered with TAC should be conducted in the future. In conclusion, the optimal dose of EVR provided with TAC was 3.59-fold higher than that with CsA. Administration of a higher EVR dose is recommended when provided in conjunction with TAC than with CsA to prevent adverse events caused by immunosuppression, that could lead to acute kidney rejection.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105772.

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