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# Extrapolation of physiologically based pharmacokinetic model for tacrolimus from renal to liver transplant patients

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**Abstract**

Physiologically based pharmacokinetic (PBPK) modeling is useful for evaluating differences in drug exposure among special populations, but it has not yet been employed to evaluate the absorption process of tacrolimus. In this study, we developed a minimal PBPK model with a compartmental absorption and transit model for renal transplant patients using available data in the literature and clinical data from our hospital. The effective permeability value of tacrolimus absorption and parameters for the single adjusting compartment were optimized via sensitivity analyses, generating a PBPK model of tacrolimus for renal transplant patients with good predictability. Next, we extrapolated the pharmacokinetics of tacrolimus for liver transplant patients by changing the population demographic parameters of the model. When the physiological parameters of a population with normal liver function were changed to those of a population with impaired hepatic function (Child-Pugh class A) in the constructed renal transplant PBPK model, the predicted tacrolimus concentrations were consistent with the observed concentrations in liver transplant patients. In conclusion, the constructed tacrolimus PBPK model for renal transplant patients could predict the pharmacokinetics in liver transplant patients by slightly reducing the hepatic function, even at three weeks post-transplantation.

**Keywords:** PBPK, tacrolimus, renal transplantation, liver transplantation, Simcyp

## 1. Introduction

Tacrolimus is used as a key immunosuppressant drug in organ transplantation. Therapeutic drug monitoring (TDM) of tacrolimus is important for the prevention of organ rejection and adverse drug reactions, as it has a narrow therapeutic range and large inter- and intra-individual variabilities [1-4]. Tacrolimus is metabolized by cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5, respectively) in the liver and small intestine. *CYP3A5* exhibits genetic polymorphism, including the wild-type allele *CYP3A5*1* and the variant allele *CYP3A5*3.* Individuals harboring at least one *CYP3A5*1* allele express high levels of the functional CYP3A5 protein [extensive metabolizer (EM)], which is expressed at low or undetectable levels in those harboring *CYP3A5*3/*3* variants [poor metabolizer (PM)] [5]. Previous studies have shown that genetic polymorphisms of hepatic and intestinal *CYP3A5* affect the pharmacokinetics of tacrolimus [6-8]. Tacrolimus is a substrate of P-glycoprotein (P-gp), or multidrug resistance protein 1 (MDR1), encoded by the *ATP-binding cassette sub-family B member 1 (ABCB1)* gene, which actively transports the drug back into the intestinal lumen [9]. Therefore, it is necessary to consider the effects of this transporter and CYP3A4 and CYP3A5 metabolism on the absorption profile of tacrolimus to precisely determine its pharmacokinetics.

The physiologically based pharmacokinetic (PBPK) model is a mathematical model that can quantitatively estimate the mechanisms by which physiological and physiochemical factors affect the pharmacokinetics of a compound [10]. There are several approaches for developing a PBPK model, including the “bottom-up” approach based on *in vitro* data and the “top-down” approach based on observed clinical data [11]. Furthermore, the “middle-out” approach combines both approaches and is known for its feasibility in PBPK model development [12]. In the “middle-out” approach, an initial model is constructed based on *in vitro* data, and then refined using clinical data. We previously reported a PBPK model of tacrolimus in liver transplant patients using the “middle-out” approach, which demonstrated good predictability when the fraction of dose absorbed (Fa) was designated as the low value of 0.6 [13]. In the previous report, we could not evaluate permeability efficacy and/or transporter function due to insufficient tacrolimus pharmacokinetic data during the absorption process [14]. To the best of our knowledge, no reports have evaluated the absorption process of tacrolimus using PBPK modeling thus far. Although total body clearance of tacrolimus in liver transplant patients was reportedly lower than that in renal transplant patients [14], directly comparing tacrolimus pharmacokinetics between different types of organ

transplantation is difficult because only one specific organ transplant population was analyzed in each previous study.

In this study, we established a PBPK model of tacrolimus for renal transplant patients considering absorption phase using time-course blood concentration data after oral administration, as well as available data in the literature. Drug exposure in a population with various levels of hepatic impairment was simulated using the constructed renal transplant PBPK model, considering physiological changes unique to each population, and was compared with reported clinical data for liver transplant patients. Our main objective was to determine whether tacrolimus pharmacokinetics in liver transplant patients could be extrapolated from the renal transplant PBPK model by changing the population demographics from “healthy” to “hepatic impairment”.

## 2. Methods

### Study design and ethics

This study was performed in accordance with the Declaration of Helsinki and its amendments, and was approved (No. R0545-1) by the Ethics Committee of Kyoto University Graduate School, Faculty of Medicine and Kyoto University Hospital.

To develop the PBPK model of tacrolimus, we investigated a total of 18 Japanese renal transplant patients whose time-course data following oral administration of tacrolimus were collected at Kyoto University Hospital from July 2018 to September 2019. Blood samples were collected for three months post-transplantation, sampling before morning administration of tacrolimus and at 1, 2, 3, and 4 h after administration. Tacrolimus concentrations in blood were measured using a chemiluminescent enzyme immunoassay system (ARCHITECT; Abbott, Tokyo, Japan). Previously reported time-course data of tacrolimus at three weeks post living-donor liver transplantation [15] were used for comparison. Supplemental Table S1 lists the characteristics of renal and liver transplant patients examined in this study.

**Development of the PBPK model**

The workflow for tacrolimus PBPK modeling is shown in Figure 1. The Simcyp Population-Based Absorption, Distribution, Metabolism, and Excretion (ADME) Simulator version 17 (Certara UK Limited, Simcyp Division, Sheffield, UK) was used to develop the PBPK model of tacrolimus. The population characteristics and parameter values used to develop the PBPK model of tacrolimus are shown in Supplemental Table S2 [13, 16-20]. The model structure is shown in Supplemental

Figure S1. Minimal PBPK and compartmental absorption and transit (CAT) [21] models were selected as the distribution and absorption models, respectively. Tacrolimus is metabolized by CYP3A4 and CYP3A5 in the liver and small intestine, and less than 1% of tacrolimus is excreted in urine [1]. Therefore, the pharmacokinetics of tacrolimus in patients with renal transplantation, which does not affect the metabolism pathway, was assumed to be similar to that in healthy adults. Namely, physiological parameters were based on default Japanese population data provided by Simcyp, whereas the mean abundances of CYP3A5 in the liver and small intestine were changed from the default values of 82.3 pmol/mg protein and 20.5 pmol/whole gut to 20.5 pmol/mg protein and 7.97 pmol/whole gut, respectively. These modified abundance values of CYP3A5 in Japanese population were obtained by multiplying the default abundance value of CYP3A4 in the liver and small intestine for Japanese population built-in Simcyp by the ratio of CYP3A5: CYP3A4 in the liver and small intestine of Caucasian described in the literature [16, 17], respectively. The abundances of CYP3A4 in the liver and small intestine were used the default value of 112 pmol/mg and 54.2 pmol/whole gut built-in Simcyp, assuming that the abundances of CYP3A4 were not changed in renal transplant patients compared to healthy adults. The steady-state volume of distribution ($V_{ss}$) was set to 20.2 L/kg, according to our previous study [13]. First, the base model for

tacrolimus absorption was constructed using an effective permeability ($P_{eff}$) value of $5.95 \times 10^{-4}$ cm/s, based on apparent permeability data in the presence of a P-gp inhibitor [18]. Then, the simulated pharmacokinetic parameters using the constructed base model were compared with observed clinical data from renal transplant patients.

The $P_{eff}$ value was optimized both by performing a sensitivity analysis and by comparing the geometric means of the observed and predicted values of the dose-corrected area under the concentration-time curve from 0 to 12 h ($AUC_{0\text{-}12h}$). The observed dose-corrected $AUC_{0\text{-}12h}$ value was calculated using the linear trapezoidal method, hypothesizing that the tacrolimus blood concentration 12 h after administration was equivalent to the tacrolimus trough concentration. The predicted dose-corrected $AUC_{0\text{-}12h}$ values using several $P_{eff}$ values ($0.05 \times 10^{-4}$ to $10 \times 10^{-4}$ cm/s, in increments of $0.05 \times 10^{-4}$) were compared to the geometric mean of the observed dose-corrected $AUC_{0\text{-}12h}$ values. $P_{eff}$ values were optimized when the absolute percentage prediction error (%PE) of dose-corrected $AUC_{0\text{-}12h}$ values was minimal, as shown in the following equation:

$$\%\text{PE} = \frac{Predicted - Observed}{Observed} \times 100\ (\%)$$

In the next step, the single adjusting compartment was incorporated to fit the predicted to the observed time-concentration profiles (Supplemental Figure S1) [22].

The volume of a single adjusting compartment ($V_{sac}$), input rate constant ($k_{in}$), and output rate constant ($k_{out}$) values were optimized by performing sensitivity analyses to compare observed and predicted values for $AUC_{0\text{-}12h}$, maximum blood concentration ($C_{max}$), trough blood concentration ($C_{min}$), and time-to-maximum blood concentration ($T_{max}$). The geometric mean of predicted dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $T_{max}$, and $C_{min}$ values using a range of $V_{sac}$ ($1 \times 10^{-5}$ to 20 L/kg, in increments of 0.1), $k_{in}$ (0.01 to 1 /h, in increments of 0.01), and $k_{out}$ (0.01 to 1 /h, in increments of 0.01) values were compared to the geometric means of the observed values. $V_{sac}$, $k_{in}$, and $k_{out}$ values were optimized when the absolute %PE of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $T_{max}$, and $C_{min}$ was minimal.

The predictions by the constructed model were considered reliable when %PE was within ± 50% for each pharmacokinetic parameter [23]. In this simulation, all subjects were dealt with as a single population. The simulations were performed using 100 subjects per simulation, employing similar demographic data for age and male/female ratio as the observed data. The virtual subjects received multiple oral doses (1 mg twice a day) of tacrolimus for 60 days. Furthermore, simulation was performed using 10 trials of 18 virtual individuals to check the goodness of the constructed model.

**Model Verification**

Using the constructed model, the tacrolimus pharmacokinetic parameters were estimated for each *CYP3A5* phenotype and compared to previously reported parameters at early and maintenance stages after renal transplantation [24]. The simulation was performed using similar demographic data for age, sex, male/female ratio, and mean hematocrit value as reported in the literature [24]. The predicted values of $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ were compared to literature values.

Furthermore, time concentration profiles of intravenous and oral administration of tacrolimus were visually compared to those in the literature [25], the data from which were extracted using WebPlotDigitizer ver 4.4 (https://automeris.io/WebPlotDigitizer). The simulation was performed using similar demographic data for age, sex, and male/female ratio as reported in the literature [25]. The hematocrit value at the early stage after transplantation was assumed to the same as the literature value [24] due to lack of information. In the simulation, intravenous and oral doses of tacrolimus were set at 0.075 mg/kg for 4 h infusion and 0.15 mg/kg twice a day, respectively. The predicted time-concentration profiles on day 1 for intravenous infusion and on day 8 for oral administration were compared with the literature data [25].

**Sensitivity analysis for the model of tacrolimus for renal transplant patients**

Sensitivity analyses were performed focusing on dose (0.02-0.20 mg/kg/day), hematocrit (15-50%), albumin (2.0-6.0 g/dL), and the abundance of CYP3A4 and CYP3A5 in the liver and small intestine, which were known as variability factors for blood concentration of tacrolimus, to explore the impact of these factors on the trough concentration. The simulation design comprised the oral administration of tacrolimus twice a day for 60 days in a representative virtual subject (dose = 0.08 mg/kg/day, hematocrit = 40%, albumin = 5.0 g/dL, abundance of CYP3A4 in the liver = 112 pmol/mg, abundance of CYP3A5 in the liver = 20.5 pmol/mg, abundance of CYP3A4 in the small intestine = 54.2 pmol/whole gut, abundance of CYP3A5 in the small intestine = 7.97 pmol/whole gut).

**Extrapolation of PBPK model from renal to liver transplant patients**

Previously reported tacrolimus time-concentration data three weeks after liver transplantation were used as observational data [15]. First, we examined whether the final PBPK model of tacrolimus for renal transplant patients could precisely predict each pharmacokinetic parameter in liver transplant patients. In Simcyp, the built-in parameters for the frequency of *CYP3A5* EM and PM in the Japanese population were

42% and 58%, respectively. In liver transplant patients, *CYP3A5* genotypes in the liver and small intestine are derived from the donor and recipient, respectively. Therefore, in the simulation estimating the pharmacokinetic parameters of liver transplant patients, the frequencies of the four phenotypes were assumed to be 18% for *CYP3A5* EM in both graft liver and small intestine, 24% for *CYP3A5* EM in graft liver and *CYP3A5* PM in the small intestine, 24% for *CYP3A5* PM in the graft liver and *CYP3A5* EM in the small intestine, and 34% for *CYP3A5* PM in both liver and small intestine. In Simcyp, the CYP phenotype in the liver and small intestine cannot be selected individually. Therefore, the frequency of patients with *CYP3A5* EM was set to 1 and the abundance of CYP3A5 in the liver or small intestine was modified to 0 when estimating the pharmacokinetic parameters of liver transplant patients with *CYP3A5* PM in the liver and *CYP3A5* EM in the small intestine or with *CYP3A5* EM in the liver and *CYP3A5* PM in the small intestine, respectively. The simulations were performed using 100 subjects per simulation, employing similar demographic data for age and male/female ratio as the observed data [15]. The default values of physiological parameters, such as hematocrit and albumin, for healthy Japanese population shown in Supplemental Table S3 were used in this simulation. In this simulation, all subjects were dealt with as a single population. The %PE of each pharmacokinetic parameter (dose-corrected $AUC_{0-}$

$_{12h}$, $C_{max}$, $T_{max}$, or $C_{min}$) was calculated using the geometric means of the observed and predicted values.

A previous meta-analysis of tacrolimus reported that the total body clearance of tacrolimus in liver transplant patients was lower than that in renal transplant patients [14]. Therefore, we hypothesized that liver function was drastically reduced in liver transplant patients compared with that in renal transplant patients, and we investigated model predictability by changing the physiological parameters from a healthy Japanese population to those with hepatic impairment. In the Simcyp simulator, the built-in parameter values for patients in Child-Pugh classes A, B, and C (CP-A, CP-B, and CP-C) were based on Caucasian population. Therefore, to determine the physiological parameters intended for modification to Japanese CP-A, CP-B, and CP-C, we calculated the ratio of each parameter in the healthy Caucasian adult population with that in the CP-A, CP-B, and CP-C Caucasian populations. Each ratio was then multiplied by the corresponding healthy Japanese population parameter. The altered physiological parameters in the CP-A, CP-B, and CP-C Japanese populations, compared to a healthy Japanese population, are summarized in Supplemental Table S3. Finally, we examined whether the PBPK model of tacrolimus for CP-A patients could improve the

predictability of each pharmacokinetic parameter by changing the $P_{eff}$ value ($0.60 \times 10^{-4}$ to $0.75 \times 10^{-4}$ cm/s, in increments of $0.05 \times 10^{-4}$).

**Effects of CYP3A5 phenotype in renal and liver transplant patients**

The trough blood concentration/dose ($C_{min}$/D) ratios in renal and liver transplant patients were calculated for each *CYP3A5* phenotype using the final PBPK model of tacrolimus for renal transplant patients employing the demographic data of healthy and CP-A Japanese populations, respectively. The simulations were independently performed for each CYP3A5 phenotype with 100 subjects per simulation, an equal proportion of females to males, and an age range of 20-70 years. Then, the recommended tacrolimus dose for each *CYP3A5* phenotype was calculated for renal and liver transplant patients. The oral administration dosage that maintained a tacrolimus trough concentration of 10 ng/mL, which is a target concentration at one month after transplantation, was calculated.

## 3. Results

**Optimization and verification of tacrolimus model for renal transplantation**

The geometric means of the observed dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $C_{min}$, and $T_{max}$ values in renal transplant patients are shown in Table 1. In the initial model building step, the $P_{eff}$ value was set at $5.95 \times 10^{-4}$ cm/s in the base model, in which the contribution of P-gp was not considered. When this value was used for the simulation, the %PE of each pharmacokinetic parameter was considerable (Table 1). Therefore, we considered the effect of P-gp during development of the PBPK model of tacrolimus for renal transplant patients. Since we could not obtain *in vitro* kinetic data for P-gp-mediated tacrolimus efflux from the previous literature, the efflux transporter effect was mimicked by changing the $P_{eff}$ value.

The result of the $P_{eff}$ sensitivity analysis is shown in Supplemental Figure S2. The $P_{eff}$ value was optimized to $0.65 \times 10^{-4}$ cm/s when the minimum difference was obtained between the observed and predicted geometric mean $AUC_{0\text{-}12h}$ values. Next, the $V_{sac}$, $k_{in}$, and $k_{out}$ values were optimized to fit the predicted to the observed time-concentration profiles. Three-dimensional plots of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $C_{min}$ $T_{max}$ vs. $k_{in}$ and $k_{out}$ for the three representative $V_{sac}$ values are shown in Figure 2. The optimum values of $V_{sac}$ (11.8 L/kg), $k_{in}$ (0.37 /h), and $k_{out}$ (0.06 /h) were obtained when the absolute %PE values of $AUC_{0\text{-}12h}$, $C_{max}$, $T_{max}$, and $C_{min}$ were minimal.

The geometric mean and %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $C_{min}$, and $T_{max}$ predicted by the base model and the parameter-optimized (final) model for renal transplant patients are also shown in Table 1. The values of %PE for dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$, and $T_{max}$ values were within ± 10% in the final model. The tacrolimus time-concentration profiles predicted by the final model and the observed results in renal transplant patients are shown in Figure 3a. The observed concentrations were distributed around the median, within the 90% prediction interval (PI) of the predicted concentrations. The comparison of the observed and predicted dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$, and $T_{max}$ values in 10 trial are shown in Supplementary Figure S3.

The comparison of published observed [24] and predicted pharmacokinetic values of $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ for each *CYP3A5* phenotype at maintenance and early stages after transplantation are shown in Supplemental Table S4. All %PE values were within ± 50%.

The comparison of published observed [25] and predicted time-concentration profiles of intravenous and oral administration is shown in Supplemental Figure S4. The observed values were almost within the 90% PI of the predicted time-concentration profile.

**Sensitivity analysis**

The effect of dose on the $C_{min}$ of tacrolimus was shown in Figure 4. The $C_{min}$ of tacrolimus increased almost linearly in the clinically used range from 0.05 to 0.2 mg/kg/day.

The impacts of hematocrit, albumin, and the abundance of CYP3A4 and CYP3A5 in the liver and small intestine on the $C_{min}$ of tacrolimus were also evaluated via sensitivity analysis, revealing that $C_{min}$ values were sensitive to all six parameters (Figure 4).

**Extrapolation of tacrolimus PBPK model from renal to liver transplant patients**

The geometric means of our observed dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $C_{min}$, and $T_{max}$ values in liver transplant patients [15] are shown in Table 1. We then compared tacrolimus pharmacokinetics in liver and renal transplant patients. First, the pharmacokinetic parameters were predicted using the final PBPK model of tacrolimus for renal transplant patients by setting the *CYP3A5* phenotype in the liver and small intestine independently, assuming there were no other differences. The %PE values for all pharmacokinetic parameters were negative, although within ± 50% (Table 1), when

comparing the predicted parameters with those reported for liver transplant patients three weeks post-transplantation [15]. Next, we examined whether the predictability of tacrolimus pharmacokinetics could be improved by changing the population demographic data. The geometric mean and %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $C_{min}$, and $T_{max}$ predicted using the demographic data of healthy, CP-A, CP-B, and CP-C Japanese populations are also shown in Table 1. The %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ were also negative, but were improved when using the demographic data of the CP-A Japanese population. In contrast, the %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ were > 50% when using the demographic data of CP-B and CP-C Japanese populations. Therefore, we determined that the PBPK model of tacrolimus for renal transplant patients best described the tacrolimus pharmacokinetics of liver transplant patients using the CP-A demographic data.

The CP-A and CP-B tacrolimus time-concentration profiles predicted by the renal transplant PBPK model are shown in Figure 3b. In the CP-A Japanese population, all observed concentrations in Japanese liver transplant patients [15] were within the 90% PI, except for those of one patient.

The pharmacokinetic parameters were predicted using the PBPK model of tacrolimus with CP-A population using several the $P_{eff}$ value ($0.60 \times 10^{-4}$ to $0.75 \times 10^{-4}$

cm/s, in increments of $0.05 \times 10^{-4}$). The absolute %PE of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, $T_{max}$, and $C_{min}$ was minimal when using the $P_{eff}$ value of $0.65 \times 10^{-4}$ cm/s.

**Effects of CYP3A5 phenotype in renal and liver transplant patients**

The tacrolimus $C_{min}$/D ratio simulated using the final PBPK model for each *CYP3A5* phenotype in renal transplant patients is shown in Figure 5a. The median $C_{min}$/D ratios for patients with *CYP3A5* EM and PM were predicted to be 1.33 (90% PI: 0.0807-4.03) and 2.43 (0.128-10.5) ng/mL/mg, respectively. Based on the final PBPK model for renal transplant patients, the recommended tacrolimus dosages to maintain the blood concentration at 10 ng/mL in patients with *CYP3A5* EM and PM were calculated to be 0.133 and 0.0682 mg/kg/day, respectively.

The $C_{min}$/D ratio calculated for each *CYP3A5* phenotype using the CP-A renal transplant PBPK model is shown in Figure 5b. The median $C_{min}$/D ratios were predicted to be 1.68 (90% PI: 0.125 - 5.75) ng/mL/mg for patients with *CYP3A5* EM in both the graft liver and small intestine, 2.10 (0.178-7.82) ng/mL/mg for patients with *CYP3A5* EM in the graft liver and *CYP3A5* PM in the small intestine, 2.63 (0.144-8.44) ng/mL/mg for patients with *CYP3A5* PM in the graft liver and *CYP3A5* EM in the small intestine, and 3.35 (0.175-12.6) ng/mL/mg for patients with *CYP3A5* PM in both the

liver and small intestine. Based on the final PBPK model for renal transplant patients using the CP-A demographic data, the recommended tacrolimus dosages to maintain the blood concentration at 10 ng/mL were calculated to be 0.103 mg/kg/day for patients with *CYP3A5* EM in both the graft liver and small intestine, 0.0867 mg/kg/day for patients with *CYP3A5* EM in the graft liver and *CYP3A5* PM in the small intestine, 0.0675 mg/kg/day for patients with *CYP3A5* PM in the graft liver and *CYP3A5* EM in the small intestine, and 0.0550 mg/kg/day for patients with *CYP3A5* PM in both the liver and small intestine.

## 4. Discussion

Using available literature and observed clinical data, we successfully constructed a PBPK model of tacrolimus for renal transplant patients considering absorption phase. The constructed tacrolimus PBPK model for renal transplant patients could predict the pharmacokinetics in liver transplant patients by slightly reducing the hepatic function, even at three weeks post-transplantation.

In Simcyp, the default values of the mean CYP3A5 abundance in the liver and small intestine in the Japanese population were set as 82.3 pmol/mg protein and 20.5 pmol/whole gut, respectively. Using these default CYP3A5 abundance value in the liver

and small intestine, the simulated tough concentration for patients with *CYP3A5* PM were 5.6 times higher than that with *CYP3A5* EM (data not shown), which was inconsistent with the results in the previous report [24]. Previous studies using PBPK modeling demonstrated that the observed total body clearance or blood concentrations of tacrolimus were adequately predicted by changing the abundance of CYP3A5 in the liver and small intestine [13, 17]. Therefore, we modified the built-in values of CYP3A5 in the liver and small intestine according to previously reported ratios of the abundance of CYP3A4 to that of CYP3A5 in the liver or small intestine [16, 17], which showed a good predictability.

When the $P_{eff}$ value was changed from $5.95 \times 10^{-4}$ to $0.65 \times 10^{-4}$ cm/s, tacrolimus pharmacokinetics were well predicted, as shown in Table 1 and Figure 3a. We hypothesized that the predictability of the PBPK model could be improved by using a lower $P_{eff}$ value, which allowed consideration of the pumping-out function of P-gp at the absorption site. Since tacrolimus is classified as a biopharmaceutics classification system class II drug with low solubility and high membrane permeability, its Fa should be more than 85% [26, 27]. In this study, the mean Fa value was calculated as 61% by the final tacrolimus PBPK model for renal transplant patients. Therefore, we considered

that P-gp pumping tacrolimus back into the intestinal lumen would contribute 20-40% to the apparent Fa.

In this study, tacrolimus dosage was changed among patients, according to routinely monitored blood concentration data. Since tacrolimus is generally treated as linear pharmacokinetics [1-3], we evaluated using dose-normalized pharmacokinetic parameters. Indeed, the sensitivity analysis results revealed that the blood concentration of tacrolimus increased almost linear in the clinically used range. Since hematocrit and albumin values are known to strongly affect the blood concentration of tacrolimus, as also shown in Figure 4, these factors should be taken into consideration when adjusting the tacrolimus dosage based on TDM data.

The simulations evaluating the effects of the *CYP3A5* phenotype in renal transplantation indicated that the recommended dosage to maintain the tacrolimus blood concentration at 10 ng/mL in renal transplant patients with *CYP3A5* EM was approximately 1.8 times higher than that in patients with PM (Figure 5a). The coefficient of variation of the tacrolimus blood concentration was larger in patients with *CYP3A5* PM (CV 95.2%) than that in patients with EM (CV 81.2%). This would be because the trough concentration of tacrolimus increased nonlinearly as the abundance of CYP3A4 or CYP3A5 decreased as shown in the Figure 4, which results in relatively

larger variation in patients with *CYP3A5* PM group with lower total amount of CYP3A4/5 enzyme. Although information on genotype-guided initial dosing design would be useful, the individual maintenance dosage should be adjusted based on TDM measurements due to the large inter- and intra-individual variabilities of tacrolimus pharmacokinetics, especially in patients with *CYP3A5* PM.

Since %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ were within ± 50% using the CP-A Japanese parameters (Table 1), and the observed concentrations were within the 90% PI (Figure 3b) except for one patient and one point in another patient, we suggested that the tacrolimus PBPK model for renal transplant patients would sufficiently predict the tacrolimus pharmacokinetics in liver transplant patients. Although the predicted concentrations using the CP-B Japanese population parameters approached the observed extremely high concentrations in one patient (Figure 3b), the %PE values of dose-corrected $AUC_{0\text{-}12h}$, $C_{max}$, and $C_{min}$ were > 50% (Table 1). These results indicated that most liver transplant patients would present mildly recovered hepatic function at three weeks post-transplantation, but some would present with moderate liver dysfunction. When transplanted, small-for-size grafts can regenerate to nearly suitable size within a few months after living-donor liver transplantation [28-31].

Unfortunately, information on hematocrit and albumin values of the liver transplant patients used in this study was not obtained. A previous report showed that the liver volume recovered to about 88% of normal liver volume and the albumin value was about 32 g/L four weeks after living-donor liver transplantation [31]. In addition, previous reports of liver transplantation in Chinese patients showed that the albumin and hematocrit values about three weeks after liver transplantation were about 37 g/L and 31%, respectively [32-35]. The demographic data of CP-A patients used in Simcyp showed that the liver size was scaled 0.89 times larger than normal liver size and the median albumin and hematocrit value were 40.8 g/dL and 37.0%, respectively. Although the hematocrit and albumin values in the CP-A population were slightly higher than those in the liver transplant patients in the literature, the liver size was almost the same level. Therefore, it would be reasonable to use the demographic data of CP-A population for liver transplant patients.

The $P_{eff}$ value was optimized to $0.65 \times 10^{-4}$ cm/s in the CP-A population for the liver transplant patients, and it was the same value for the original renal transplant model. Considering these findings, we suggest that hepatic function in liver transplant patients would be slightly lower than that in renal transplant patients, although the size of the liver would almost recover at three weeks post-transplantation, and that the

absorption process in liver transplant patients would not largely differ from that in renal transplant patients. The present study indicated that the differences of pharmacokinetics in renal and liver transplant patient. These findings may allow for consideration of the changes in the kinetics of other hepatically metabolized drugs used in transplant patients, and lead to optimized use of drugs for renal and liver transplant patients.

There are limitations in this study. First, the CAT model [21] was employed to study the absorption process. This model can consider the permeability of the drug, but not its solubility. Solubility is a rate-controlling factor for absorption of a drug with low solubility, such as tacrolimus. This must be considered to more accurately predict the absorption profile of tacrolimus. The advanced dissolution and metabolite (ADAM) model [37], which can consider the effect of drug dissolution, was not selected in this study because the blood concentrations of tacrolimus predicted by the ADAM model were markedly higher than the observed values (data not shown). A previous report indicated that the ADAM model demonstrates poor predictability when used for the pharmacokinetic estimation of a drug with gut availability below 0.33 [38]. Indeed, the gut availability of tacrolimus was reported as 0.39, which is as low as 0.33, and the predicted value of the gut availability by the ADAM model was about 0.59, indicating a poor predictability in the case of tacrolimus [38]. Therefore, for a more precise

consideration of the pharmacokinetics of the absorption process, the ADAM model must be improved to ensure predictability of drugs with low gut availability. Second, the present model could not distinguish between the apparent Fa due to P-gp transporting the drug back into the intestinal lumen and the fraction of unabsorbed (true Fa), because *in vitro* tacrolimus kinetics data with P-gp could not be obtained in the literature. Furthermore, the effect of *MDR1* genetic polymorphism was not considered in this study due to a lack of clinical data. The genetic polymorphisms of *MDR1* might affect the expression and function of P-gp [39], although their effects on tacrolimus dosage are controversial [6, 7, 40, 41]. Further studies are warranted to clarify the effects of *MDR1* genetic polymorphism and the inter-individual variation of P-gp function on tacrolimus pharmacokinetics. Finally, in this study, it would be difficult to clearly distinguish the effects of liver function and absorption on the pharmacokinetics of tacrolimus in renal and liver transplant patients, because of the small clinical sample size. Further studies are needed to understand the differences of the pharmacokinetics of tacrolimus in renal and liver transplantations more precisely.

## 5. Conclusions

We developed a PBPK model of tacrolimus for renal transplant patients considering its pharmacokinetics at the absorption phase using observed clinical data and available data in the literature. The contribution of P-gp function was considered by reducing the $P_{eff}$ value to one tenth of that used in the base model for tacrolimus absorption. The simulation using the final PBPK model indicated that renal transplant patients with *CYP3A5* EM require a dose that is approximately 1.8 times higher than the dose required for patients with *CYP3A5* PM to maintain the same tacrolimus blood concentration. Using the model to compare data from renal and liver transplant patients, hepatic function was slightly decreased in liver transplant patients compared to renal transplant patients, even at three weeks post-transplantation.

**Author contributions**

KI contributed to the study concept and design, data acquisition, interpretation, analysis, and wrote the manuscript. IY supervised all stages of the project and contributed to the study concept and design, interpretation, and revised the manuscript. SN, AY, TO, SI, TN, and KM contributed to the interpretation, and revised the manuscript. AS, TK, AT, KS, KT, and OO contributed the study design, data acquisition, and interpretation. The authors read and approved the final manuscript.

## Declaration of competing interest

None of the authors have any competing interests to declare.


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## References


[1]. Venkataramanan R, Swaminathan A, Prasad T, et al. Clinical pharmacokinetics of tacrolimus. Clin Pharmacokinet. 1995;29(6):404-30. https://doi.org/10.2165/00003088-199529060-00003

[2]. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet. 2004;43(10):623-53. https://doi.org/10.2165/00003088-200443100-00001

[3]. Masuda S, Inui K. An up-date review on individualized dosage adjustment of calcineurin inhibitors in organ transplant patients. Pharmacol Ther. 2006;112(1):184-98. https://doi.org/10.1016/j.pharmthera.2006.04.006

[4]. Kahan BD, Keown P, Levy GA, Johnston A. Therapeutic drug monitoring of immunosuppressant drugs in clinical practice. Clin Ther. 2002;24(3):330-50. https://doi.org/10.1016/s0149-2918(02)85038-x

[5]. Staatz CE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. Clin Pharmacokinet. 2010;49(3):141-75. https://doi.org/10.2165/11317350-000000000-00000

[6]. Tada H, Tsuchiya N, Satoh S, et al. Impact of CYP3A5 and MDR1(ABCB1) C3435T polymorphisms on the pharmacokinetics of tacrolimus in renal transplant recipients. Transplant Proc. 2005;37(4):1730-2. https://doi.org/10.1016/j.transproceed.2005.02.073

[7]. Soda M, Fujitani M, Michiuchi R, et al. Association between tacrolimus pharmacokinetics and cytochrome P450 3A5 and multidrug resistance protein 1 exon 21 polymorphisms. Transplant Proc. 2017;49(6):1492-8. https://doi.org/10.1016/j.transproceed.2017.03.093

[8]. Uesugi M, Kikuchi M, Shinke H, et al. Impact of cytochrome P450 3A5 polymorphism in graft livers on the frequency of acute cellular rejection in living-

donor liver transplantation. Pharmacogenet Genomics. 2014;24(7):356-66. https://doi.org/10.1097/FPC.0000000000000060

[9]. Hebert MF. Contribution of hepatic and intestinal metabolism and P-glycoprotein to cyclosporine and tacrolimus oral drug delivery. Adv Drug Deliv Rev. 1997;27(2-3):201-14. https://doi.org/10.1016/s0169-409x(97)00043-4

[10]. Huang SM, Rowland M. The role of physiologically based pharmacokinetic modeling in regulatory review. Clin Pharmacol Ther. 2012;91(3):542-9. https://doi.org/10.1038/clpt.2011.320

[11]. Jamei M, Dickinson GL, Rostami-Hodjegan A. A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: A tale of 'bottom-up' vs 'top-down' recognition of covariates. Drug Metab Pharmacokinet. 2009;24(1):53-75. https://doi.org/10.2133/dmpk.24.53

[12]. Tsamandouras N, Rostami-Hodjegan A, Aarons L. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. Br J Clin Pharmacol. 2015;79(1):48-55. https://doi.org/10.1111/bcp.12234

[13]. Itohara K, Yano I, Tsuzuki T, et al. A minimal physiologically-based pharmacokinetic model for tacrolimus in living-donor liver transplantation: Perspectives related to liver regeneration and the cytochrome P450 3A5 (CYP3A5) Genotype. CPT Pharmacometrics Syst Pharmacol. 2019;8(8):587-95. https://doi.org/10.1002/psp4.12420

[14]. Nanga TM, Doan TTP, Marquet P, Musuamba FT. Toward a robust tool for pharmacokinetic-based personalization of treatment with tacrolimus in solid organ transplantation: A model-based meta-analysis approach. Br J Pharmacol. 2019;85(12):2793-823. https://doi.org/10.1111/bcp.14110

[15]. Yano I, Masuda S, Egawa H, et al. Significance of trough monitoring for tacrolimus blood concentration and calcineurin activity in adult patients undergoing primary living-donor liver transplantation. Eur J Clin Pharmacol. 2012;68(3):259-66. https://doi.org/10.1007/s00228-011-1129-x

[16]. Achour B, Barber J, Rostami-Hodjegan A. Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: a meta-analysis. Drug Metab Dispos. 2014;42(8):1349-56. https://doi.org/10.1124/dmd.114.058834

[17]. Guo Y, Lucksiri A, Dickinson GL, Vuppalanchi RK, Hilligoss JK, Hall SD. Quantitative prediction of CYP3A4- and CYP3A5-mediated drug interactions. Clin Pharmacol Ther. 2020;107(1):246-56. https://doi.org/10.1002/cpt.1596

[18]. Gertz M, Houston JB, Galetin A. Physiologically based pharmacokinetic modeling of intestinal first-pass metabolism of CYP3A substrates with high intestinal extraction. Drug Metab Dispos. 2011;39(9):1633-42. https://doi.org/10.1124/dmd.111.039248

[19]. Dai Y, Hebert MF, Isoherranen N, et al. Effect of CYP3A5 polymorphism on tacrolimus metabolic clearance in vitro. Drug Metab Dispos. 2006;34(5):836-47. https://doi.org/10.1124/dmd.105.008680

[20]. Barter ZE, Perrett HF, Yeo KR, Allorge D, Lennard MS, Rostami-Hodjegan A. Determination of a quantitative relationship between hepatic CYP3A5*1/*3 and CYP3A4 expression for use in the prediction of metabolic clearance in virtual populations. Biopharm Drug Dispos. 2010;31(8-9):516-32. https://doi.org/10.1002/bdd.732

[21]. Yu LX, Amidon GL. A compartmental absorption and transit model for estimating oral drug absorption. Int J Pharm. 1999;186(2):119-25. https://doi.org/10.1016/s0378-5173(99)00147-7

[22]. Ando H, Izawa S, Hori W, Nakagawa I. Utility of a single adjusting compartment: a novel methodology for whole body physiologically-based pharmacokinetic modelling. Theor Biol Med Model. 2008;5:19. https://doi.org/10.1186/1742-4682-5-19

[23]. Abduljalil K, Cain T, Humphries H, Rostami-Hodjegan A. Deciding on success criteria for predictability of pharmacokinetic parameters from in vitro studies: an analysis based on in vivo observations. Drug Metab Dispos. 2014;42(9):1478-84. https://doi.org/10.1124/dmd.114.058099

[24]. Satoh S, Kagaya H, Saito M, et al. Lack of tacrolimus circadian pharmacokinetics and CYP3A5 pharmacogenetics in the early and maintenance stages in Japanese renal transplant recipients. Br J Clin Pharmacol. 2008;66(2):207-14. https://doi.org/10.1111/j.1365-2125.2008.03188.x

[25]. Japanese FK 506 Study Group. Japanese study of kidney transplantation: 1. Results of early phase II study. Transpl Int. 1992;5(Suppl 1):S524-8. https://doi.org/10.1007/978-3-642-77423-2_154

[26]. Custodio JM, Wu CY, Benet LZ. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug

absorption. Adv Drug Deliv Rev. 2008;60(6):717-33. https://doi.org/10.1016/j.addr.2007.08.043

[27]. US FDA, CDER. Guidance for Industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. https://www.fda.gov/media/70963/download. (2017). Accessed 20 July 2020.

[28]. Yagi S, Iida T, Taniguchi K, et al. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. Liver Transpl. 2005;11(1):68-75. https://doi.org/10.1002/lt.20317

[29]. Iida T, Isaji S, Yagi S, et al. Assessment of liver graft function and regeneration by galactosyl-human serum albumin (99mTc-GSA) liver scintigraphy in adult living-donor liver transplantation. Clin Transplant. 2009;23(2):271-7. https://doi.org/10.1111/j.1399-0012.2008.00933.x

[30]. Marcos A, Fisher RA, Ham JM, et al. Liver regeneration and function in donor and recipient after right lobe adult to adult living donor liver transplantation. Transplantation. 2000;69(7):1375-9. https://doi.org/10.1097/00007890-200004150-00028

[31]. Akamatsu N, Sugawara Y, Tamura S, Imamura H, Kokudo N, Makuuchi M. Regeneration and function of hemiliver graft: right versus left. Surgery. 2006;139(6):765-72. https://doi.org/10.1016/j.surg.2005.12.011

[32]. Zhu L, Yang J, Zhang Y, Jing Y, Zhang Y, Li G. Effects of CYP3A5 genotypes, ABCB1 C3435T and G2677T/A polymorphism on pharmacokinetics of tacrolimus in Chinese adult liver transplant patients, Xenobiotica. 2015;45(9):840-6. https://doi.org/10.3109/00498254.2015.1021733

[33]. Lu YX, Su QH, Wu KH, Ren YP, Li L, Zhou TY, et al. A population pharmacokinetic study of tacrolimus in healthy Chinese volunteers and liver transplant patients, Acta Pharmacol Sin. 2015;36(2):281-8. https://doi.org/10.1038/aps.2014.110

[34]. Shao J, Wang C, Fu P, Chen F, Zhang Y, Wei J. Impact of donor and recipient CYP3A5*3 genotype on tacrolimus population pharmacokinetics in Chinese adult liver transplant recipients Ann Pharmacother. 2020;54(7):652-61. https://doi.org/10.1177/1060028019897050.

[35]. Chen B, Shi HQ, Liu XX, Zhang WX, Lu JQ, Xu BM, et al. Population pharmacokinetics and Bayesian estimation of tacrolimus exposure in Chinese liver transplant patients. J Clin Pharm Ther. 2017;42(6):679-88.

https://doi.org/10.1111/jcpt.12599.

[36]. Ohtani H, Barter Z, Minematsu T, Makuuchi M, Sawada Y, Rostami-Hodjegan A. Bottom-up modeling and simulation of tacrolimus clearance: prospective investigation of blood cell distribution, sex and CYP3A5 expression as covariates and assessment of study power. Biopharm Drug Dispos. 2011;32(9):498-506. https://doi.org/10.1002/bdd.777.

[37]. Darwich AS, Neuhoff S, Jamei M, Rostami-Hodjegan A. Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the "Advanced Dissolution, Absorption, Metabolism (ADAM)" model. Curr Drug Metab. 2010;11(9):716-29. https://doi.org/10.2174/138920010794328913

[38]. Yau E, Petersson C, Dolgos H, Peters SA. A comparative evaluation of models to predict human intestinal metabolism from nonclinical data. Biopharm Drug Dispos. 2017;38(3):163-86. https://doi.org/10.1002/bdd.2068

[39]. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A. 2000;97(7):3473-8. https://doi.org/10.1073/pnas.050585397

[40]. Li D, Gui R, Li J, Huang Z, Nie X. Tacrolimus dosing in Chinese renal transplant patients is related to MDR1 gene C3435T polymorphisms. Transplant Proc. 2006;38(9):2850-2. https://doi.org/10.1016/j.transproceed.2006.08.089

[41]. Prasad N, Jaiswal A, Behera MR, et al. Melding Pharmacogenomic effect of MDR1 and CYP3A5 gene polymorphism on tacrolimus dosing in renal transplant recipients in Northern India. Kidney Int Rep. 2019;5(1):28-38. https://doi.org/10.1016/j.ekir.2019.09.013

**Figure legends**

**Figure 1.** Workflow for development of physiologically based pharmacokinetic (PBPK) model in this study.

**Figure 2.**

Sensitivity analysis for the dose-normalized area under the concentration-time curve from 0 to 12 h ($AUC_{0\text{-}12h}$), the maximum blood concentration ($C_{max}$), the trough blood concentration ($C_{min}$), and the time to maximum blood concentration ($T_{max}$) vs. input rate constant ($k_{in}$) and output rate constant ($k_{out}$) for the representative $V_{sac}$ value ($V_{sac}$=1 x $10^{-5}$, 11.8, and 20.0 L/kg).

The blue and red layers represent simulated and observed values, respectively.

**Figure 3.** The physiologically based pharmacokinetic model-predicted *vs.* observed time concentration profiles corrected for a dosage of 1 mg of tacrolimus in renal transplant patients (n=18; a) and liver transplant patients (n=13; b). The closed circles represent dose-normalized observed concentrations. The crosses represent dose-normalized observed concentrations in a patient which were outside the 90% prediction

interval using the Child-Pugh A (CP-A) Japanese population. The red, blue, and purple lines represent the median, 5$^{th}$, and 95$^{th}$ percentiles of predicted concentrations, respectively. The predicted concentrations were the results of each simulation performed using 100 subjects. The solid and broken lines represent the concentration profile predicted by the renal transplant model using the demographics of the CP-A and Child-Pugh B (CP-B) Japanese populations, respectively.

**Figure 4.** Sensitivity analysis of the dose of tacrolimus (a), hematocrit (b), albumin (c), abundances of CYP3A4 and CYP3A5 in the liver and small intestine (d-g) for the trough concentration ($C_{min}$). Each red circle shows the value in a representative virtual subject used in this simulation.

**Figure 5.** Simulated trough blood concentration/dose ($C_{min}$/D) ratio of tacrolimus in renal (a) and liver (b) transplant patients in each cytochrome P450 3A5 (CYP3A5) phenotype, respectively. Each box plot represents an interquartile range with a 90% prediction interval. The closed circles represent the data points outside the 5$^{th}$ to 95$^{th}$ percentiles. Each simulation was performed using 100 subjects, a female patient

proportion of 50%, and an age range of 20-70 years. EM; extensive metabolizer, PM; poor metabolizer

**Table 1.** Observed and predicted pharmacokinetic parameters of tacrolimus

| Parameters | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Renal transplantation | Observed (n=18) | | Base model ($P_{eff}$=5.95×10$^{-4}$) | | Final model ($P_{eff}$=0.65×10$^{-4}$) | | | | | |
| | GM | GSD | GM | %PE | GM | %PE | | | | |
| $AUC_{0\text{-}12h}$/dose, ng·h/mL/mg | 31.8 | 1.48 | 153 | 381 | 31.9 | 0.224 | | | | |
| $C_{max}$/dose, ng/mL/mg | 4.23 | 1.49 | 14.9 | 253 | 3.95 | -6.47 | | | | |
| $C_{min}$/dose , ng/mL/mg | 1.63 | 1.65 | 11.0 | 576 | 1.52 | -6.53 | | | | |
| $T_{max}$, h | 2.48 | 1.55 | 1.48 | -40.5 | 2.31 | -6.77 | | | | |
| Liver transplantation | Observed[1] (n=13) | | Renal transplant model with Healthy Japanese | | Renal transplant model with CP-A Japanese | | Renal transplant model with CP-B Japanese | | Renal transplant model with CP-C Japanese | |
| | GM | GSD | GM | %PE | GM | %PE | GM | %PE | GM | %PE |
| $AUC_{0\text{-}12h}$/dose, ng·h/mL/mg | 40.9 | 2.56 | 32.9 | -19.5 | 38.8 | -5.04 | 66.5 | 62.7 | 97.7 | 139 |
| $C_{max}$/dose, ng/mL/mg | 4.59 | 2.56 | 4.03 | -12.4 | 4.53 | -1.56 | 7.05 | 53.2 | 9.83 | 114 |
| $C_{min}$/dose , ng/mL/mg | 2.86 | 2.57 | 1.56 | -45.1 | 2.00 | -29.7 | 4.00 | 40.4 | 6.39 | 124 |
| $T_{max}$, h | 2.55 | 1.54 | 2.33 | -8.80 | 2.37 | -6.89 | 2.48 | -2.70 | 2.54 | -0.24 |

$P_{eff}$: effective permeability, GM: geometric mean, GSD: geometric standard deviation, %PE: percentage prediction error, $AUC_{0\text{-}12h}$: area under the concentration-time curve from 0 to 12 h, $C_{max}$: maximum blood concentration, $C_{min}$: trough blood concentration, $T_{max}$: time to maximum blood concentration

The predicted values were the results of each simulation performed using 100 subjects

1) Yano I et al. Eur J Clin Pharmacol. 2012;68(3):259-66.