Model-based tacrolimus follow-up dosing in adult renal transplant recipients: a simulation trial

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Model-Based Tacrolimus Follow-up Dosing in Adult Renal Transplant Recipients: A Simulation Trial

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Background: Initial algorithm-based dosing appears to be effective in predicting tacrolimus dose requirement. However, achieving and maintaining the target concentrations is challenging. Model-based follow-up dosing, which considers patient characteristics and pharmacological data, may further personalize treatment. This study investigated whether model-based follow-up dosing could lead to more accurate tacrolimus exposure than standard therapeutic drug monitoring (TDM) in kidney transplant recipients after an initial algorithm-based dose.

Methods: This simulation trial included patients from a prospective trial that received an algorithm-based tacrolimus starting dose followed by TDM. For every measured tacrolimus predose concentration ($C_{0,obs}$), model-based dosing advice was simulated using the InsightRX software. Based on previous tacrolimus doses and C_0, age, body surface area, *CYP3A4* and *CYP3A5* genotypes, hematocrit, albumin, and creatinine, the optimal next dose, and corresponding tacrolimus concentration ($C_{0,pred}$) were predicted.

Results: Of 190 tacrolimus C_0 values measured in 59 patients, 121 (63.7%; 95% CI 56.8–70.5) $C_{0,obs}$ were within the therapeutic range (7.5–12.5 ng/mL) versus 126 (66.3%, 95% CI 59.6–73.0) for $C_{0,pred}$ (P = 0.89). The median absolute difference between the tacrolimus C_0 and the target tacrolimus concentration (10.0 ng/mL) was 1.9 ng/mL for $C_{0,obs}$ versus 1.6 ng/mL for $C_{0,pred}$. In a historical cohort of 114 kidney transplant recipients who received a body weight–based starting dose followed by TDM, 172 of 335 tacrolimus C_0 (51.3%) were within the therapeutic range (10.0–15.0 ng/mL).

Conclusions: The combination of an algorithm-based tacrolimus starting dose with model-based follow-up dosing has the potential to minimize under- and overexposure to tacrolimus in the early posttransplant phase, although the additional effect of model-based follow-up dosing on initial algorithm-based dosing seems small.

Key Words: kidney transplantation, pharmacokinetics, simulation trial, tacrolimus, therapeutic drug monitoring

(*Ther Drug Monit* 2022;44:606–614)

INTRODUCTION

Tacrolimus is the cornerstone of immunosuppressive therapy after kidney transplantation. Therapeutic drug monitoring (TDM) is commonly used to tailor doses to established target exposure ranges.[1] However, many patients are under- or overexposed to tacrolimus in the early phase after kidney transplantation, despite TDM.[1–3] Population pharmacokinetic (popPK) models that incorporate variables associated with tacrolimus PK, such as age, hematocrit, and *cytochrome P450 (CYP) 3A* genotype, may be able to predict an individual's tacrolimus dose requirement even before TDM has been initiated.[1,4–22] Recently, we prospectively tested a tacrolimus starting dose algorithm (developed by our group) that included age, body surface area, and *CYP3A4* and *CYP3A5* genotypes as covariates.[17,23] The algorithm successfully predicted the starting tacrolimus dose in adult recipients of living-donor kidneys.

However, not only achieving but also maintaining tacrolimus C_0 within the target range is challenging. Tacrolimus intrapatient variability can be partly explained by posttransplant changes in factors that affect tacrolimus PK, such as hematocrit, due to blood transfusions, restoration of renal function, and erythropoietin production, and altered hepatic metabolism resulting from the clearance of uremic toxins.[7] The use of model-based follow-up dosing algorithms may further individualize tacrolimus treatment after the initial

Received for publication August 2, 2021; accepted February 24, 2022.

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D. A. Hesselink has received grant support, paid to his institution, from Astellas Pharma, Chiesi Farmaceutici SpA, and Bristol Myers-Squibb, as well as lecture and consulting fees from Astellas Pharma, Chiesi Farmaceutici SpA, Novartis Pharma, and Vifor Pharma, over the past 3 years. R. J. Keizer is a stockholder and employee of InsightRX, a precision dosing software company. T. van Gelder received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Thermo Fisher, Vitaeris, CSL Behring, Astellas, and Aurinia Pharma. T. van Gelder neither has employment nor stock ownership at any of these companies, he does not have patents or patent applications. All other authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.drug-monitoring.com).

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algorithm-based starting dose and may translate into improved efficacy and reduced toxicity.

This hypothesis was confirmed in a clinical study by Størset et al.[24] After the initial body weight–based dosing, adult renal transplant recipients were randomized to receive either a tacrolimus follow-up dose based on a computer model or a standard tacrolimus dose prescribed by experienced transplant physicians. The pharmacokinetic model included the patient's previously measured tacrolimus concentration, tacrolimus dosing history, fat-free mass, hematocrit, and time after transplantation. Model-based dosing led to a higher proportion of patients with tacrolimus concentrations within the target range than the standard dosing method. In addition, the computer-dosed group showed significantly lower 2-hour plasma glucose concentrations after the oral glucose tolerance test. The authors concluded that model-based dosing improved the achievement of the tacrolimus therapeutic range in adult renal allograft recipients compared with standard physician-based TDM and that this may translate into better clinical outcomes. The observation of a beneficial effect of model-based dosing on a patient's glucose metabolism supports this notion.[24]

The ultimate goal was to personalize tacrolimus treatment by optimizing tacrolimus exposure in individual patients. Because we previously demonstrated the benefits of using algorithm-based starting doses and Størset et al demonstrated the benefits of model-based follow-up dosing, we hypothesized that the combination of algorithm-based start and model-based follow-up dosing might further improve tacrolimus target exposure attainment by combining algorithm-based dosing, to determine a patient's starting dose, with model-based follow-up dosing. The aim of this simulation trial was to investigate whether model-based follow-up tacrolimus dosing could lead to more accurate tacrolimus exposure than standard TDM following an algorithm-based tacrolimus starting dose.

METHODS

Patient Population

This study included patients who participated in a prospective, single-arm, therapeutic intervention trial, in which patients were prescribed a tacrolimus starting dose based on a previously developed dosing algorithm rather than a standard body weight–based tacrolimus starting dose.[23] Adult renal transplant recipients were eligible for participation if they received a human leukocyte antigen (HLA) and blood group ABO-compatible kidney transplantation from a living donor in the Erasmus MC, University Medical Center Rotterdam, and were administered tacrolimus as an initial immunosuppressive treatment.[23] Patients were excluded if they used comedication known to interact with tacrolimus, except for prednisolone, 28 days before transplantation.[23] The interacting drugs are listed in **Supplemental Digital Content** (see **Table S1**, http://links.lww.com/TDM/A556). Three patients were excluded because they used interacting drugs (carbamazepine, n = 2; amiodarone, n = 1). The effects of prednisolone on tacrolimus PK were tested in this model. Because prednisolone use did not significantly affect tacrolimus PK, it was not included in the model as a covariate.

Immunosuppression

Patients received basiliximab (Simulect; Novartis Pharma, Arnhem, the Netherlands) induction therapy, followed by triple immunosuppression consisting of prednisolone, mycophenolate mofetil (Cellcept; Roche Pharmaceuticals, Woerden, the Netherlands), and tacrolimus (Prograft; Astellas Pharma, Leiden, the Netherlands).[23] The tacrolimus target predose concentrations were 7.5–12.5 ng/mL.

Study Design and Data Collection

This study was a post hoc analysis of the prospective, single-arm, clinical intervention trial described above.[23] As part of this study, the patients were genotyped for *CYP3A4* and *CYP3A5*. DNA was extracted from the buccal mucosa collected using a buccal swab. For every patient, the presence of *CYP3A4*1/*22* and *CYP3A5*1/*3* single-nucleotide polymorphisms was analyzed using Autogenomics INFINITY microarrays (Autogenomics, Carlsbad, CA) in an ISO15189-certified laboratory. Patients carrying at least one *CYP3A5*1* allele were considered as CYP3A5 expressers. Patients were prescribed a starting tacrolimus dose based on a previously developed dosing algorithm.[17,23] On day 3 after transplantation, at the first steady state, the initial tacrolimus C_0 was measured. Thereafter, tacrolimus C_0 was measured on days 5, 7, and 10 and whenever deemed necessary by the treating physician, for as long as the patient was hospitalized. After the first tacrolimus C_0 measurement on day 3, dose adjustments were made by the treating physician according to standard TDM based on whole-blood tacrolimus C_0 ($dose_{physician}$). Data on patient characteristics, tacrolimus concentration, and tacrolimus dosage were collected.

For every measured tacrolimus C_0, a model-based dosing advice and corresponding tacrolimus C_0 were predicted using simulations from the popPK model.[17] Tacrolimus dosing advice by the computer ($dose_{comp}$) was obtained from InsightRX Nova software (version 1.26) from a Maximum A Posteriori Bayesian fit based on the following individual PK parameters: all previously administered tacrolimus doses, all previously measured tacrolimus C_0, and a previously developed dosing algorithm that included age, body surface area, *CYP3A4* and *CYP3A5* genotype, hematocrit, serum albumin, and serum creatinine as covariates.[17] The target tacrolimus C_0 level was 10 ng/mL.

Multiple tacrolimus C_0 were simulated (see **Figure S1**, **Supplemental Digital Content**, http://links.lww.com/TDM/A556):

1. The expected tacrolimus C_0 that patients would have had if they had received the tacrolimus dose based on the computer's recommendation (ie, the predicted tacrolimus concentration; $C_{0,pred}$). $C_{0,pred}$ was calculated from the observed tacrolimus C_0 ($C_{0,obs}$), $dose_{physician}$, and $dose_{comp}$ according to the following formula:

$$C_{0,\mathrm{pred}} = \left(\mathrm{dose}_{\mathrm{comp}} C_{0,\mathrm{obs}}\right) / \mathrm{dose}_{\mathrm{physician}}$$

2. The expected tacrolimus C0 at steady state, simulated by InsightRX Nova, if $dose_{comp}$ would have been selected and administered ($C_{0,comp\text{-}ss}$).

3. Tacrolimus concentration was predicted by InsightRX Nova on the same day and time as the next observed predose concentration ($C_{0,comp,fu}$).

Tacrolimus concentrations were excluded from this simulation if (1) the patient received fewer than 3 equal doses before tacrolimus C_0 measurement and (2) tacrolimus peak concentration was measured.

To evaluate the effect of the method of determining the tacrolimus starting dose and the value of model-based follow-up dosing, apart from an algorithm-based starting dose, the proportion of tacrolimus concentrations within the target range following TDM after a body weight–based starting dose (Tac_{BW} C_0) was calculated. For this calculation, we used a historical cohort of patients who received a body weight–based tacrolimus starting dose, followed by standard TDM, aiming for a tacrolimus C_0 of 10.0–15.0 ng/mL.[2] All Tac_{BW} C_0 values were measured until day 10 after transplantation. The first tacrolimus concentration after the initial body weight–based dosing was excluded to evaluate the effect of follow-up tacrolimus dosing only.

Study End points

The aim of this study was to evaluate whether model-based follow-up dosing after initial model-based dosing would lead to a higher proportion of tacrolimus C_0 within the therapeutic range than follow-up dosing according to standard TDM by the treating physician. The primary end point of this simulation trial was the proportion of tacrolimus C_0 within the therapeutic range (7.5–12.5 ng/mL) following model-based tacrolimus dosing ($C_{0,pred}$) versus the proportion tacrolimus C_0 within the therapeutic range following standard TDM ($C_{0,obs}$) after the first steady-state concentration measurement (day 3 after transplantation) until day 10 after transplantation.

Secondary end points were (1) the proportion of tacrolimus C_0 below 7.5 ng/mL or above 12.5 ng/mL, the therapeutic range following model-based tacrolimus dosing ($C_{0,pred}$) versus standard TDM ($C_{0,obs}$) after the first steady-state concentration measurement up until day 10 after transplantation, (2) the difference between the predicted tacrolimus concentration and the target tacrolimus concentration following model-based dosing ($C_{0,pred}$) versus standard TDM ($C_{0,obs}$), (3) the proportion of tacrolimus C_0 within the therapeutic range (7.5–12.5 ng/mL) following model-based tacrolimus dosing ($C_{0,pred}$) versus the proportion of tacrolimus C_0 within the therapeutic range (10.0–15.0 ng/mL) in a historical cohort in which patients received a body weight–based starting dose following standard TDM (Tac_{BW} C_0) after the first steady-state concentration measurement up until day 10 after transplantation, and (4) the effect of the timing of blood sampling, measured as the difference between the simulated tacrolimus C_0 at steady state if administering $dose_{comp}$ ($C_{0,comp-ss}$) and the tacrolimus concentration following model-based dosing at the time of the observed tacrolimus concentration ($C_{0,comp,fu}$).

Statistical Analysis

Statistical analyses were performed using R software (version 4.0.1). Categorical variables were described as the number of cases as a percentage of the total number of patients. Nonnormally distributed continuous variables were described as medians with interquartile ranges (IQRs). Differences in proportions were calculated using a two-sample test for equality of proportions with continuity correction.

RESULTS

Baseline Characteristics

A total of 59 kidney transplant recipients were included in the analysis. Table 1 shows the baseline characteristics of the patients. The majority of patients were men (n = 37, 63%). The median patient age was 59 years (IQR, 48–67 years). *CYP3A4* and *CYP3A5* genotype frequencies were in accordance with the Hardy–Weinberg equilibrium (χ^2 = 0.40; P = 0.53 and χ^2 = 1.03; P = 0.31, respectively). None of the patients was on

TABLE 1. Baseline Characteristics

Recipient Characteristics	Study Population (n = 59)
Gender	
Female/male	22 (37%)/37 (63%)
Age (yrs)	59 (IQR, 48–67; range, 19–83)
Body weight (kg)	80.0 (IQR, 71.2–90.0; range, 49.3–119.5)
Length (cm)	176.0 (IQR, 170.0–180.5; range, 156.0–202.0)
BMI (kg/m^2)	26.2 (IQR, 23.5–28.9; range, 17.7–37.2)
BSA (m^2)	1.99 (IQR, 1.85–2.08; range, 1.47–2.53)
Ethnicity	
African	3 (5%)
Asian	1 (2%)
Caucasian	53 (90%)
Other	2 (3%)
CYP3A4 genotype	
*22 carrier/*22 noncarrier	9 (15%)/50 (85%)
CYP3A5 genotype	
Expresser*/nonexpresser	14 (24%)/45 (76%)
RRT before kidney transplantation	
Hemodialysis	14 (24%)
Peritoneal dialysis	9 (15%)
Preemptive	36 (61%)
Number of kidney transplantations	
1st/2nd/3rd	58 (98%)/0 (0%)/1 (2%)
Donor type	
Living related/living unrelated	20 (34%)/39 (66%)
PRA current	
<15%/>15%	55 (93%)/4 (7%)
PRA peak	
<15%/>15%	56 (95%)/3 (5%)

Continuous variables are described as median (IQR; range); categorical variables are represented as number of cases (%). This table is similar to Table 1 in the study of Francke et al.[23]

*Carrier of at least one *CYP3A5*1* allele.

BMI, body mass index; PRA, panel reactive antibodies; RRT, renal replacement therapy.

comedication known to interact with tacrolimus during the study period.

Within this cohort of 59 patients, 293 tacrolimus follow-up C_0 values were measured during the first 10 days after transplantation. For this simulation trial, a total of 44 tacrolimus C_0 values were excluded because tacrolimus concentrations were not measured at steady state fewer than 3 unaltered dose administrations before the tacrolimus C_0 measurement (n = 43) or tacrolimus concentrations were measured after dose administration (peak concentrations; n = 1). Moreover, as the present study investigated follow-up tacrolimus dosing, the first tacrolimus C_0 (on day 3; n = 59) was not included or simulated. In the final analysis, 190 tacrolimus C_0 values were simulated and included (Fig. 1).

Achievement of the Tacrolimus Target Concentration

Table 2 shows the doses and concentrations of administered and simulated tacrolimus. The median last $dose_{physician}$ was 6.0 mg (IQR, 4.5–8.0), and the median $dose_{comp}$ was 5.5 mg (IQR, 4.0–8.5). The median $C_{0,obs}$ was 10.0 ng/mL (IQR, 8.1–11.9), and the median tacrolimus $C_{0,pred}$ was 9.8 ng/mL (IQR, 8.3–11.4).

The proportion of observed tacrolimus concentrations within the therapeutic range following TDM was not significantly different from that of predicted tacrolimus concentrations within the therapeutic range following model-based follow-up dosing. Of the 190 tacrolimus C_0, 121 (63.7%, 95% CI 56.8–70.5) $C_{0,obs}$ were within the

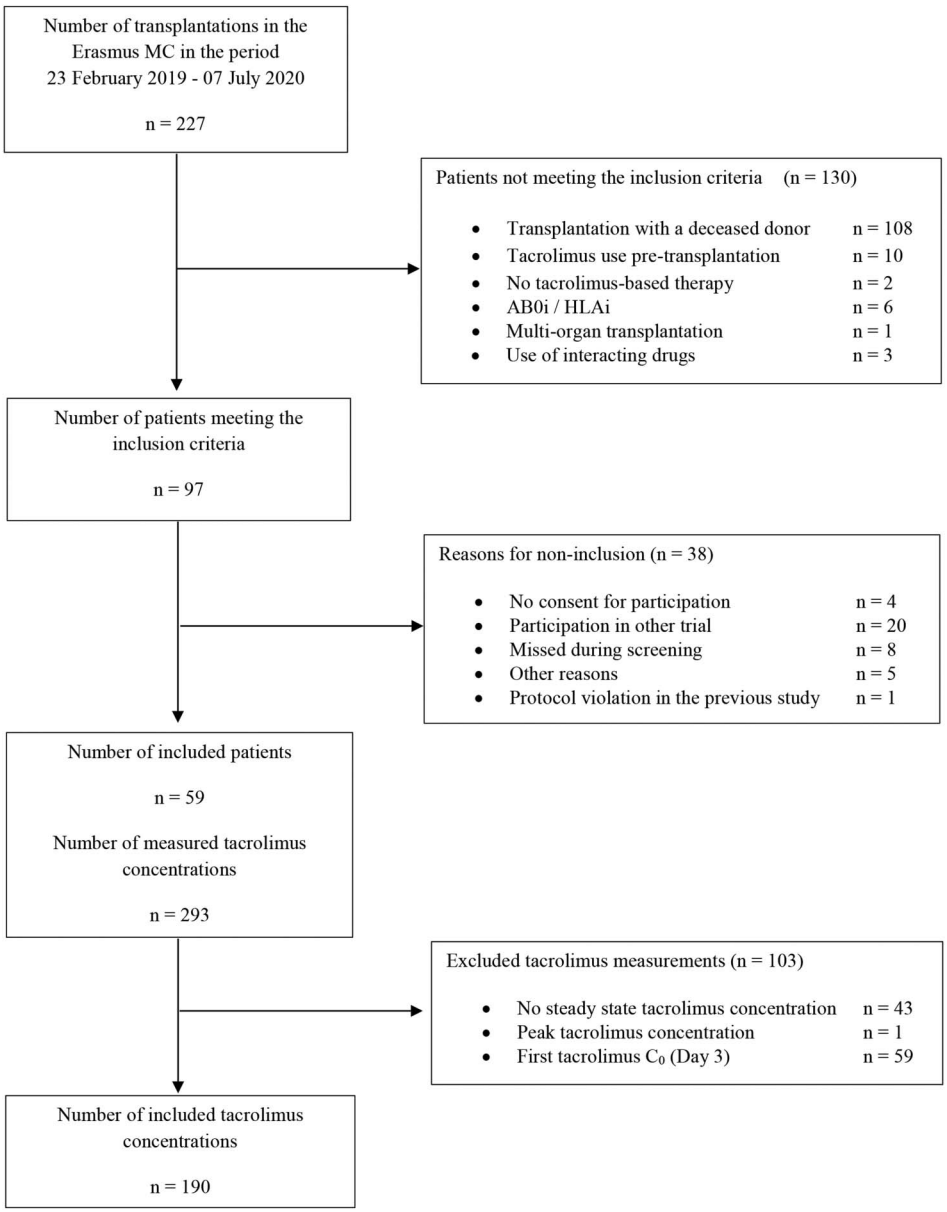

FIGURE 1. Depicts the inclusion of patients and samples for this simulation trial. ABOi, blood group ABO incompatibility; HLAi, human leukocyte antibody incompatibility. *Interacting drugs are listed in **Supplemental Digital Content** (see **Table S1**, http://links.lww.com/TDM/A556).

TABLE 2. Observed Versus Simulated Tacrolimus Doses and Concentrations

	Observed (n = 190)	Simulated (n = 190)	*P*
Tacrolimus dose (mg)	6.0 (4.5–8.0)	5.5 (4.0–8.5)	
Tacrolimus C_0 (ng/mL)	10.0 (8.1–11.9)	9.8 (8.3–11.4)	
7.5–12.5 ng/mL (%)	63.7 (95% CI 56.8–70.5)	66.3 (95% CI 59.6 to 73.0)	0.89
<7.5 ng/mL (%)	15.8 (95% CI 10.6–21.0)	16.8 (95% CI 11.5 to 22.2)	0.89
>12.5 ng/mL (%)	20.5 (95% CI 14.8–26.3)	16.8 (95% CI 11.5 to 22.2)	0.43
<5.0 ng/mL (%)	0	1.6 (95% CI −0.2 to 3.4)	0.25
>20.0 ng/mL (%)	2.6 (95% CI 0.4–4.9)	1.6 (95% CI −0.2 to 3.4)	0.72
Absolute difference from 10 ng/mL	1.9 (0.9–3.0)	1.6 (0.7–2.9)	
Absolute difference from 7.5 to 12.5 ng/mL	0 (0–0.5)	0 (0–0.5)	

Continuous variables are described as median (IQR); categorical variables are represented as number of cases (%; 95% CI). *P* values were calculated using a two-sample test for equality of proportions.

C_0, predose concentration; n, number of samples.

therapeutic range (7.5–12.5 ng/mL) versus 126 (66.3%, 95% CI 59.6–73.0) for $C_{0,pred}$ (P = 0.89). The proportion of patients with low tacrolimus $C_{0,obs}$ (<7.5 ng/mL) was 15.8% (95% CI 10.6–21.0) versus 16.8% (95% CI 11.5–22.2) for $C_{0,pred}$. The proportion of patients with high tacrolimus $C_{0,obs}$ (>12.5 ng/mL) was 20.5% (95% CI 14.8–26.3) versus 16.8 (95% CI 11.5–22.2) for $C_{0,pred}$. None of the tacrolimus $C_{0,obs}$ were <5.0 ng/mL versus 3 (1.6%, 95% CI −0.2 to 3.4) for $C_{0,pred}$. The proportion of extremely high tacrolimus $C_{0,obs}$ (>20.0 ng/mL) was 2.6% (95% CI 0.4–4.9) versus 1.6 (95% CI −0.2 to 3.4) for $C_{0,pred}$.

The median absolute difference between the tacrolimus concentration and the target tacrolimus concentration (10.0 ng/mL) was 1.9 ng/mL (IQR 0.9–3.0) for tacrolimus $C_{0,obs}$ versus 1.6 ng/mL (IQR 0.7–2.9) for $C_{0,pred}$ (Table 2). The median absolute difference of the tacrolimus concentration from the target range (7.5–12.5 ng/mL) was 0 ng/mL (IQR 0–0.5) for tacrolimus $C_{0,obs}$ versus 0.0 ng/mL (IQR 0–0.4) for $C_{0,pred}$ (Table 2).

Achievement of the Target Range Following Body weight–Based Dosing

In the historical cohort, in which the tacrolimus starting dose was based on each patient's body weight, a total of 451 tacrolimus follow-up concentrations were measured in 116 patients in the first 10 days after transplantation. Out of the 451 tacrolimus C_0 measurements, 210 (46.6%, 95% CI 42.0–51.2) Tac_{BW} C_0 were within the therapeutic range (10.0–15.0 ng/mL).

For the evaluation of follow-up dosing only, a total of 335 tacrolimus follow-up concentrations were available after excluding all first tacrolimus concentrations following the initial body weight–based dosing. The proportion of tacrolimus concentrations within the therapeutic range following TDM was significantly lower than that of predicted tacrolimus concentrations within the therapeutic range following model-based follow-up dosing. Of the 335 tacrolimus C_0 measurements, 172 (51.3%, 95% CI 46.0–56.7) Tac_{BW} C_0 was within the therapeutic range (10.0–15.0 ng/mL) versus 126 out of 190 (66.3%, 95% CI 59.6–73.0) for tacrolimus $C_{0,pred}$ (therapeutic range 7.5–12.5 ng/mL; P = 0.0012). The proportion of patients with low Tac_{BW} C_0 (<10.0 ng/mL) was 20.0% (95% CI 15.7–24.3) versus 16.8% (95% CI 11.5–22.2) for tacrolimus $C_{0,pred}$ (<7.5 ng/mL). The proportion of patients with high Tac_{BW} C_0 (>15.0 ng/mL) was 28.7% (95% CI 23.8–33.5) versus 16.8 (95% CI 11.5–22.2) for tacrolimus $C_{0,pred}$ (>12.5 ng/mL) (Fig. 2).

The Effect of Time

In clinical practice, tacrolimus C_0 is often measured approximately 10 hours after dose administration, whereas InsightRX Nova provides a tacrolimus dosing recommendation to reach tacrolimus C_0 12 hours after dose administration ($C_{0,comp\text{-}ss}$). To evaluate the effect of the timing of tacrolimus measurements on the present results, the tacrolimus concentration at the time of the next tacrolimus measurement ($C_{0,comp,fu}$) was simulated. Overall, the tacrolimus $C_{0,pred}$ was slightly higher than the tacrolimus $C_{0,comp,fu}$ with a median difference of 0.2 ng/mL (ranging from −5.1 to 15.7).

In addition, InsightRX Nova provides dosing advice for reaching a steady-state concentration of 10 ng/mL. However, 47 of the 190 follow-up tacrolimus concentrations were measured after fewer than 5 unaltered dosages (ie, before the steady state was officially reached). The median difference between the tacrolimus $C_{0,comp\text{-}ss}$ and $C_{0,comp,fu}$ was 0.3 (ranging from −4.1 to 3.4).

Furthermore, the last tacrolimus C_0 that was measured was used to determine the follow-up doses. Higher last C_0, on which the dosing advice was based, appeared to exhibit lower simulated tacrolimus $C_{0,comp\text{-}ss}$ than $C_{0,comp,fu}$, whereas lower last C_0 tended to result in higher tacrolimus $C_{0,comp\text{-}ss}$ than $C_{0,comp,fu}$ (Fig. 3).

DISCUSSION

In this simulation trial, model-based follow-up dosing did not lead to a significantly higher proportion of tacrolimus concentrations within the therapeutic range compared with standard TDM following initial algorithm-based tacrolimus dosing. In addition, the difference in the target concentration

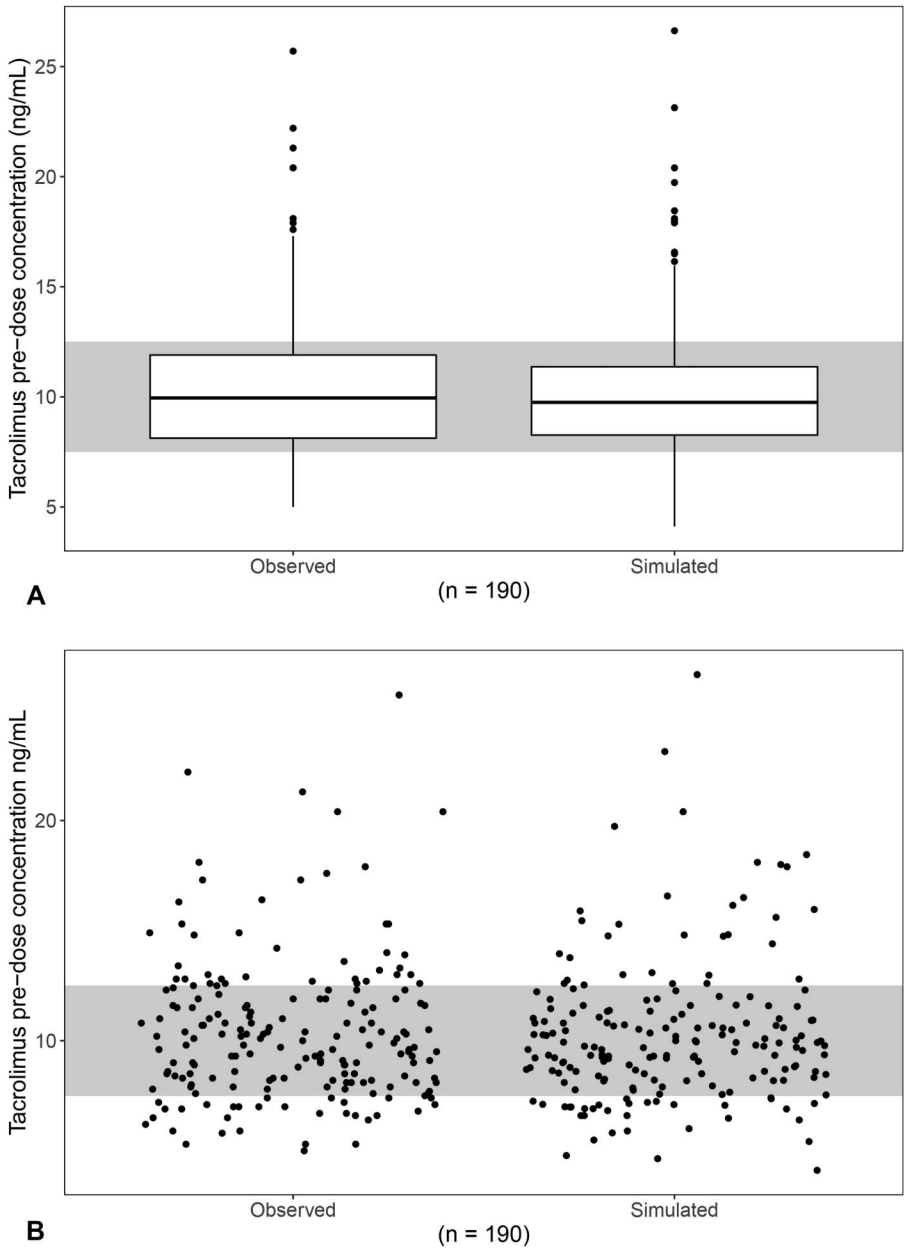

FIGURE 2. A, Boxplot of the tacrolimus C0 following standard TDM and model-based dosing. The box corresponds with the 25th percentile (lower boundary), the median (middle line), and the 75th percentile (upper boundary). The upper whisker reaches the highest value until 1.5 times the interquartile range (IQR). The lower whisker reaches the lowest value until 1.5 times the IQR. Values outside these ranges are considered outliers and are represented as dots. B, Dot plot of the tacrolimus C0 following standard TDM and model-based dosing. The gray areas represent the target tacrolimus C0 range (7.5–12.5 ng/mL).

was not significantly different when comparing tacrolimus concentrations following model-based dosing (simulated) to standard TDM (observed). However, in a historical cohort of patients who received a body weight–based tacrolimus dose followed by standard TDM, the proportion of follow-up tacrolimus concentrations within the target range was lower than that of predicted follow-up tacrolimus concentrations within the target range in patients with a model-based follow-up dose after an initial algorithm-based dosing.

This is the first study to evaluate the effect of model-based follow-up dosing after an initial algorithm-based starting dose in kidney transplant recipients. In a study by Fukudo et al,[25] 40 liver transplant recipients received either a tacrolimus dose based on standard TDM or a tacrolimus dose based on Bayesian forecasting in the first 2 weeks after transplantation. The Bayesian group had lower interpatient variability and higher tacrolimus target achievement than the TDM group. This is in line with the results of a randomized controlled trial by Størset et al,[24] in which 78 renal transplant recipients were, after an initial body weight–based dosing, randomized to receive either a model-based follow-up dose or a dose based on standard TDM by experienced transplant physicians. In this trial, the proportion of tacrolimus concentrations within the therapeutic range in the first 8 weeks after transplantation was significantly higher following model-based dosing than standard TDM. In our study, we found

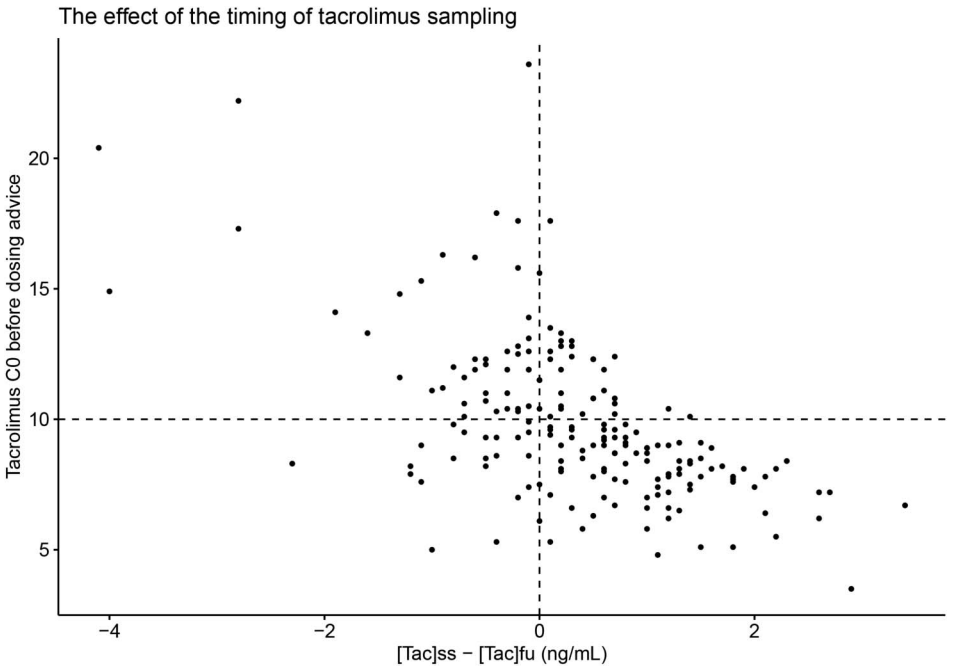

FIGURE 3. Scatterplot of the effect of the timing of the blood sampling. [Tac]ss, simulated tacrolimus predose concentration at steady state; [Tac]fu, simulated tacrolimus predose concentration at the time of real blood sampling.

no significant beneficial effects of model-based follow-up dosing with tacrolimus exposure. An important difference between these studies and this simulation trial is the method in which the starting dose of tacrolimus was determined, namely, body weight–based versus algorithm-based dosing. With algorithm-based dosing, 58% of the patients had a tacrolimus concentration within the target range at the first steady state, whereas in a historical cohort that received a kidney transplantation in our center, only 37.4% of the patients had a tacrolimus concentration within the therapeutic range following body weight–based tacrolimus dosing.[2,23] Consequently, by basing the tacrolimus starting dose on a dosing algorithm rather than body weight, a higher proportion of patients were already on target before the start of follow-up dosing. Therefore, the benefit of model-based follow-up dosing may be lower following initial algorithm-based dosing than following initial body weight–based dosing. This hypothesis is further supported by our secondary analysis, which showed that in a historical cohort in which 114 kidney transplant recipients received a body weight–based tacrolimus dose, only 51.3% of the follow-up tacrolimus concentrations were within the target range within the first 10 days after transplantation compared with 63.7% in the cohort that received an algorithm-based starting dose. Moreover, the model by Andrews et al[17] has a considerable interoccasion variability component in the clearance of tacrolimus. The use of TDM and model-based dosing can reduce the interindividual variability component but not all interoccasion variability (IOV) or residual error. Using simulations, we assessed the realistic upper limit of target attainment for TDM and model-based dosing. It was found that for the target range in this study (7.5–12.5 ng/mL), the upper limit was around 69.5%, which is in line with the results of the present study (details and assumptions are provided in **Supplementary Data I**, **Supplemental Digital Content**, http://links.lww.com/TDM/A556). Hence, it seems that both the model-based dosing arm and standard-of-care arm were already close to the theoretical upper limit of the model-based approach. With a relatively wider therapeutic range (for instance, the 3–7 ng/mL target in the standard-risk group in the trial by Størset et al), higher target attainment would be possible. The present results, together with those of Størset et al,[24] indicate that an algorithm-based tacrolimus starting dose in combination with model-based tacrolimus follow-up dosing can minimize tacrolimus under- and overexposure. However, model-based follow-up dosing appears to be especially effective in optimizing tacrolimus exposure after body weight–based dosing.

Another factor that might explain the limited benefit of model-based dosing over TDM following initial algorithm-based dosing is that not all follow-up concentrations were measured at a steady state, which is officially reached after >5 unaltered dosages. In fact, 143 of the 190 tacrolimus concentrations were measured after at least 5 unaltered dosages. Moreover, higher last predose concentrations on which the dosing advice was based tended to have lower simulated tacrolimus $C_{0,comp\text{-}ss}$ than $C_{0,comp,fu}$, whereas lower last predose concentrations tended to have higher tacrolimus $C_{0,comp\text{-}ss}$ than $C_{0,comp,fu.}$ In addition, the difference between tacrolimus $C_{0,comp\text{-}ss}$ and $C_{0,comp,fu}$ ranged from −4.1 to 3.4 ng/mL. Together, these results indicate that the concentration at the time of measurement was not always a steady-state concentration, and more time would have been needed to reach the tacrolimus C_0 belonging to the model-based dose. However, as tacrolimus $C_{0,pred}$ was calculated based on tacrolimus $C_{0,obs}$, the fact that $C_{0,obs}$ was not a steady-state measurement

may have affected the present results. Better results are expected when model-based follow-up dosages are administered for a longer period, so that a steady-state concentration is reached.

The follow-up period in this study was relatively short (10 days). Størset et al[24] showed that the benefits of model-based dosing were greatest 4–6 weeks after transplantation. Model-based dosing uses albumin, creatinine, and hematocrit values to simulate tacrolimus exposure together with all previous pharmacological data to predict an individual's dose requirement. The more information the computer has, the better the predictions are expected to be, whereas a physician may not always consider changes in values other than tacrolimus to change their dosing recommendation. Therefore, better results would be expected with more time after transplantation, more laboratory measurements, and follow-up dosages.

Even if the additional effect of model-based follow-up dosing after initial algorithm-based dosing is small, considering optimizing tacrolimus exposure, the method has multiple other advantages. First, model-based follow-up dosing can standardize tacrolimus dosing, which makes it possible for hospital employees other than experienced transplant physicians to provide sound tacrolimus dosing advice. Second, by combining the information of the model and expertise of transplant physicians, it may be possible to attain a higher target achievement than the theoretical upper limit. Model-based dosing advice can be used to check whether a physician's dosing advice would be similar to the dosing advice of the computer. When dosing advice differs, an investigation could determine which dose may be the best fit for the patient and why. Third, if the computer could correctly provide dosing advice to reach a certain tacrolimus exposure at steady state, tacrolimus concentrations could be monitored less frequently. In clinical practice, tacrolimus concentrations are frequently measured in the early phase after transplantation, but these are not always steady-state concentrations. In the present study, 52 of the 59 patients underwent more than 2 follow-up tacrolimus measurements. When measuring in steady state only, every patient would only need 2 follow-up tacrolimus concentration measurements within the first 10 postoperative days. In 59 patients, 118 tacrolimus concentrations were measured instead of 190. This reduction in tacrolimus measurements may save time and money for transplant physicians and laboratory technicians. In addition, it may prevent physicians from making new dose adjustments too early, leading to inadequate follow-up dosages.

The main limitation of the present study is that model-based dosages and tacrolimus concentrations were simulated, which has several disadvantages over a prospective trial. First, the tacrolimus dose recommended by InsightRX was never administered, and the dosing recommendation and tacrolimus concentrations were simulated for every tacrolimus concentration that was measured. In contrast, the TDM dose was administered and adjusted according to the concentrations that resulted from the administered dose. This may negatively affect the results of the model-based dosing. Second, as described above, a considerable number of tacrolimus concentrations were measured before steady state was reached, although these values were still used to estimate tacrolimus $C_{0,pred}$, and the concentration corresponding to the $dose_{comp}$ may not have been reached. To limit the effect of non–steady-state tacrolimus concentrations, we excluded samples with fewer than 3 unaltered dosages before tacrolimus measurement. Moreover, we believe that without conducting a prospective trial, this simulation trial is the best we could do, and it can provide information on the effect of model-based follow-up dosing, which can be used for the design of future prospective trials. Ideally, the model-based dosing approach (algorithm-based starting dose followed by model-based follow-up dosing) should be compared with the dosing approach used in standard clinical care (body weight–based starting dose followed by TDM) in a randomized controlled trial. Besides, the optimization of tacrolimus target attainment, model-based tacrolimus dosing may have other important advantages and implications that require clinical investigation. Besides PK end points (eg, the time within the therapeutic range), we suggest including clinical end points (eg, the occurrence of rejection and drug-related toxicity such as posttransplant diabetes mellitus) and those regarding the clinical implementation of model-based dosing. The latter may include the number of tacrolimus concentration measurements required to guide tacrolimus dosing, cost-effectiveness, and the quality of life of patients. Finally, and arguably most importantly, such an implementation study should investigate the willingness and ability of transplant physicians to use model-based dosing in routine clinical care.

CONCLUSION

The combination of an algorithm-based tacrolimus starting dose with model-based follow-up dosing has the potential to minimize under- and over-exposure to tacrolimus in the early posttransplant phase. However, the additional effect of model-based follow-up dosing on the initial algorithm-based dosing may be limited. Future studies should prospectively investigate the efficacy of the combination of an algorithm-based starting dose and model-based follow-up dosing in terms of tacrolimus target exposure, clinical outcomes, and the feasibility of implementing such a strategy. The present simulation study may serve as the basis for such a trial.

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