Model-Informed Dosing Optimization of Tacrolimus for Concomitant Administration With Itraconazole to Japanese Lung Transplant Recipients

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Model-informed dosing optimization of tacrolimus under itraconazole concomitant use in Japanese lung transplant recipients

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Abstract

Background: Tacrolimus is an immunosuppressant used in patients undergoing lung transplantation. Itraconazole is often used concomitantly to prevent fungal infections and increase tacrolimus concentration. However, the pharmacokinetics of tacrolimus in Japanese lung transplant recipients and effect of itraconazole on tacrolimus pharmacokinetics have not adequately evaluated. Population pharmacokinetic (PPK) analysis was conducted to develop an optimal dose-adjustment method when itraconazole was initiated in Japanese lung transplant recipients.

Methods: This study included Japanese lung transplant recipients whose blood tacrolimus and itraconazole concentrations were measured between January 2017 and December 2019. A nonlinear mixed-effects modeling program was used to explore the covariates of tacrolimus pharmacokinetics and the effects of concomitant itraconazole use. Based on the constructed model, the optimal initial tacrolimus dose and the dose adjustment method when itraconazole was concomitantly used were calculated.

Results: A total of 1693 tacrolimus trough blood concentrations and 85 itraconazole trough plasma concentrations from 43 patients were analyzed. Postoperative day, albumin level, and administration route were extracted as covariates of tacrolimus pharmacokinetics. The drug-drug interaction between tacrolimus and itraconazole could

be predicted more accurately by considering the concentration-dependent inhibition of itraconazole. The optimal initial tacrolimus dose was calculated to be 2.0 mg twice daily for tube administration and 1.5 mg twice daily for oral administration. To maintain the target concentration, the tacrolimus dose was reduced by 60% when itraconazole was initiated.

Conclusions: This is the first PPK analysis investigating the interaction between tacrolimus and itraconazole in patients undergoing lung transplantation. These results would provide useful insights for optimizing the initial tacrolimus dose when itraconazole is administered.

key words: tacrolimus, itraconazole, population pharmacokinetics, lung transplantation, drug-drug interaction

INTRODUCTION

Tacrolimus is a calcineurin inhibitor used as a key immunosuppressant in lung transplantation. As the lung is continuously exposed to the outside environment and stimulated by infectious and non-infectious agents, which may play a part in upregulating the immune response to the allograft, lung transplant recipients often experience acute rejection.[1] Previous reports have shown that only 24–40% of recipients remain free from acute rejection at 1 year after transplantation.[2] Therefore, tacrolimus should maintain high blood concentrations to prevent acute rejection. However, tacrolimus has high inter- and intra-individual variability in pharmacokinetics and a narrow therapeutic window of blood concentration, and therapeutic drug monitoring (TDM) is essential to avoid adverse effects.[3] Several population pharmacokinetic (PPK) studies have been conducted to analyze the pharmacokinetics of tacrolimus in transplant patients.

Infection is one of the most prominent causes of death after lung transplantation.[4] Fungal infections are a common complication of lung transplantation and are associated with high mortality.[5] To prevent fungal infections, lung transplant recipients often take antifungal drugs, such as itraconazole. Itraconazole is also known as a strong competitive inhibitor of CYP3A4/5.[6,7] When tacrolimus and itraconazole are concomitantly used, tacrolimus blood concentrations are significantly increased due to the inhibition of

CYP3A4/5 by itraconazole.[8] Several previous studies have reported that the tacrolimus concentration per dose (C/D) ratio gradually increased after initiation of itraconazole, and the tacrolimus C/D ratio was related to itraconazole concentrations.[8-10] The authors hypothesized that the variation in tacrolimus blood concentration after initiation of itraconazole could be reduced by considering the plasma concentration of itraconazole. The relationship between high blood tacrolimus concentration and toxicity, such as nephrotoxicity, has been documented.[11] In addition, the authors reported that a decrease in the time in therapeutic range of tacrolimus is a predictor of acute rejection 4 weeks after lung transplantation.[12] Therefore, it is important to reduce the variability in tacrolimus blood concentrations at the start of concomitant itraconazole use to reduce the risk of toxicity and rejection. However, there have been few PPK studies in lung transplant recipients,[13-17] and there are no reports analyzing detail of tacrolimus pharmacokinetics when itraconazole is initiated.

This study aimed to build a PPK model of tacrolimus and an optimal dose adjustment method when itraconazole is initiated to provide appropriate tacrolimus therapy in Japanese lung transplant recipients.

MATERIALS AND METHODS

Patients and Data Collection

Japanese patients who underwent lung transplantation at Kyoto University Hospital between January 2017 and December 2019 and received tacrolimus and itraconazole were enrolled in this study. Patients who used strong CYP3A4/5 inhibitors, except itraconazole (e.g., erythromycin, clarithromycin, and voriconazole), were excluded. For each patient, the following data were retrospectively collected from electronic medical records: tacrolimus and itraconazole concentrations and doses, sex, age, body weight, postoperative days (POD), administration route, concomitant drug, and clinical laboratory data. All patients were administered a combination of tacrolimus, mycophenolate mofetil, and corticosteroids. The initial tacrolimus dose was determined at the discretion of the transplantation team, and 2.0 mg twice daily was usually administered. The tacrolimus concentration was measured twice daily immediately post-transplantation and less frequently after stabilization of blood concentrations. The tacrolimus dose was adjusted to maintain trough concentrations of 10–15 ng/mL based on TDM during the first 3 months after transplantation. To prevent fungal infections, itraconazole oral solution or tablets were administered when patients tolerated oral intake. Because the exact time of administration and blood collection could not be extracted from the electronic medical records, the timing of tacrolimus administration was assumed to

be 9:00/21:00, and the timing of itraconazole administration was assumed to be as directed by the prescription. In addition, the blood collection time was assumed to be 7:00/19:00 for tacrolimus and 7:00 for itraconazole.

Supplemental Digital Content 1 provides the detailed measurement methods of tacrolimus and itraconazole.

This study was performed in accordance with the Declaration of Helsinki and its amendments and was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (No. R0545-2).

Procedure of PPK modeling

PPK analysis was performed using a nonlinear mixed-effects modeling (NONMEM) program version 7.5.0 (ICON, Ellicott City, MD, USA) with a first-order conditional estimation method with interaction. Perl-speaks-NONMEM (version 5.3.1) and R 4.2.2 (R-project.org) were used to evaluate the goodness-of-fit and to visualize the output.

The modeling was conducted as follows. Initially, a tacrolimus model was developed prior to the concomitant use of itraconazole (tacrolimus model). The effect of concomitant use of itraconazole was evaluated by developing two PPK models: (1) a

model incorporating the concomitant use of itraconazole as a categorical covariate (categorical model) and (2) a model combining the tacrolimus model and an itraconazole PPK model that considered itraconazole concentration-dependent inhibition (combined model).

PPK modeling of tacrolimus

A one-compartment model was selected as the structural model of tacrolimus, and the absorption rate constant of tacrolimus (Ka_{TAC}) was fixed at 4.48 /h based on a previous report because only trough concentrations were collected in this study.[18] An exponential error model was used for the inter-individual variability (IIV) of the pharmacokinetic parameters. The additive, proportional, and mixed (additive and proportional) error models were tested for residual variability. The residual error model was selected based on the Bayesian information criterion (BIC).[19] Given that clearance (CL) and volume of distribution (Vd) per body weight of tacrolimus varies with age,[20] the effect of body weight was not incorporated as a prior assumption. To assess the influence of continuous covariates, such as age and clinical laboratory data, on the apparent clearance of tacrolimus (CL/F_{TAC}), covariate analysis was conducted using the following equation:

$$\theta_{tv} = \theta_p \times (COV/COV_{med})^{\theta_{cov}}$$

where θ_{tv} is the typical value of the pharmacokinetic parameters, θ_p is the mean parameter to be estimated, and θ_{cov} is a factor contributed by the covariates. COV indicates the actual value for each patient and COV_{med} is the median value at baseline. Furthermore, to account for the decrease in metabolic enzyme activity immediately after surgery[21], the effect of POD on CL/F_{TAC} was analyzed using the following equation:

$$CL/F_{TAC} = \begin{cases} \theta_p \times \left(\frac{POD}{X}\right)^{\theta_{cov}} & (POD \leq X) \\ \theta_p & (POD > X) \end{cases}$$

X was evaluated as an integer ranging from 6 to 11. To assess the influence of categorical covariates, such as sex, presence of a concomitant drug on CL/F_{TAC}, and administration route on the relative bioavailability (F_{rel}) of tacrolimus, covariate analysis was conducted using the following equation:

$$\theta_{tv} = \theta_p \times {\theta_{cov}}^{COV}$$

where COV is 1 for females or 0 for males when evaluating the effect of sex, and COV is 1 when the concomitant drug is used, or 0 otherwise when evaluating the effect of the concomitant drug; COV is 1 for administration via gastric or enteral tube, or 0 for oral administration when evaluating the effect of the administration route.

The influence of each covariate on CL/F_{TAC} or F_{rel} was evaluated based on the difference in the objective function values (OBJ) between the previous model and the

model that included the covariates. In the stepwise forward inclusion and stepwise backward elimination methods, changes in OBJ were considered significant at a minimum value of 3.84 (χ^2 test; $p < 0.05$) and 7.88 (χ^2 test; $p < 0.005$), respectively, with a 1 degree of freedom implying the addition of one more parameter. In the forward inclusion step, once a parameter was incorporated, then parameters correlating with the included parameter were excluded from the subsequence inclusion step. Additionally, the relative standard errors for the parameter estimates were calculated and considered in the model selection. The individual predicted concentrations were obtained using empirical Bayesian estimation in the first-order conditional estimation method.

PPK modeling of tacrolimus with itraconazole

Categorical model

It was assumed that the concomitant use of itraconazole would affect CL/F_{TAC} independent of the covariate extracted by the tacrolimus model construction. The values of pharmacokinetic parameters, such as CL/F_{TAC}, apparent volume of distribution (V/F_{TAC}), F_{rel}, and the values of θ_{cov} were fixed at their estimated values in the tacrolimus model, and only the magnitude of the effect of concomitant use of itraconazole, IIV, and residual variability were estimated.

182

183 **Combined model**

184 First, an itraconazole PPK model was constructed; Supplemental Digital Content
185 1 presents the detailed procedure. The tacrolimus and itraconazole PPK models were
186 combined, and Supplementary Figure S1 presents a schematic representation of the
187 combined model. Inhibitory ratios were calculated using the I_{max} model. I_{max} was
188 described by the following logistic formulation with θ_{Imax}, and inter-individual variability
189 was incorporated as an additive error to θ_{Imax}. The differential equation for the central
190 compartment of tacrolimus was expressed as follows:

191 $$\text{Inhibition ratio} = \frac{I_{max} \times C_{ITCZ}}{IC_{50} + C_{ITCZ}}$$

192 $$I_{max} = \frac{\exp(\theta_{I_{max}})}{1 + \exp(\theta_{I_{max}})}$$

193 $$\frac{dA(2)}{dt} = Ka_{TAC} \times A(1) - \frac{CL/F_{TAC}}{V/F_{TAC}} \times (1 - \text{Inhibition ratio}) \times A(2)$$

194 where I_{max} is the maximum inhibitory effect of itraconazole on the elimination of
195 tacrolimus, IC_{50} is the itraconazole concentration yielding 50% of I_{max}, and C_{ITCZ} is the
196 concentration of itraconazole. A(1) and A(2) are the amounts of tacrolimus in the depot
197 and central compartments of tacrolimus, respectively.

198 Similar to the development of the categorical model, the θ_p and θ_{cov} values of
199 tacrolimus and itraconazole were fixed to the estimated values using the tacrolimus model

and itraconazole model, respectively, and only the parameters involved in the inhibition ratio, IIV, and residual variability were estimated.

Model evaluation

The constructed models were evaluated using goodness-of-fit plots and visual predictive checks (pcVPC). The goodness-of-fit plots were as follows: observed concentration (OBS) versus population predicted value (PRED) or individual predicted value (IPRED); conditional weighted residuals (CWRES) versus PRED; and the time after the first dose to identify any bias corresponding to model misspecification. pcVPC was performed using a simulation of 1000 datasets from the final model. Based on a previous report,[22] the 50th percentile curve of the observed data was overlaid on the 95% confidence intervals of the 50th percentile and visually evaluated. The estimated final model parameters were assessed using bootstrapping. Bootstrapping was conducted using 500 datasets with 43 randomly sampled participants (with replacements) from the 43 participants in the original dataset. The model parameters were estimated for each bootstrap replicate using NONMEM.

Simulation

Tacrolimus trough concentrations 48 h after the first administration were calculated based on the final tacrolimus model using Monte Carlo simulations. One thousand pharmacokinetic profiles were simulated for patients with each combination with administration route and various albumin (ALB) levels (2.9, 3.6, and 4.3 g/dL). The trough concentration was simulated for each dosing regimen from 1.0 mg to 3.0 mg twice daily. The dose that most frequently achieved the target trough concentrations of 10–15 ng/mL was selected as the optimal initial dose.

The effects of concomitant itraconazole use were examined using categorical or combined models, whichever had better predictability. The typical concentration-time profile of itraconazole and the change in the inhibition ratio during the first week after initiating repeated doses of 200 mg itraconazole oral solution were estimated.

One thousand combinations of CL/F_{TAC} and V/F_{TAC} for typical patients at steady state immediately before initiating itraconazole (oral administration and ALB=3.6 g/dL) were obtained using Monte Carlo simulations based on the tacrolimus model, and the dose that achieved a trough concentration of 12.5 ng/mL at steady state was calculated for each individual. Then, the concentrations 24 h after the initiation of co-administration of 200 mg itraconazole oral solution were calculated using Monte Carlo simulations for each dose reduction method (30–70% reduction from baseline), assuming that the blood

236 tacrolimus concentration was 12.5 ng/mL before initiating itraconazole and the dose of
237 tacrolimus was reduced at the same time as the initiation of itraconazole.
238
239 **RESULTS**
240 **Patient Characteristics**
241 The baseline patient characteristics are summarized in Table 1. A total of 732
242 tacrolimus trough blood concentrations measured before the concomitant use of
243 itraconazole in 43 patients were used to construct a tacrolimus model. A total of 1693
244 tacrolimus trough blood concentrations were used to construct the categorical and
245 combined models. All patients had the blood concentration value for tacrolimus, both
246 without and with itraconazole. Ninety itraconazole trough plasma concentrations were
247 measured, and five samples below the lower limit of quantification (100 ng/mL) were
248 excluded from the analysis. Diltiazem was extracted as a concomitant drug that could
249 affect the pharmacokinetics of tacrolimus and was used in only two patients.
250
251 **PPK modeling of tacrolimus model and model evaluation**
252 A one-compartment model with first-order absorption and elimination accurately
253 described the tacrolimus concentration data. For the IIV, exponential error models for

CL/F_{TAC} and V/F_{TAC} were included in the model. For residual variability, a proportional error model was selected considering the BIC and shrinkage. Supplementary Figure S2 illustrates the correlation plot of covariates. The results of the covariate analysis are shown in Supplementary Table S1. After the forward inclusion and backward elimination steps, CL/F_{TAC} was significantly affected by POD and ALB, whereas F_{rel} was significantly affected by administration route. The final models for CL/F_{TAC} and F_{rel} are as follows:

$$CL/F_{TAC} = \begin{cases} 18.1 \times \left(\frac{POD}{10}\right)^{0.812} \times \left(\frac{ALB}{3.6}\right)^{-0.477} & (POD \leq 10) \\ 18.1 \times \left(\frac{ALB}{3.6}\right)^{-0.477} & (POD > 10) \end{cases} \quad (L/h)$$

$$F_{rel} = 1 \times 0.731^{Route}$$

where route is 1 for administration via the gastric or enteral tube and 0 for oral administration. The final PPK parameter estimates of the tacrolimus model and the relative standard errors are listed in Table 2. The inclusion of these covariates improved the model, as the ΔOBJ between the base and final models was approximately −567.

Of the 500 bootstrap runs performed for model evaluation, the percentage of successful runs was 100%. The median values of the bootstrap replicates and final parameter estimates were similar (Table 2), indicating that the final parameters were accurately estimated. Goodness-of-fit plots of the final model are shown in Figure 1A-D. The plots of OBS versus IPRED approached unity. Moreover, CWRES were evenly

distributed around zero against time after first dose and most of the CWRES were within ±2. The OBS versus PRED and CWRES versus PRED plots showed bias. The pcVPC plots showed that the model described the central tendency (Supplementary Figure S3A).

Categorical model

The concomitant use of itraconazole significantly reduced CL/F_{TAC} by 73.9% ($\Delta OBJ = -1406$). The estimated parameter values for the categorical model are presented in Table 3.

Combined model

For the itraconazole PPK model, an exponential and proportional error models were selected for IIV of CL_{ITCZ} and residual variability, respectively. Supplementary Table S2 presents the results of the covariate analysis. The estimated power index of time after the administration of CL_{ITCZ} was -0.533, indicating that CL_{ITCZ} decreased in a time-dependent manner. Supplementary Table S3 presents the final itraconazole PPK model parameters. Supplementary Figure S3B and S4 present the goodness-of-fit and pcVPC plots of the itraconazole model. The itraconazole PPK and tacrolimus models were then combined. The estimates of the PPK parameters and the standard relative errors

for the final combined model are listed in Table 3. After transformation to the 0-1 scale, the typical value of I_{max} was estimated to be 0.951. The inclusion of inhibitory ratio significantly improved model predictability (ΔOBJ = −3240).

Model evaluation of categorical and combined model

The goodness-of-fit plots and pcVPC of the categorical and combined models are shown in Figure 1E-L and Supplementary Figure S3C and S3D. Focusing on the CWRES plots, the categorical model showed a clear bias against PRED and time (Figure 1G and 1H). This bias was reduced in the combined model (Figure 1K and 1L). Based on these results, the authors concluded that the combined model had better predictability and then combined model was used for the subsequent simulation. Of the 500 bootstrap runs performed for model evaluation, the percentage of successful runs was 100%. The median values of the bootstrap replicates and final parameter estimates were similar (Table 3), indicating that the final parameters were accurately estimated. The pcVPC plot showed that the model described the central tendency (Supplementary Figure S3D).

Simulation

Trough concentrations 48 h after the first administration were calculated using

a Monte Carlo simulation based on the final tacrolimus model. Figure 2A shows the trough concentrations of each dosing regimen (1.0, 1.5, 2.0, 2.5, 3.0 mg twice daily) for each administration route with various ALB levels (2.9, 3.6, and 4.3 g/dL). The initial dose that most frequently achieving the target trough concentration was 1.5 mg twice daily for oral administration (target attainment ratio was 26.9%) and 2.0 mg for tube administration (target attainment ratio was 27.8%).

The typical concentration-time profile of itraconazole and the change in the inhibition ratio based on the combined model are shown in Figure 2B. Figure 2C shows the tacrolimus trough concentrations 24 h after the administration of 200 mg itraconazole oral solution for each dose reduction method. The target achievement rate was the highest when the tacrolimus dose was reduced by 60% of the baseline (target attainment ratio was 44.1%).

DISCUSSION

The PPK model was constructed using routinely obtained clinical data; POD, ALB, and administration route were extracted as significant covariates of tacrolimus pharmacokinetics, and time after the first dose of itraconazole was extracted as a significant covariate of itraconazole pharmacokinetics.

In the final tacrolimus model, most data were from patients with tube administration, and the typical values of CL/F and V/F were calculated 24.8 L/h and 332 L, respectively. According to the previous PPK model in lung transplant recipients, the CL/F values were reported to be 13.1–36.5 L/h, which is consistent with our estimated values.[13,15-17] In contrast, the reported value of V/F was 444–752 L, which is slightly higher than our estimates.[13,15-17] The discrepancy would be explained by the median body weight (51.8 kg) being typically lower than that of previous studies (63–73.5 kg). In this study, CL/F increased with POD after lung transplantation, which is consistent with a previous PPK study of tacrolimus in lung transplant recipients.[13] It has been reported that acute inflammation decreases several CYP3A activities.[21] Therefore, the effect of POD on CL/F would reflect a temporary decrease in CYP3A activity before lung transplantation. In this study, there was a negative correlation between the CL/F of tacrolimus and ALB levels, which is consistent with a previous report in liver transplant patients.[23] As tacrolimus was highly bound to plasma proteins, with approximately 1.0% of the drug unbound in plasma,[23,24] the CL/F of tacrolimus may have increased due to an increase in the unbound fraction as ALB decreased. However, it should be noted that the bootstrapping resulted in uncertain estimates of ALB effect (including 0) and that the observed ALB range was limited. The administration route was extracted as a covariate

343 of tacrolimus bioavailability. One reason for the decrease in bioavailability with gastric
344 or enteral administration may be the adsorption of tacrolimus on the polyvinyl chloride
345 tube.[25] However, the effect of tube administration on tacrolimus trough concentration
346 varies in the literature. [26,27] Therefore, further studies are necessary because the influence
347 of the administration route varies depending on various factors, such as the type of tube
348 and insertion position. Although goodness-of-fit plot shows a bias in the PRED, the
349 predictability of IPRED was good, suggesting that the presence of unknown factors
350 remained related to IIV.

351 To build the combined model, an itraconazole PPK model was constructed, and
352 the time after the first dose of itraconazole was extracted as a covariate. Itraconazole is a
353 substrate of CYP3A4 and inhibitor of CYP3A4. A model that expresses the autoinhibition
354 of itraconazole metabolism by adding a hypothetical inhibition compartment has been
355 reported.[28] Therefore, it is possible that the effect of time after dosing on itraconazole
356 CL/F reflects the autoinhibition of itraconazole metabolism. The CL of itraconazole was
357 expected to stop decreasing when its concentration reached a steady state. In contrast, the
358 CL/F of itraconazole continuously decreased in our model. Because the purpose of this
359 study was to adjust the tacrolimus dose in the early stages after combination therapy, this
360 discrepancy was not expected to be a major issue. In this study, a model considering auto-

361 inhibition depending on itraconazole concentration was also evaluated (data not shown),
362 but it did not improve predictability compared to the model that incorporated time after
363 dose. This could be attributed to the small number of itraconazole measurements required
364 to verify autoinhibition. Similarly, biosynthetic models of CYP3A were not considered
365 because of insufficient data.

366 The IC_{50} value of itraconazole for midazolam, a probe drug of CYP3A, was
367 reported to be 20.5–106 ng/mL.[7,29,30] Therefore, the estimated IC_{50} values of 85.7 ng/mL
368 was reasonable. However, the lower limit of itraconazole measurement in the present
369 study was 100 ng/mL. To obtain accurate estimates, a system that can measure lower
370 concentrations is required. In this study, the inhibitory effects of itraconazole on the CL
371 and F values of tacrolimus were not estimated separately. Furthermore, inhibition of P-
372 glycoprotein by itraconazole was not evaluated. Hydroxyitraconazole, a metabolite of
373 itraconazole, also inhibits CYP3A.[7] However, the measured concentrations of
374 itraconazole and hydroxyitraconazole were positively correlated (R^2=0.780) and it was
375 difficult to estimate the inhibitory effect separately; therefore, the effect of
376 hydroxyitraconazole was not evaluated. To evaluate a more detailed mechanism, further
377 studies using a mechanism-based model, such as a physiologically based pharmacokinetic
378 model, are necessary.

The goodness-of-fit plot of the categorical model showed a bias toward higher predictions immediately after the start of itraconazole treatment and lower predictions thereafter than the observed value. However, this tendency was improved in the combined model. In addition, the pcVPC plot and parameter estimates of IIV and residual variability were worse in the categorical model than those in the combined model. Therefore, model misspecification was markedly better in the combined model. As shown in Figure 2B, the inhibition ratio gradually increased. The poor predictability of the categorical model could be attributed to the binary variables predicting a markedly low CL in the early period of concomitant itraconazole use when the itraconazole concentration was low. In contrast, the combined model can consider the concentration of itraconazole and thus accurately predict the enhancement of the inhibitory effect as the concentration increases.

The simulation results based on the final tacrolimus model showed that the initial dose should be adjusted according to the administration route. On the one hand, the effect of ALB on trough concentration was small, and an initial dose adjustment based on ALB would not be necessary. Simulation results based on the combined model showed that the median estimated trough concentration could be maintained within the target trough concentration by reducing the dose by 60% before initiating itraconazole. As the itraconazole concentration increased, further dosage adjustment of tacrolimus was

397 required. Therefore, frequent tacrolimus TDM before itraconazole initiation is necessary.
398 On the other hand, as this study was conducted at a single institution, and the model was
399 constructed based on sparse itraconazole blood concentration data, further studies are
400 required to accurately adjust the dosage.

401 This study had some limitations. First, almost all the observed concentrations
402 were trough concentrations and the exact dosing and blood sampling time points were
403 unavailable. Therefore, it is possible that parameters related to body size could not be
404 extracted as covariates for tacrolimus. To calculate precise pharmacokinetic parameters,
405 precise and further sampling, including the absorption phase, is needed. Data on
406 itraconazole are especially sparse; therefore, closer sampling is needed to more accurately
407 examine its inhibitory effect on tacrolimus. Second, tacrolimus was measured by
408 performing a chemiluminescent immunoassay, which has a small bias compared with the
409 LC-MS/MS method.[31] This difference may need to be considered for external validation.
410 Third, information on *CYP3A5* genotype was not available because the data were
411 collected retrospectively. Tacrolimus is primarily metabolized by CYP3A5, and the
412 *CYP3A5* genotype affect tacrolimus pharmacokinetics. In fact, various studies have
413 reported the effects of the *CYP3A5* genotype on tacrolimus pharmacokinetics.[13,15,31]
414 Further investigation is needed, including information on the genetic polymorphisms of

CYP3A5. Fourth, the food effect could not be evaluated because food intake could not be accurately collected. Fifth, when assessing the effect of itraconazole, the tacrolimus parameters were fixed because estimating all parameters markedly worsened the prediction of tacrolimus concentrations in the absence of itraconazole.

CONCLUSION

PPK models show that POD, ALB, and administration route affect tacrolimus pharmacokinetics in Japanese lung transplant recipients. The drug-drug interaction between tacrolimus and itraconazole could be predicted more accurately by considering the concentration-dependent inhibition of itraconazole. According to the simulations, the optimal initial tacrolimus dose was calculated to be 2.0 mg twice daily for tube administration and 1.5 mg twice daily for oral administration. To maintain the target concentration, the tacrolimus dose was reduced by 60% when itraconazole was initiated. These results would provide useful insights for determining the initial tacrolimus dose and the dose adjustment method when itraconazole is initiated in lung transplantation patients.

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Figure legend

Figure 1. Goodness-of-fit plots for the tacrolimus model (A-D), categorical model (E-H) and the combined model (I-L). The observed (OBS) vs. population predicted value (PRED) (A, E, I); OBS vs. individual predicted value (IPRED) (B, F, J); conditional weighted residuals (CWRES) vs. PRED (C, G, K); CWRES vs. Time after first dose (D, H, L). Each black and red circle denotes the observed tacrolimus concentration without and with the concomitant use of itraconazole, respectively. The dotted line shows loess splines. The OBS, PRED and IPRED are trough concentrations.

Figure 2. Simulation of tacrolimus trough concentration in the 1000-replication datasets for a typical patient classified by dosing regimen, albumin (ALB), and administration route (A). The typical concentration-time profile of itraconazole and change of inhibition ratio after administration of 200 mg of itraconazole solution based on the combined model

(B). Simulation of tacrolimus trough concentration 24 h after initiation of 200 mg of itraconazole solution for each dose reduction method. (C). Each box plot represents the interquartile range and 90% prediction interval of the predicted tacrolimus trough concentration. %TA, target attainment rate

FIGURE 1

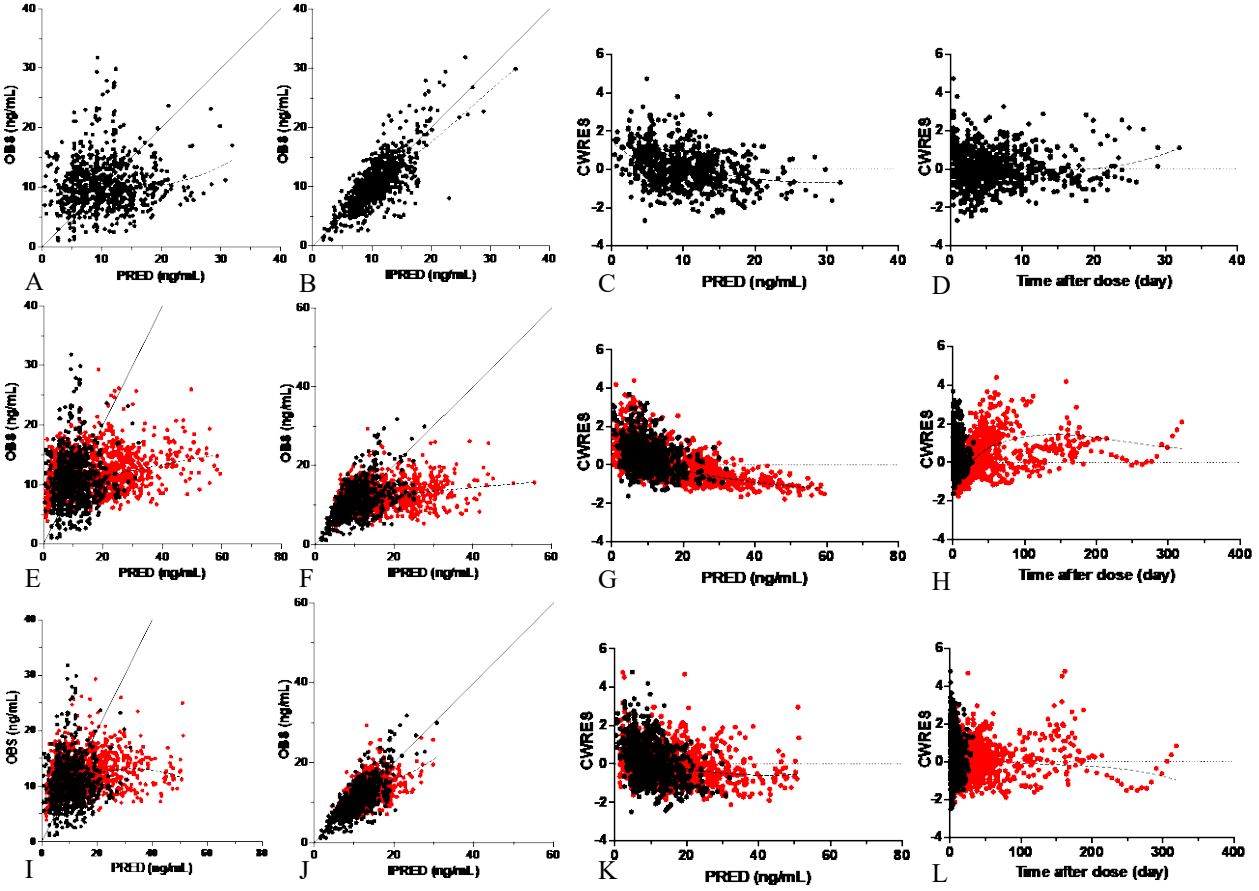
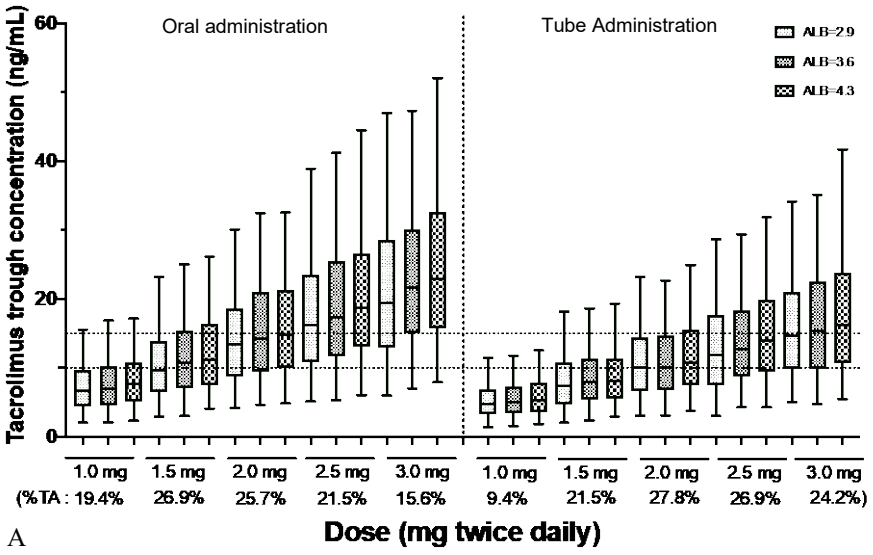
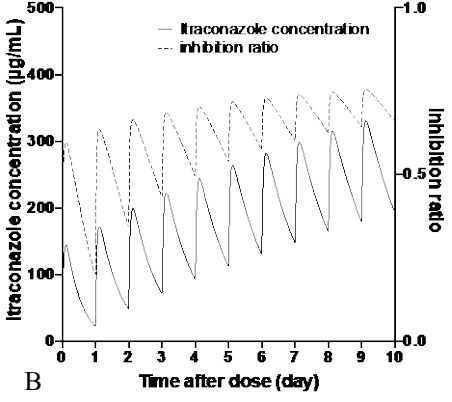

OBS (ng/mL)
PRED (ng/mL)
A
OBS (ng/mL)
IPRED (ng/mL)
B
CWRES
PRED (ng/mL)
C
CWRES
Time after dose (day)
D
OBS (ng/mL)
PRED (ng/mL)
E
OBS (ng/mL)
IPRED (ng/mL)
F
CWRES
PRED (ng/mL)
G
CWRES
Time after dose (day)
H
OBS (ng/mL)
PRED (ng/mL)
I
OBS (ng/mL)
IPRED (ng/mL)
J
CWRES
PRED (ng/mL)
K
CWRES
Time after dose (day)
L

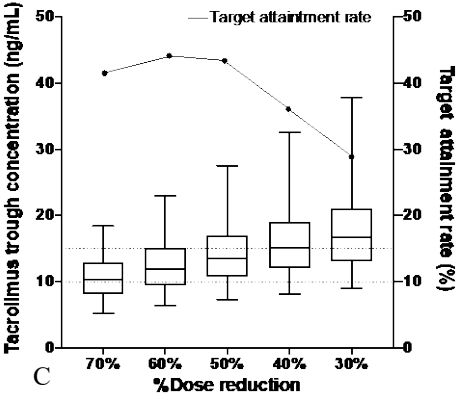
FIGURE 2


Oral administration
Tube Administration
ALB=29
ALB=36
ALB=43
Tacrolimus trough concentration (ng/mL)
60
40
20
0
1.0 mg
1.5 mg
2.0 mg
2.5 mg
3.0 mg
1.0 mg
1.5 mg
2.0 mg
2.5 mg
3.0 mg
(%TA : 19.4%
26.9%
25.7%
21.5%
15.6%
9.4%
21.5%
27.8%
26.9%
24.2%)
Dose (mg twice daily)

A


Itraconazole concentration
inhibition ratio
Itraconazole concentration (μg/mL)
Inhibition ratio
500
400
300
200
100
0
1.0
0.5
0.0
0 1 2 3 4 5 6 7 8 9 10
Time after dose (day)

B


Target attainment rate
Tacrolimus trough concentration (ng/mL)
Target attainment rate (%)
50
40
30
20
10
0
70%
60%
50%
40%
30%
%Dose reduction

C

Table 1 Patient characteristics

Characteristics	Number or median	Range
Male/Female	22/21	
Age (years)	47	6–64
Body weight (kg)	51.8	14.9–79.9
AST (U/L)	51	19–615
ALT (U/L)	16	8–837
T-Bil (mg/dL)	1.1	0.4–4.9
ALB (g/dL)	3.6	2.9–4.3
HCT (%)	30.3	24.9–44.8
HGB (g/dL)	10.6	9.2–15.1
CRE (mg/dL)	0.62	0.29–1.28
eGFR (mL/min)	91.9	44.6–450
TP (g/dL)	5.8	4.5–6.7
Daily dose (mg/day)	4.0	2.0–6.0
Concomitant use of diltiazem	2	
Number of blood samples of tacrolimus		
without itraconazole (tube/oral)	732 (583/149)	
with itraconazole (tube/oral)	961 (36/925)	
Number of blood samples of tacrolimus per patient	34	18–111

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total-bilirubin; ALB, albumin; HCT, hematocrit; HGB, hemoglobin; CRE, serum creatinine; eGFR, estimated glomerular filtration rate; TP, total protein

Table 2 Population pharmacokinetic parameters of tacrolimus model

	Final model		Bootstrap results (N=500)	
Parameter	Estimates	%RSE	Median	95%CI
$CL/F_{TAC} = \begin{cases} \theta_1 \times (POD/10)^{\theta_2} \times (ALB/3.6)^{\theta_3} & (POD \leq 10) \\ \theta_1 \times (ALB/3.6)^{\theta_3} & (POD > 10) \end{cases}$ (L/h)				
θ_1 (L/h)	18.1	11.5	18.2	14.2–22.8
θ_2	0.812	12.0	0.798	0.577–0.960
θ_3	-0.477	45.3	-0.465	-1.0–0.0433
$F_{rel} = 1 \times \theta_4^{Route}$				
θ_4	0.731	9.69	0.739	0.625–0.892
V/F_{TAC} (L)	243	13.9	245	187–317
Ka_{TAC} (/h)	4.48	Fixed	4.48	-
Interindividual variability				
$\omega_{V/F,TAC}$ (%CV)	62.6	10.0	61.3	47.3–75.8
$\omega_{CL/F,TAC}$ (%CV)	65.0	11.2	62.5	47.3–82.3
Residual variability				
$\sigma_{pro,TAC}$ (%CV)	25.8	5.70	25.6	22.5–28.4

The percentage of successful bootstrap runs was 100% (500/500 run). RSE, relative standard error; CI, confidence interval; CL/F_{TAC}, apparent clearance of tacrolimus (L/h); POD, postoperative days (days); ALB, albumin; F_{rel}, relative bioavailability of tacrolimus; V/F_{TAC}, apparent volume of distribution of tacrolimus (L); CV, coefficient of variation

Route is 1 for administration via gastric or enteral tube and 0 for oral administration.

Table 3 Population pharmacokinetic parameters of Categorical and Combined model

	Final model		Bootstrap results (N = 500)	
Parameters	Estimates	%RSE	Median	95%CI
Categorical model				
$CL/F_{TAC} = \begin{cases} 18.1 \times (POD/10)^{0.812} \times (ALB/3.6)^{-0.477} \times \theta_1{}^{ITCZ} & (POD \le 10) \\ 18.1 \times (ALB/3.6)^{-0.477} \times \theta_1{}^{ITCZ} & (POD > 10) \end{cases}$ (L/h)				
θ_1	0.261	10.7	0.262	0.208–0.311
$F_{rel} = 1 \times 0.731^{Route}$				
Ka_{TAC} = 4.48 (/h)				
V/F_{TAC} = 243 (L)				
$\omega_{V/F,TAC}$ (%CV)	75.0	9.61	74.3	54.7–91.0
$\omega_{CL/F,TAC}$ (%CV)	68.4	8.69	68.0	53.9–83.0
$\sigma_{pro,TAC}$ (%CV)	44.5	4.13	44.2	40.5–47.7
Combined model				
Tacrolimus				
$CL/F_{TAC} = \begin{cases} 18.1 \times (POD/10)^{0.812} \times (ALB/3.6)^{-0.477} & (POD \le 10) \\ 18.1 \times (ALB/3.6)^{-0.477} & (POD > 10) \end{cases}$ (L/h)				
$F_{rel} = 1 \times 0.731^{Route}$				
Ka_{TAC} = 4.48 (/h)				
V/F_{TAC} = 243 (L)				
$\omega_{V/F,TAC}$ (%CV)	61.1	10.6	60.5	47.8–75.3
$\omega_{CL/F,TAC}$ (%CV)	60.4	12.0	59.8	47.5–78.6
$\sigma_{pro,TAC}$ (%CV)	26.1	3.59	26.0	24.1–27.6
Inhibition ratio				
$I_{max} = \exp(\theta_2)/(1+\exp(\theta_2))$				
θ_2	2.96	13.9	2.92	2.22–4.02
IC_{50} (ng/mL)	85.7	16.1	83.8	61.1–114
$\omega_{Imax,TAC}$	1.77	22.9	1.73	1.07–2.62
Itraconazole				
$CL_{ITCZ} = 99.3 \times (TAD)^{-0.533}$ (L/h)				
Ka_{tab} = 0.0900 (/h)				
Ka_{so} = 0.960 (/h)				
V_{ITCZ} = 1070 (L)				

F_{tab} = 0.599				
F_{sol} = 1				
$\omega_{CL,ITCZ}$ (%CV)	51.2	20.2	51.0	35.7–67.7
$\sigma_{pro,ITCZ}$ (%CV)	50.3	24.7	50.0	35.9–70.3

The percentages of successful bootstrap runs in both models were 100% (500/500 run). RSE, relative standard error; CI, confidence interval; CL/F_{TAC}, apparent clearance of tacrolimus (L/h); POD, postoperative days (days); ALB, albumin; F_{rel}, relative bioavailability of tacrolimus; Route, administration route; V/F_{TAC}, apparent volume of distribution of tacrolimus (L); I_{max}, maximum inhibition ratio; IC_{50}, itraconazole concentration yielding 50% of the I_{max}; CL_{ITCZ}, apparent clearance of itraconazole (L/h); TAD, time after first dose of itraconazole; Ka_{tab}, absorption rate constant of itraconazole tablet; Ka_{sol}, absorption rate constant of itraconazole solution; F_{tab}, bioavailability of itraconazole tablet; F_{sol}, bioavailability of itraconazole solution; CV, coefficient of variation

ITCZ is 1 when itraconazole is used concomitantly and 0 otherwise.

Route is 1 for administration via gastric or enteral tube and 0 for oral administration.