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ORIGINAL ARTICLE

Toward a robust tool for pharmacokinetic-based personalization of treatment with tacrolimus in solid organ transplantation: A model-based meta-analysis approach

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Aims: The objective of this study is to develop a generic model for tacrolimus pharmacokinetics modelling using a meta-analysis approach, that could serve as a first step towards a prediction tool to inform pharmacokinetics-based optimal dosing of tacrolimus in different populations and indications.

Methods: A systematic literature review was performed and a meta-model developed with NONMEM software using a top-down approach. Historical (previously published) data were used for model development and qualification. In-house individual rich and sparse tacrolimus blood concentration profiles from adult and paediatric kidney, liver, lung and heart transplant patients were used for model validation. Model validation was based on successful numerical convergence, adequate precision in parameter estimation, acceptable goodness of fit with respect to measured blood concentrations with no indication of bias, and acceptable performance of visual predictive checks. External validation was performed by fitting the model to independent data from 3 external cohorts and remaining previously published studies.

Results: A total of 76 models were found relevant for meta-model building from the literature and the related parameters recorded. The meta-model developed using patient level data was structurally a 2-compartment model with first-order absorption, absorption lag time and first-time varying elimination. Population values for clearance, intercompartmental clearance, central and peripheral volume were 22.5 L/h, 24.2 L/h, 246.2 L and 109.9 L, respectively. The absorption first-order rate and the lag time were fixed to 3.37/h and 0.33 hours, respectively. Transplanted organ and time after transplantation were found to influence drug apparent clearance whereas body weight influenced both the apparent volume of distribution and the apparent clearance. The model displayed good results as regards the internal and external validation.

Conclusion: A meta-model was successfully developed for tacrolimus in solid organ transplantation that can be used as a basis for the prediction of concentrations in different groups of patients, and eventually for effective dose individualization in different subgroups of the population.

The present work did not include new interventions performed with human subjects/patients and or substances administered. Therefore, there is no principal investigator.

KEYWORDS
meta-analysis, pharmacometrics, pharmacokinetics, pharmacodynamics, population analysis, statistics, study design, tacrolimus

1 | INTRODUCTION

Tacrolimus (TAC) is the first-line immunosuppressive drug in the prevention of graft rejection after solid-organ transplantation.[1] Currently, >90% of solid organ transplant recipients worldwide are discharged after transplantation with a TAC-based immunosuppressive regimen.[2,3] TAC is used either as monotherapy or in combination with other immunosuppressive drugs, in different types of solid organ transplantations (renal, liver, pulmonary, heart etc.) and different subpopulations (adults, children, elderly etc.), but also in other indications such as auto immune diseases.[4-8] It is well established that TAC is characterized by a narrow therapeutic window and a large pharmacokinetic (PK) variability.[9] As a consequence, therapeutic drug monitoring of TAC is an integral part of patient care and is even compulsory in many countries and is highly recommended in others.[9,10] For the purpose of dosing optimization, several population PK models in different indications and populations have been published.[11] Inconsistencies can be seen in some of the results with regards to final structural models, in estimated parameter values, covariates selected and their effects on PK parameters.[12,13] As an illustration, Vadcharavivad et al. described population clearance value ranging from 10.02 to 38.4 L/h with highly variable covariates and related effects across studies in adult kidney transplantation.[11] Therefore, while all the available models aim at ensuring that patient exposure (blood drug concentrations) are within effective and safe margins with the implemented dosing regimen, different PK-based algorithms are proposed within and across solid organ transplant populations. Some of these dosing algorithms employ MAP Bayesian estimation methods for dose individualization: when using these methods, concentrations of TAC should be measured in individual patients at informative time points for better results. Sometimes inconsistencies are noted between the proposed methods for dose optimization for the same population by different research teams[11-13] preventing prescribers without quantitative training from using the proposed tools at the maximum of their potential.

The differences between the dosing algorithms published so far for TAC have been described and discussed in previous review papers.[10,12,13] This could mostly be attributed to the data-driven approach taken to develop these models: the final models could only reflect what was possible, given the different study designs (e.g. available covariate data, number of patients included for different subgroups, number of samples and sampling times, time after transplantation). There is an unmet need to conciliate the current quantitative description of TAC PK behaviour across populations and indications as well as the determinants of its variability.[11-13] Indeed, quantitative analysis and meta-model development for TAC PK across indications and populations have not been performed so far, despite the large amount of information on this topic available in the scientific literature.

What is already known about this subject

- Several population pharmacokinetics models have been published for tacrolimus in different indications and populations with some inconsistencies in the results with regards to estimated parameter values and covariates effects on parameters.

What this study adds

- This is the first meta-model for tacrolimus in solid organ transplantation that can be used as a basis for the prediction of concentrations and dose individualization in different indications and subgroups of patients.

TAC PK as described in different populations and indications in previous publications share a drug-related component and sources of variability such as indications, age and body size, that can be characterized quantitatively. The optimal characterization of each of these model components is an important step towards optimal and robust PK tools for TAC personalized used. In order to achieve this, 2 different approaches are possible: the mechanism-based bottom-up approach using physiologically based PK (PBPK) modelling, and the data-driven top-down approach using population PK modelling.[14] In the present study, the latter approach was used: a model-based meta-analysis (meta-model development) was performed, aiming at using the important amount of data on TAC PK available in-house and in the scientific literature to the maximum of their potential to characterize TAC PK across populations and indications using a generic model.[15-17] The principle of meta-modelling is to analyse and integrate findings (results) from several individual studies in order to generate new summary estimates at the population level. Model-based meta-analysis can be used to re-evaluate data in situations involving mixed or contradictory results. This approach has successfully been applied to PK modeling[18] and to other applications such as summarizing available PD disease progression,[19] drug efficacy[15,17,20,21] or safety[20,21] data.

The specific objectives of this study were to compile the currently available (published) quantitative descriptions of TAC PK across populations and types of transplantation, and to propose a

PK meta-model relevant to all contexts of drug usage in solid organ transplantation.

2 | METHODS

2.1 | Literature review

Searches were conducted in PubMed MEDLINE from database inception to 17 May 2017. An update of the search from May 2017 to 4 June 2018 was performed, and relevant data were retrieved and added to the review. The search was limited to studies published in English and based on the combination of the following key words: ((“population pharmacokinetics”[All Fields] OR “population pharmacokinetic”[All Fields])) AND tacrolimus. Subsequently, the identified studies were reviewed and their references examined to identify further potential articles. No publication date or location restrictions were applied.

A set of criteria was established to define the types of studies to be reviewed. Our inclusion criteria were as follows: (1) the study reports the dose used and at least 1 PK parameter of interest for TAC in solid organ transplantation; (2) the data are described in the form of a peer-reviewed article or case series; (3) nonlinear mixed effects approach is used for data analysis. The review did not cover animal studies, case reports, or studies not containing original research or data. The full texts were retrieved and read in full. Data from studies presented in multiple publications were identified to avoid duplications and were reported as a single study, with all other relevant publications listed.

A PRISMA flow diagram was used to present the results from each step of the review process, with an overall summary of the number and types of articles included in the review (see Figure 1). In addition, a summary table was built that included the most relevant information. The following modelling information was extracted from the articles: model structure, typical population, PK parameters, inter- and intra-individual variability, residual variability, and covariates.

2.2 | Meta-model development

After literature review, the meta-model was developed and validated both internally and externally. Individual-level data (including in-house and unpublished data and data received from some of the authors of published studies[22-26]) were used for model development, internal and external validation (Table 1), while summary-level data were only used for external validation of the model. Individual-level data are from paediatric and adult recipients of a kidney, liver, heart or lung at different times after transplantation.

2.2.1 | Meta-model building

Nonlinear mixed effects modelling was performed using NONMEM v7.3.0. (double precision, Icon Development Solutions, Ellicott City, MD, USA) and Perl-speaks-NONMEM (PsN)-toolkit,[27] a programming library containing a collection of computer intensive statistical methods for nonlinear mixed effects modelling, Xpose 4.0,[28] and R

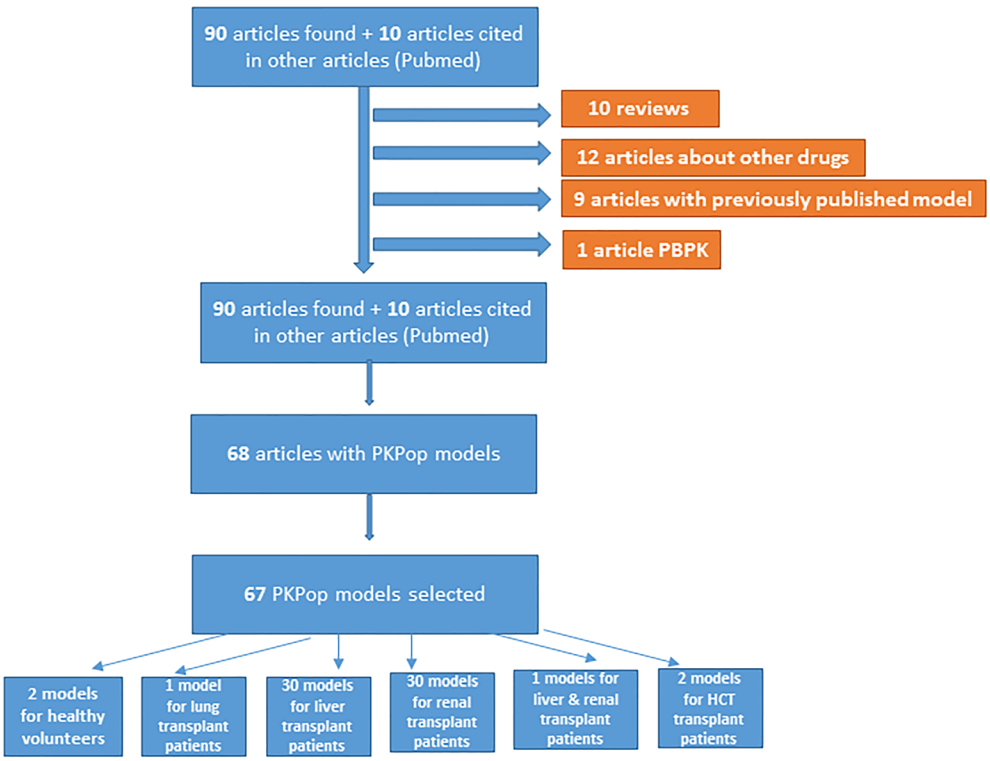

FIGURE 1 Sigma plot of the scientific literature review of population pharmacokinetic (PKPop) models for tacrolimus. PBPK, physiologically based pharmacokinetics

TABLE 1 Patient-level databases available

Database	Adults/children	Organ transplanted	No of patients	No of observations	PK dosage (time after last dose, h)	Analytic method	Time after transplantation in days	Model-building or external evaluation patients	Data source
1	Children	Liver	42	1344	C0	MEIA/CMIA	D1–D394	Model-building	[22]
2	Children	Liver	15	166	0, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12	MEIA	D15	Model-building	[23]
3	Children	Liver	82	1024	C0	MEIA	D1–D15	Model-building	[24]
4	Adults	Kidney	65	423	0, 0.248, 0.64, 0.98, 1.37, 2.38, 11.03	MEIA	D15	Model-building	[25]
5	Adults	Patient on waiting list for kidney transplantation	19	191	1, 2, 4, 8, 12	LC–MS/MS	-	Model-building	[26]
6	Adults	Liver	14	88	2, 4 C0, 1, 2, 4, 6, 8, 12	MEIA	D2 D8	Model-building	In-house
7	Adults	Liver	57	430	C0	MEIA	D1-D8	Model-building	In-house
8	Adults	Lung	61	2471	C0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24	EMIT	D1–D459	External evaluation patients	Stimmugrep trial
9	Adults	Heart	20	548	C0, 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, 12	LCMS	D8–D468	External evaluation patients	Pigrec trial
10	Adults	Kidney	32	1528	C0, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 9, 12	LCMS	D6-D208	External evaluation patients	PCCP trial

CMIA: chemiluminescent microparticle immunoassay; EMIT: enzyme multiplied immunoassay technique; LCMS: liquid chromatography-mass spectrometry LC–MS/MS: liquid chromatography with tandem-mass spectrometry; MEIA: microparticle enzyme immunoassay; PK, pharmacokinetic

software version 3.3.2.[29] The first-order conditional estimation method with interaction was used to model TAC PK.

i. Structural model

The following structural models were tested: 1- and 2-compartment disposition models with first order elimination, 0 or first-order absorption and with and without lag time and Erlang model of absorption. Time dependency was subsequently tested on absorption and on elimination. Assessment of model adequacy and decisions about increasing model complexity were driven by the data and guided by goodness-of-fit criteria, including (i) visual inspection of diagnostic scatter plots, (ii) successful convergence of the minimization routine, (iii) results of likelihood ratio tests, (iv) plausibility of parameter estimates, (v) precision of parameter estimates, and (vi) correlation between model parameter estimates <0.95.

ii. Stochastic model

All interindividual error terms were described by an exponential error model or log-normal parameter distribution (see equation (1)).

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

where: *Pi* is the estimated parameter value for individual i. TVp is the typical population value (geometric mean) of the parameter and η_i are individual-specific interindividual random effects for individual i and parameter P and are assumed to be symmetrically distributed, zero-mean random variables with a variance that is estimated as part of model fitting.

For PK observations in this analysis, the residual error model was initially described by a combined additive and proportional error model (see Equation (2)):

$$Y = F \times (1 + \varepsilon_1) + \varepsilon_2 \quad (2)$$

where Y represents the observed concentration, F is the individual predicted concentration and ε_1 and ε_2 are the proportional and the additive error terms on TAC concentrations, respectively. ε'S were supposed to be symmetrically distributed, zero-mean random variables with variance terms that are estimated as part of the population model-fitting process.

iii. Covariate model

Known physiological relationships such as effects of body size on TAC distribution and elimination were incorporated into the covariate–parameter models when permitted by available data. For example, the change in apparent clearance and volumes of distribution as functions of body weight was empirically described by an allometric model (see equation (3)).

$$P_i = TVp \times \left(\frac{WT_i}{WT_{med}}\right)^{\theta_{WT}} \quad (3)$$

where P_i, the parameter value in individual *i*, was described as a function of typical PK parameter value (TVP) and of weight (WT) for individual *i* (WT_i), normalized by the median WT (WT_{med}). θ_{WT} is an estimated parameter describing the normalized power function.

The effects of categorical covariates were similarly assessed as shown in equation (4).

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

where P_i is the parameter value for an individual patient, TV_P is the reference parameter value, θ_{COV} is the parameter characterizing the covariate effect and COV is the covariate value in the dataset, which was coded as 0 or 1 for binary categorical variables.

A covariate modelling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. First, predefined covariate–parameter relationships were identified based on exploratory graphics, scientific interest, mechanistic plausibility of prior knowledge, and a full model was constructed with care to avoid correlation or collinearity in predictors (covariates with correlation coefficients >0.6 were not simultaneously included as potential predictors). Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision (asymptotic standard errors, bootstrap 95% confidence intervals or log-likelihood profile).

Covariates tested on apparent volumes of distribution and clearance included: body weight, age, type of transplantation and time after transplantation.

2.2.2 | Meta-model internal evaluation

In addition to plausibility of estimated parameter, standard methods as described by Owen and Fiedler-Kelly[30] were used for internal validation of the model. They include diagnosis scatter plots, prediction-corrected visual predictive checks (pcVPCs) and the bootstrap.

Diagnosis scatter plots, also called goodness-of-fit plots, consist in a series of graphs, such as observed concentrations *vs* predicted concentrations and normalized prediction distribution errors and conditional weighted residuals *vs* time.

To generate the pcVPC, the original data set is simulated many times using the final model. The 90% prediction interval of the simulated concentration time profiles should cover 90% of the observed concentrations. A good overlapping between predicted and observed drug concentrations enables to conclude that the model is adequately adjusted to data. One thousand simulation replicates of the original data set were generated using the final model. Overlay plots of the observed concentrations *vs* time with the 95% prediction interval of the simulated data were generated.

Bootstrapping consists in generating a large number of new databases by sampling individuals with replacement from the original

TABLE 2 Published tacrolimus pharmacokinetic population models (results of systematic review)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
Kidney 70	Adults	1-CMT model with first-order absorption	*Dosage with ELISA*: CL/F = 31.3 V/F = 854 T½ = 22.2 * *Dosage with LC–MS/MS*: CL/F = 33.5 L/h V/F = 898 L T ½ =18.6 h	* dosage with ELISA: IIV CL/F = 47% IIV V/F = 247% AddRE = 4.1 ng/mL * dosage with LC–MS/MS: IIV CL/F = 42% IIV V/F = 111% AddRE = 3.7 ng/mL	Staatz et al.[32]
Kidney 70	Adults	1-CMT model with first-order absorption And elimination	*CL/F* = 23.6+(31.9/*DOT*)+(76.7/*AST*) V/F = 1070 Ka = 4.48 (fixed)	IIV CL/F = 42% IIV V/F = 111 L AddRE = 3.7 ng/mL	Staatz et al.[33]
Kidney 43	Adults	2-CMT model with first-order absorption with a lag time	F = 0.23 (fixed) Tlag = 0.956 Ka = 0.58 Ke = 0.517 V1 = 0.18 L/kg K12 = 2.85 K21 = 0.384	NA	Scholten et al.[34]
Kidney 83	Adults	1-CMT model with first-order absorption and elimination	$CL = 1.81 \times [1+(POD^{2.54}/(POD^{2.54}+3.81^{2.54}))] \times (1.575, \textit{if concomitant prednisone} > 25mg)$ Vd = 98.4 F = 0.137 Ka = 4.5 (fixed)	IIV CL =31% IIV V = 79% IIV F = 32% AddRE = 0.96 ng/mL PropRE = 18.6%	Antignac et al.[35]
Kidney 31	Adults	2-CMT model With first-order absorption and first-order elimination	$F = 0.23 \times [1 - (DD/(25+DD))] \times (0.85$ if prednisolone < 10mg) Ka = 3.7 (once-daily dosing) Ka = 1.6 (twice-daily dosing) CL = 3.7 (CYP3A5*3/*3) CL = 5.5 (CYP3A5*1/*3) Vc = 61 (once-daily dosing) Vc = 42 (twice-daily dosing) Q = 10 Vp = Vc	IIV CL = 19% IIV Vc = 28% IOV F = 22% PropRE = 23%	Press et al.[36]
Kidney 32	Adults	2-CMT model, 3 transit absorption CMTs	*CL/F* = 863/*HCT* HCT (%) = 28.6 [21–39] CL/F range with/without HCT were 3–128 L/h and 6–77 L/h, Ktr = 6.5 Vc/F = 147 Vp/F = 500 (fixed) Q/F = 60	IIV Ktr = 15% IIV Vc/F 26% IIV CL/F = 30% IIV Q/F = 63% IOV Ktr = 24% IOV Vc/F = 71% IOV CL/F = 27% PropRE = 10%	Benkali et al.[37]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
				AddRE = 0.7 ng/mL	
Kidney 19	Adults	2-CMT model with first-order absorption.	Ka = 2.18 Ka = 2.02 (night) Vc/F = 142 Vp/F = 192 Q = 43 $CL = 22+34^{CYP3A5}+10^{ABCB1}$ CYP3A5 = 1 if CYP3A5 *1 carriers, otherwise CYP3A5 = 0 ABCB1: Not clear how it was categorized.	IIV CL/F = 6% IIV V1/F = 33% IIV V2/F = 192% AddRE =0,02 ng/mL PropRE = 29% $PropRE_{MEIA}$ = 22%	Musuamba et al.[26]
Kidney 12	Adults	1-CMT model with double γ absorption and first-order elimination	C_0 = 0.816 ± 0.441 a1 = 13.358 ± 6.182 b1 = 20.414 ± 6.564 a2 = 7.397 ± 1.581 b2 = 2.183 ± 0.273 *r* = 0.684 ± 0.146 F*A_IV = 1.846 ± 1.359 a = 0.199 ± 0.178 Mean values (± SD) on day 14 post-transplant; a1, b1, a2 and b2 are the parameters of the γ distribution, r is the fraction of drug absorbed through the first route, F is the bioavailability, A_IV is the initial concentration; α is the apparent elimination rate after intravenous bolus administration of a unit dose, C0 is the trough concentration.	NA	Saint Marcoux et al.[38]
Kidney 46 building, 17 validation	Adults	1-CMT model with first-order absorption	Ka = 4.5 (fixed) $CL = 0.862+(0.32 \times DD)+(1.16$ if concomitant prednisolone > 25mg) V = 1661 L F = 1.18	Prop RE = 31.0%	Velickovic-Radovanovic et al.[39]
Kidney 41	Adults	2-CMT model, 3 transit absorption CMTs	CL/F = 19,if CYP3A5*3/*3 or = 40.85,if CYP3A5*1/*1 & CYP3A5*1/*3 Vc/F = 486 Ktr = 3.3 K12 = 0.73 K21 = 0.09	IIV K_{tr} = 52% IIV Vc/F = 53% IIV CL/F = 35% IIV k_{12} = 54% PropRE = 8% AddRE = 0.7 ng/mL	Benkali et al.[40]
Kidney 73	Adults	2-CMT model with Erlang absorption (*n* = 3) and first-order elimination	$K_{tr1} = 3.34 \times (1.53$ if Prograf®) $CL/F = 21.2 \times (HCT/35)^{-1.14} \times$ (2 *if CYP3A5 expressers*) Q/F = 79	IIV Ktr = 24% IIV CL/F = 28% IIV Q/F = 54% IIV Vc/F = 31%	Woillard et al.[41]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			$Vc/F = 486 \times (0.29$ if Prograf®$)$ Vp/F = 271	IIV Vp/F = 60% PropRE = 14.9%	
Kidney 45	Adults	1-CMT model with γ absorption, with 2 parallel absorption routes, and first-order elimination	CL/F = 26.3 ± 12.2 L/h (LC–MS/MS) # CL/F = 23.4 ± 12.1 L/h (CMIA)# CL/F = 23.4 ± 12.1 L/h (EMIT)# Vd/F = 405 ± 171 L (LC–MS/MS)#,§ Vd/F = 321 ± 168 L (CMIA)c Vd/F = 264 ± 125 L (EMIT)#,§ #mean values (±SD) § variance of log transformed parameter (approximately equal to the coefficient of variation squared), unitless	NA	Saint Marcoux et al.[42]
Kidney 681	Adults	NR	$CL/F = 38.4 \times [(0.86,$ if POD 6 – 10)or(0.71, POD 11 – 180) $] \times [(1.69,$ if CYP3A5 * 1/ * 3)or(2.00, if CYP3A5 * 1/ * 1)$] \times (0.70,$ if receiving a transplant at a steroid sparing center $) \times [(AGE/50)^{-0.4}] \times (0.94,$ if CCB is present)	IIV CL/F = 40.1% AddRE = 3.19	Passey et al.[43]
Kidney 70	Adults	2-CMT model with first-order elimination, first-order absorption with lag time	$\frac{CL}{F} = 16.3 + (20.6 \times HCT/21) + (15.4,$ if CYP3A5*1$) + (7.6,$ ifABCB1 1236CC,2677GG and 3435CC$)$ $ka = 0.45/h$ Vc/F = 86.4 Vp/F = 1115 Q/F = 58.2 Tlag = 0.1	IIV Ka = 91% IIV Vc = 55% IIV Vp = 48% IIV CL = 32% IIV Tlag = 61% PropRE = 13% AddRE = 0.88 ng/mL	Musuamba et al.[25]
Kidney 80	Adults	1-CMT model with first-order absorption and elimination	$CL/F = 22.9 \times exp\begin{bmatrix}[0.2225 if\ CYP3A5^{*}1/1] \\ or \\ [0.17 if\ CYP3A5^{*}1/3] \\ or \\ [0.0525 if\ CYP3A5^{*}3/3]\end{bmatrix} \times exp[[0.297 if\ HCT \le 33] or [0.117 if\ HCT > 33]] \times POD^{-0.00762}$ $V/F = 716 \times exp(0.355 \times WT/59.025)$ Ka = 4.5 (fixed)	IIV CL/F = 49.8% IIV V/F = 48.7% PropRE = 40%	Han et al.[44]
from 4 previous models	Adults	2-CMT model with first-order absorption with a lag time	Ka = 1.68 Tlag = 0.045 CL/F = 3.85 Vc/F = 221 Vp/F = 521	IIV Ka = 199% IIV Tlag = 350% IIV CL/F = 185% IIV V1/F = 133% IIV V2/F = 144%	Musuamba et al.[45]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
		and first-order elimination	Q/F = 21.9	AddRE = 0.97 ng/mL PropRE = 1%	
Kidney 161	Adults	1-CMT model with first-order absorption and elimination	V/F = 1020 Ka = 3.09 $CL/F = 26.6 \times (HCT/27.9)^{-0.45} \times$ (1.21 if CYP3A5 * 1/ * 1 or CYP3A5 * 1/ * 3, CYP3A4 * 1/ * 1G) × (0.982 if CYP3A5 * 1/ * 1 or CYP3A5 * 1/ * 3, CYP3A4 * 1/ * 1) × (0.77 if CYP3A5 * 3/ * 3, CYP3A4 * 1/ * 1G or CYP3A4 * 1G/ * 1G) × (0.577 if CYP3A5 * 3/ * 3, CYP3A4 * 1/ * 1) Vd/F = 1090	IIV CL/F = 44.2% V/F = 56.6% AddRE = 1.47 ng/mL PropRE = 19.8%	Zuo et al.[46]
Kidney 102	Adults	2-CMT model with first-order absorption with lag time	$CL/F = 20.7 \times (AGE/50)^{-0.78} \times$ (2.03 if CYP3A5 expressers) × (1.40 if MRP2 genotype H2/H2 or H1/H2) Vc/F = 234 Vp/F = 1319 Q/F = 70.7 Ka = 0.544 $Tlag = 0.183 \times$ (2.60 for patient with diabetes)	IIV CL/F = 43.9% IIV Vc/F = 157% PropRE = 18.4%	Ogasawara et al.[47]
Kidney 99	Adults	3-CMT nonparametric model with first-order absorption and a lag time	CL/F_{CYP}=26.7 CL/F_{noCYP}=21.2 Q/F = 19.5 Vc/F = 177 Vp/F = 3707 Tlag1 = 1.00 (POD = first week) Tlag2 = 0.15 (POD = week 2–4) Tlag3 = 0.59 (POD > 1 month)	NA	Åsberg et al.[48]
Kidney 69	Adults	2-CMT model, first-order absorption with a lag time	$CL/Fn = 20.5 \times (FFM/60)^{0.75}$ $Vc/Fn = 107 \times (FFM/60)$ $Q/Fn = 37.3 \times (FFM/60)^{0.75}$ $Vp/Fn = 424 \times (FFM/60)$ Ka = 1.14 Ka (study 2) = 0.37 Tlag = 0.22 Tlag (study 2) = 0.81 $F = [2.04+(1 - 2.04)/(1+(POD/2.5)^{-9.4})] \times [1+0.28/(1+(POD/31)^{-2.5})] \times [Fmin_{age}+(1 -$	IIV CL/Fn = 33% IIV Vc/Fn = 14% IIV Q/Fn = 91% IIV Vp/Fn = 52% IIV HillFlate = 117% R (CL/Fn, Q/Fn) = 0.75 IOV Fn = 16% IOV Ka = 63% PropRE = 16.7% Factor for residual variability:	Storset et al.[49]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			$Fmin_{age}$)/(1+(AGE/47)$^{-14}$)] × 0.51 if CYP3A5 expressers $Fmin_{age}$ = 0.43 in females and 0.66 in males; Fn, bioavailability at baseline nadir (5 days after transplantation)	Study 2: 0.57 Study 3: 0.73	
Kidney 173	Adults	2-CMT model with first-order absorption with a lag time	CL/F = 25.5 × (1.6, if CYP3A5 expressers) × [1+(−1.01 × (HCT − 0.33))] × (WT/70)$^{0.75}$ × [1+(−0.0021 × (POD − 22.7))] Vc/F = 113 × [1+(−0.0028 × ($PRED$ − 155.5))] Q/F = 67.9 Vp/F = 1060 Ka = 0.35 Tlag = 0.44 PRED = Cmax value of free prednisolone (nmol/L)	IIV CL/F = 29.5% IIV Vc/F = 46.8% IIV Vp/F = 89.4% IIV Ka = 47.6% IOV CL/F = 29.9% IOV Vc/F = 126.5% Corr R (Vc/F, ka) =67.7% R (Vc/F, Vp/F) = –4.9% R (Ka, Vp/F) = –1.3% PropRE = 18.3%	Bergmann et al.[50]
Kidney 105	Adults	1-CMT model with first-order absorption	CL/F = 10.017 × (POD/47)$^{-0.0283}$ × (WT/68)$^{0.869}$ × (TP/63)$^{0.161}$ × [1 − (0.086 × (AST − 15))] × [1 − (0.831 × (HCT − 0.31))] V/F = 0.68 (fixed) Ka = 1.3 (fixed)	IIV CL =15.2 L/h AddRE = 4.066 ng/mL	Golubovic et al.[51]
Kidney 122	Adults	1-CMT model with first-order absorption	CL/F = 21.9 × [1+0.0119 × (POD − 9.6)] × (0.816, ifCYP3A5 * 3/3)^{CYP} Ka = 3.43 Tlag = 0.25 (fixed) V/F = 205	IIV CL/F = 42.6% IIV V/F = 64.6% IIV Ka = 158.9% PropRE = 5.4% AddRE = 1.94 ng/mL	Han et al.[52]
Kidney 242	Adults	2-CMT model with first-order absorption and a lag time	Ka = 1.01 Tlag = 0.41 Model: (estimate for a typical patient with HCT 45%, FFM 60 kg, CL_{wb}/F = 16.1, Vc_{wb}/F = 125 L, Q_{wb}/F = 23.8, Vp_{wb}/F = 636 L) *Plasma* CL/F = 811 × (FFM/60)$^{0.75}$ × 1.30 (If CYP3A5 expresser) *Plasma* Vc/F = 6290 × FFM/60 *Plasma* Q/F = 1200 × (FFM/60)$^{0.75}$ *Plasma* Vp/F = 32100 × FFM/60 F = 1 × [1 − (0.67 × *Prednisolone dose*)/(35 *mg+Prednisolone dose*)] × 2.68 (If first day post − transplant) × 0.82 (If CYP3A5 expresser)	IIV CL_{wb}/F = 40% IIV Vc/F = 54% IIV Q_{wb}/F = 63% IIV Fday2 = 57% R (CL_{wb}/F, Vc_{wb}/F) = 0.43 R (CL_{wb}/F, Q_{wb}/F) = 0.62 IOV F = 23% IOV Ka = 120% PropRE = 14.9%	Storset et al.[53]
Kidney 16	Adults		CL = 16.50 L/h	IIV CL = 39%	Andreu et al.[54]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
		2-CMT model, with 3 transit absorption CMTs	Vc = 9.89 L Q = 35.56 L/h Vp = 526.03 L Ka = 0.47/h MT = 0.83 h Ktr = 3.61/h MT: (mean transit time)	IOV CL = 29% IIV K_a = 35% IIV MT = 32% PropRE = 21%	
Kidney 83	Adults	1-CMT model with first-order absorption	$CL/F = 23.3 \times [(1.04 \times Gene1)+(0.83 \times Gene2)+(0.62 \times Gene\ 3)]$ Vd/F = 204 (fixed) Gene1 = 1 if patient is CYP3A5*1 carrier and POR*28CC or CT, otherwise = 0 Gene2 = 1 if patient is CYP3A5*1 carrier but not POR*28CC or CT, otherwise = 0 Gene3 = 1 if patient is not CYP3A5*1 carrier, otherwise = 0	IIV CL/F = 26.3% IIV V/F = 10% fixed ExRE = 21.1% AddRE = 0.81 ng/mL	Zhang et al.[55]
Kidney 96	Adults	1-CMT model with first-order absorption	$CL/F = 21.5 \times e^{-0.05} \times (HB - 11.8) \times (-0.06)(DOT/125)$ V/F = 333 Ka = 7.06 fixed	IIV CL/F = 36.8% IIV V/F = 63.64% AddRE = 0.88 ng/mL PropRE = 23.17%	Vadcharavivad et al.[12]
Kidney 70	Adults	2-CMT model with first-order elimination, first-order absorption with lag time	Tlag = 0.47 h Ka = 0.23/h $CL/F = 35 \times [1+(0.45$, if CYP3A5 expressers) or (0.41, if CYP3A5 missing)$] \times (WT/70)^{0.75} \times (\gamma GT/13)^{-0.21} \times (HCT/0.34)^{-0.59}$ $Vc/F = 12 \times (WT/70)$ $Q/F = 68 \times (WT/70)^{0.75}$ $Vp/F = 109 \times (WT/70)$	IIV Ka = 58% IIV CL/F = 45% IIV V1/F = 170% IOV CL/F = 25% PropRE = 21%	Prytula et al.[56]
Kidney 83	Adults	1-CMT model with first-order absorption	$CL/F = 22.4 \times exp(-0.0526 \times (83/POD)) \times (39.1/HCT)^{0.548} \times exp(-0.32 \times CYP3A5)$ $V/F = 179 \times POD^{0.842}$ Ka = 4.5 fix	IIV CL/F = 50,0% IIV V/F = 60.4% AddRE = 2.33 ng/mL	Zhang et al.[57]
Kidney 59	Adults	1-CMT model with double γ absorption route	$C(t) = C(t)_{TPV} \times (0.77)^{CYP3A}$ $C_0 = 2.94$ $a_1 = 12.33$ $b_1 = 20.36$ $a_2 = 15.19$ $b_2 = 5.05$ $r = 0.46$ $F*A_{IV} = 24.52$ A = 1.52		Woillard et al.[58a]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
Kidney 304	Adults	2-CMT model with first-order absorption and a lag time	CL = 20.5 if *CYP3A4*1/*1* homozygotes with at least 1 active *CYP3A5*1* allele CL = 12.5 if CYP3A4*22 noncarriers with CYP3A5*3/*3 or CYP3A4*22 carriers with CYP3A5*1/*1 CL = 9.1 if CYP3A4*22 carriers with CYP3A5*3/*3 CL_AGE = −0.205 CL_AGE: The change on clearance for patients aged ≥63 years Q = 4.2 Vc = 5.02 Vp = 526 (fixed) Ka = 0.138 Tlag = 0.243	IIV CL = 27.8% IOV CL = 33.3% PropRE = 25%	Andreu et al.[59]
Liver 57 Kidney 49	Adults	1-CMT model with first-order elimination, double γ absorption	Kidney transplant patient, ITSIM: FAIV: 2.8 (μg/L) a1 = 7.9 b1 = 5.6 (/h) a2 = 13.8 b2 = 2.3 (/h) r = 0.4 α = 0.17/h Cmax = 12.1 μg/L Tmax = 6.3 h Kidney transplant patient, Pmetrics: FAIV: 2.3 (μg/L) a1 = 19.4 b1 = 5.9 (/h) a2 = 20.7 b2 = 6.8 (/h) *r* = 0.6 α = 0.15/h Cmax = 1241 μg/L Tmax = 5.4 h Liver transplant patient, ITSIM: FAIV: 2.6 (μg/L) a1 = 5.2 b1 = 5.5 (/h) a2 = 14.3 b2 = 2.9 (/h) *r* = 0.21		Woillard et al.[60]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			α = 0.18/h Cmax = 11.7 μg/L Tmax = 5.5 h Liver transplant patient, Pmetrics: FAIV: 2.0 (μg/L) a1 = 27.2 b1 = 5.5 (/h) a2 = 20.8 b2 = 8.6 (/h) *r* = 0.62 α = 0.18/h Cmax = 12.5 μg/L Tmax = 5.6 h		
Kidney 67	Adults	2-CMT model with first-order absorption and elimination and an absorption lag time	*CL*/F = 19.7 × (1.45, if CYP3A5 * 3 * 6 * 7 intermediate metabolizer) × (2.25, if CYP3A5 * 3 * 6 * 7 extensive metabolizer) *Vc*/F = 234 × (*WT*/85.9) Vp/F = 403 Q/F = 52.6 Ka = 4.21 Tlag = 0.828	IIV CL/F = 37% IIV Vc/F = 76.7% IIV Q/F = 48.6% IIV Ka = 69.4% PropRE = 9.00	Campagne et al.[61]
Kidney 50	Paediatrics	2-CMT model, first-order absorption with lag time	Tlag = 0.356 h Ka = 0.462/h V1/F = 57.9 × (WT/70) V2/F = 566 × (WT/70) Q/F = 79.7 × $(WT/70)^{0.75}$ CL/F = 13.9 × $(WT/70)^{0.75}$ × 2.26^{CYP3A5} + 7.11 × 79.7^{HCT} CYP3A5 = 0 if patient is an CYP3A5 nonexpresser, otherwise = 1; HCT = 0 if HHT level is ≥0.33, otherwise = 1.	AddRE = 3.2 IIV Ka = 76.2% IIV Q/F = 89.9% IIV V1/F = 132% IIV CL/F = 41.9%	Zhao et al.[62]
Kidney 22	Paediatrics	1-CMT model with first-order absorption and lag time	Tlag = 0.872 h Ka = 8.34/h V/F = 1100 × (WT/70) L *CL*/F = 30.6 × $(WT/70)^{0.75}$ × 1.66^{CYP3A5} CYP3A5 = 1 if CYP3A5 *1/*3 CYP3A5 = 0 if CYP3A5*3/*3	IIV Ka =150% IIV V/F = 52.1% IIV CL/F = 34.6% ExER = 22.1%	Zhao et al.[63]
Kidney 53	Paediatrics	2-CMT model with first-order input with lag time	$Ka = 0.52 \times \left[1 + \left(\begin{array}{c} -0.76 \text{ if patient is on } Limustin^{\hat{U}} \\ \text{or} \\ (-0.51 \text{ for unknown formulation}) \end{array}\right)\right]$	IIV Ka = 37% IIV Vc/F = 66% IIV F = 38% IIV RE =35%	Jacobo-Cabral et al.[64]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			$F = 100 \times e^{-0.3 \times (DD-2)} \times \left[1 + \left(\begin{array}{c}-0.53 \text{ if patient is on } Limustin^{\hat{A}\hat{U}} \text{ or} \\ (-0.53 \text{ for unknown formulation})\end{array}\right)\right]$ $CL/F = 11.98 \times \left[\begin{array}{c}1 + (0.5 \text{ for CYP3A5*1/*3}) \text{ or} \\ (0.93 \text{ for CYP3A5*1/*1})\end{array}\right]$ Vc/F = 24.16 Q/F = 32.49 L/h Vp/F = 383.5 Tlag = 0.39	AddRE = 0.12 [ln (ng/mL)]	
Kidney 69	Paediatrics	2-CMT model	$CL/F = 50.5 \times (WT/70)^{0.75} \times \left[\begin{array}{c}(1.0, \text{if CYP3A5*3/*3 or unkown}) \\ \text{or } (2.0, \text{if CYP3A5*1/*3 or CYP3A5*1/*1})\end{array}\right] \times (0.74, \text{if living donor}) \times (eGFR/69)^{0.19} \times \left[(HCT/0.3)^{-0.44}, \text{if HCT} < 0.3\right]$ Vc/F = 206 Vp/F = 1520 Q/F = 114 Ka = 0.56 Tlag = 0.37	IIV Ka = 188% IIV CL/F = 25% IIV Vc/F = 69% IIV Vp/F = 62% IOV CL/F = 18% IOV Vp/F = 35% AddRE IA =1.01 AddRE LC–MS/MS = 0.28 PropRE IA = 0.13 PropRE LC–MS/MS =0.21	Andrews et al.[65]
Liver 40	Adults	1-CMT model with first-order absorption and first-order elimination	F = 0.25 (fixed) Ka = 0.45/h Ke = 0.05 (POD 1–4 days), 0.05 (POD 5–7 days), 0.03 (POD 8–11 days), 0.07 (POD 12–14 days)/h V = 0.62 (POD 1–4 days), 0.98 (POD 5–7 days), 2.66 (POD 8–11 days), 1.43 (POD 12–14 days) L/kg	NA	Macchi-Andanson et al.[66]
Liver 35	Adults	1-CMT model	$CL = [0.737+(0.0134 \times POD)] \times 0.728^{HF} \times 0.809^{RF} \times HW/600$ HF = 1 if total bilirubin concentration > 2.5 mg/dL, otherwise = 0. RF = 1 if serum creatinine concentration > 1 mg/dL, otherwise 0 V = 1.52 L/kg F = 0.067	IIV CL = 57.4% IIV V = 39.7% IIV F = 63.0% r (CL,F) = 0.776 AddRE = 2.9 ng/mL	Fukatsu et al.[67]
Liver 68	Adults	1-CMT model with first-order absorption	CL/F = 29.6 (AST < 70) CL/F = 24.0 (AST > 70)	IIV CL/F = 43% IIV V/F = 93%	Staatz et al.[68]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			$Vd/F = 601 \times (WT/72.1)$ Ka = 4.48 (fixed)	AddRE = 3.3 ng/mL	
Liver 47	Adults	1-CMT model	$CL = (0.743+(0.0157 \times POD)) \times 0.792^{HF} \times 0.810^{RF} \times HW/600$ $V = 1.64 \times BW$ F = 0.0732 BW = bodyweight; HF = 1 if total bilirubin >2.5 mg/dL; otherwise = 0.; HW = hepatic weight; RF = 1 if serum creatinine >1 mg/dL, otherwise = 0.	IIV F = 71.2% IIV CL = 60.0% IIV V = 35.4% R (CL/F) = 0.770 AddRE = 2.75 μg/L	Fukudo et al.[69]
Liver 37	Adults	1-CMT Model with first-order absorption	$CL/F = \left(CL/F_{max} \times POD^{4.9}\right)/\left(TCL_{50}^{4.9} + POD^{4.9}\right)$ $CL/F_{max} = 36 \times (ALB/38)^{0.64}$ $TCL_{50} = 6.3 \times (ASAT/38)^{0.28}$ V/F = 1870 Ka = 4.48 (fixed) TCL_{50} is the time needed to obtain 50% of maximum CL/F	IIV CL/Fmax = 43.6% IIV TCL_{50} = 33.2% IIV V/F = 49% r (CL/F_{max},V_d/F) = 0.55 AddRE = 3.07 ng/mL	Antignac et al.[70]
Liver 67	Adults	1-CMT model with first-order absorption	$CL/F = 21.3+(9.83 \times (1 - HCT))+(3.43 \times (1 - ALB))+(22.13 \times (1 - DIL))+(27.43 \times (1 - FLU))$ V/F = 314.0 Ka = 4.5 (fixed)	IIV CL/F = 31.6% PropRE = 24.3%	Zahir et al.[71]
Liver 29	Paediatrics and adults	1-CMT model with first-order absorption	Model 1, according for blood concentration: $CL/F = 14.1+(0.237 \times (WT - 55))+(-2.93)^{ALP}+(-0.0801 \times (SCR - 60))$ $V/F = 217+(-7.83 \times (HCT - 31.1))+(179 \times (HT - 1.61))$ Ka = 2.08 With ALP = 1 if alkaline phosphatase ≥ 200 U/L, otherwise 0. SCR = serum creatinine Model 2, according for plasma concentration: $CL/F = 537+(10.5 \times (WT - 55))$ $V/F = 563+5380^{CECP}$ CECP = 1 if erythrocyte to plasma ratio of concentration ≥ 68, otherwise = 0.	Model 1: IIV CL/F = 65.7% IIV V/F = 63.8% PropRE = 34.8% Model 2: IIV CL/F = 96.0% IIV Vd/F = 105.4% AddRE = 0.548 ng/mL	Sam et al.[72]
Liver 72	Adults	1-CMT model with first-order absorption and elimination	$CL/F = 15.9 - (1.88 \times TBIL)+(7.65 \times CYPD)+(7.00 \times CYPR)$ V/F = 620 Ka = 4.48 (fixed) If total biblirubin ≤25.7, μmol/L, TBIL = 0, if biblirubin = 25.8–51.4, TBIL =1,, if biblirubin = 51.5–77.1, TBIL =	Model 2: IIV CL/F = 31.2% IIV V/F = 55.0% AddRE = 2.81 ng/mL	Li et al.[73]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			2, if biblirubin = 77.2–128.5, TBIL = 3, if biblirubin >128.5, TBIL = 4 CYPD: Donor CYP3A5*3/ *3 = 0; others = 1 CYPR: Recipient CYP3A5*3/ *3 = 0; others = 1		
Liver 14	Adults	2-CMT model with first-order absorption and first-order elimination. Hill model to describe the relationship between $AUC_{12effCNA}$ and TAC AUC_{12}	Ka = 4.03/h $CL/F = 2.85 \times 0.36^{W/S} \times 1.026^{FV}$ Q/F = 22 L/h V1/F = 87 L V2/F = 1290 L $AUC_{12effCNA}$ = Min + Delta × (1 − (AUC_{12}^{S}/(($AUC_{12})_{50}^{S}$+ AUC_{12}^{S}) This Hill model describe the relationship between tacrolimus exposure ($AUC_{12Tacrolimus}$) and the area under the calcineurin activity (CNA)-time curve over 12 hours ($AUC_{12effCNA}$) Min = 99 pmol/min/10^6 PBMC Delta = 3187 pmol/min/10^6 PBMC $(AUC_{12})_{50}$ = 164 h.mg/mL Where W/S = whole/split cadaveric liver and FV: coagulation factor V, were expressed as 0 or 1[a]	IIV ka = 0.44 IIV CL/F = 0.23§ IIV V1/F = 0.44§ IIV Q/F = 0.39§ IIV V2/F = 0.36§ IIV Min = 0.16§ IIV Delta = 0.10§ IIV (AUC12)50 = 0.076§ IIV s = 0.12d IOV ka = 13.1d IOV CL/F = 0.30d IOV V1/F = 0.74d IOV Q/F = 0.85d IOV V2/F = 1.35d IOV Min = 0.093d IOV Delta = 0.064d IOV (AUC12)50 = 0.051d IOV s = 0.15d PropRE = 0.012 g	Blanchet et al.[74]
Liver 35	Adults	1-CMT model with first-order elimination	$CL/F = (0.36+(2.01/POD) \times L) \times TBIL^{-0.23} \times$ (0.49, if POD ≤ 3) × (0.75, if INR > 1.4) × (0.86, if GRWR ≤ 1.25%) × WT V/F = 568 TBIL = 1 if total bilirubin level ≤ 1.2 mg/dL, otherwise TBIL = total bilirubin level) L = 1 if POD >35 days, otherwise L = 0:	IIV CL/F = 35.35% IIV V/F = 68.12% AddRE = 3.14 ng/mL	Lee et al.[75]
Liver 262	Adults	1-CMT model with first-order administration, first-order elimination	$CL/F = 20.9 \times (DDS/4)^{0.582} \times (HCT/35.4)^{0.418} \times (TP/69.1)^{0.780} \times 0.841^{SU}$ $V/F = 808 \times (HCT/35.4)^{1.52} \times (TP/69.1)^{1.81}$	IIV CL/F = 23.8% IIV V/F = 70.4% ExpRE = 33.6% AddRE = 0.96 ng/mL	Zhang et al.[76]
Liver 75	Adults	1-CMT model with first-order absorption and first-order elimination	Ka = 4.48 (fixed) CL/F (POD: 0–3 days) = 11.1 L/h, if AST < 500 U/L and rapid recovery CL/F (POD: 0–3 days) = 8.04 L/h for standard group	IIV CL/F (POD: 0–3 days) = 45.9% IIV Vd/F (POD: 0–3 days) = 52.2% IIV CL/F (POD:	Oteo et al.[77]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			Vd/F (POD: 0–3 days) = 328 L CL/F (POD: 4–15 days) = 24.5 L/h, if ALB <28% and HCT < 2.5 g/dL CL/F (POD: 4–15 days) = 17.8 L/h for standard group. Vd/F (POD: 4–15 days) = 568 L	4–15 days) = 36.7% IIV Vd/F (POD: 4–15 days) = 20.2%	
Liver 150	Adults	1-CMT model with first-order absorption	Ka = 4.48 (fixed) CL/F (POD: 0–3 days) = 14.5 L/h CL/F (POD: 0–3 days) = 10.1 L/h (high AST) Vd/F (POD: 0–3 days) = 365 L CL/F (POD: 4–15 days) = 19.3 L/h CL/F (POD: 4–15 days) = 23.8 L/h (low HCT/albumin) Vd/F (POD: 4–15 days) = 597 L	AddRE = 3.04 ng/mL	Valdivieso et al.[78]
Liver 47	Adults	2-CMT model with first-order absorption	$CL/F = 11.2 \times Dose^{0.371} \times POD^{0.127}$ Vc/F = 406 L Q/F = 57.2 L/h Vp/F = 503 L Ka = 0.723/h	IIV CL/F = 16.2% IIV Vc/F = 163% IIV Q/F = 19.7% IIV Vp/F = 199% IIV Ka = 74.3% PropRE = 26.54%	Zhu et al.[79]
Liver 112 healthy volunteers 40	Adults	2-CMT model with first-order absorption with lag time	$CL/F = 32.8$ for healthy volunteers $CL/F = 32.8 \times 0.562[exp(ALT/40) \times 0.0237)]$ for transplant recipients Vc/F = 22.7 Vp/F = 916 (fixed) Q/F = 76.3 Ka = 0.419 (fixed) Tlag = 0.404	IIV CL = 46.6% IIV Vc = 57.3% IIV Q = 46.0% IIV Vp = 93.5% IIV Ka = 0%* PropRE = 39.8%	Lu et al.[80]
Liver 95	Adults	1-CMT model with first-order absorption	Ka = 4.48 (fixed) CL/F = 17.6 θPOD- CL/F = 0.205 θBUN- CL/F = − 0.116 θALP- CL/F = 0.165 θTBIL- CL/F = − 0.142 θHCT- CL/F = − 0.789 θCYP- CL/F = 0.661 V/F = 225 θPOD-V/F = 0.852 θHB-V/F = − 0.813	IIV CL/F = 53.9% IIV V/F = 68.0% PropRE = 28.4% AddRE =0.606 ng/mL	Zhu et al.[81]
Liver 29	Adults	1-CMT model, with first-order absorption	Ka = 0.52/d CL/F = 6.18 L/d	IIV CL/F = 39% IIV V/F = 76%	Badri et al.[82]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			V/F = 101 L CL/F and V/F: In the present of 3 direct-acting antiviral regimen (3D) of ombitasvir, paritaprevir/ritonavir, and dasabuvir		
Liver 66	Adults	2-CMT model, with delayed first-order input 3 transit CMT for absorption	CL = 4.21, if donor and recipient are CYP3A5*1 noncarriers = 5.60 if recipient is CYP3A5*1 carrier and donor is noncarrier or recipient is CYP3A5*1 noncarrier and donor is carrier = 7.20 if both donor and recipient are CYP3A5*1 carriers Vc = 88.3 Vp = 145 Q = 14 Ka = 3.76 F = 0,23 (fixed)	IIV CL = 42.8% IIV Vc = 86.3% IIV Ka = 65.9% PropRE = 13%	Moes et al.[83]
Liver 125	Adults	2-CMT model with first-order absorption and an absorption lag time	*CL/F* = 21.9 Vc/F = 165 Q/F = 54.9 Vp/F = 594 Ka = 0.51 Tlag = 1.57		Chen et al.[84]
Liver 33	Paediatrics	1-CMT model	F = 0.19 $CL = (0.0749+0.000457 \times POD) \times [15 \times (WT/15)^{0.290}]$ $V = 2.76 \times [15 \times (WT/15)^{0.290}]$	IIV F = 21.0% IIV V = 27.4% AddRE = 3.69 (TAC concentration)$^{0.160}$ ng/L	Yasuhara et al.[85]
Liver 16	Paediatrics	1-CMT model with first-order absorption	Ka = 4.5 (fixed) $CL = 1.46 \times (1+0.339 \times (AGE - 2.25))$ $V = 39.1 \times (1+4.57(BSA - 0.49))$ $F = \theta5 \bullet (1 + \theta6 \bullet (WT-11.4) \times \theta7^{BIL}$ $F = 0.197 \times (1+0.0887 \times (WT - 11.4) \times 1.61^{BIL}$ BIL = 1 if total bilirubin ≥200 μmol/L, otherwise = 0.	IIV CL = 33.5% IIV V = 33.0% IIV F = 24.1% AddRE = 5.79 ng/mL	Sam et al.[86]
Liver 15	Paediatrics	1-CMT model	$CL = 10.4 \times (WT/70)^{0.75} \times e^{-0.00032DOT} \times e^{-0.057BILI} \times (1 - 0.079 \times ALT)$ F = 0.20 (fixed)	IIV CL = 24.3% PropRE = 29.5%	Garcia Sanchez et al.[87]
Liver 35	Paediatrics	1-CMT model with first-order absorption and elimination	CL/F = 44 (CL/F for whole liver recipients) CL/F = 5.75 (CL/F cut-down liver recipients) Vd/F = 617	IIV CL/F = 110% IIV V/F = 297% AddRE = 3.03 ng/mL	Staatz et al.[88]
Liver 130	Paediatrics	1-CMT model	Model 1: $CL/F = (0.165+0.0244 \cdot XPOD) \times SIZE \times EXP(-0.0420 \times AST/53)/Kg$ $V/F = 20 \times SIZE$	Model 1 IIV CL/F = 53% IIV V/F = 74.0%	Fukudo et al.[89]

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TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			$SIZE = 8.6 \times (BW/8.6)^{0.447}$ Model 2: $CL/F = (0.134 \times 1.8^{iFLAG} + 0.0181 \times 2^{hFLAG} \times XPOD) \times SIZE \times EXP(-0.0358 \times AST/53)$ $V/F = 17.1 \times SIZE$ $SIZE = 8.6 \times (BW/8.6)^{0.341}$ XPOD = POD if POD was <21; otherwise, XPOD = 21; hFLAG = 1 if the donor was a CYP3A5*1 carrier, otherwise hFLAG = 0. iFLAG = 1 if the intestinal MDR1 mRNA level was >0.22 amol/μg total RNA; otherwise 0	AddRE = 3.24 ng/mL Model 2 IIV CL/F = 48.7% IIV V/F = 82.6% AddRE = 3.16 ng/mL	
Liver 73	Paediatrics	1-CMT model with first-order absorption and elimination	Ka = 4.48/h $CL/F = (CL/Fo + ((CL/Fmax \times POD^{\gamma}) \times (TCL/F_{50})^{\gamma} + POD^{\gamma})))x\ WT^{0.75}$ L/h $CL/Fo = 0.148\ mL.h^{-1}.kg^{-0.75}$ $CL/Fmax = 1.37\ 0.148\ mL.h^{-1}.kg^{-0.75}$ $\gamma = 3.78$ TCL/F50 = 5.38 days. Vd/F = 17.2 x WT L/h	IIV CL/Fmax = 65% IIV TCL/F50 = 54% IIV Vd/F = 90% AddRE = 1.63 ng/mL PropRE = 29.2%	Wallin et al.[90]
Liver 42	Paediatrics	2-CMT model with first-order elimination	$CL/F = 0.001 \times \left[1 + (314 \times POD) / \frac{(17.4 + POD) \times (SWR/10.2)^{84}}{\times (HCT/Medium\ HCT)^{-0.85}}\right]$ $Vc/F = 253 \times (WT/10.2)^{0.9}$ Vp/F = 100 (fixed) Ka = 4.5 (fixed) Q/F = 115 L/day SWR = liver transplant size/Bodyweight ratio	IIV CL/F (baseline) = 30% IIV V1/F = 60% IOV CL/F = 10% AddRE = 1.78 ng/mL PropRE = 2%	Guy-Viterbo et al.[22]
Liver 43	Paediatrics	1-CMT model with first-order absorption and elimination	$CL/F = 12.9 \times (WT/13.2)^{0.75} \times exp(-0.000158 \times POD) \times (exp(0.428)$, if the recipient is CYP3A5 expresser) V/F = 30 L/kg (fixed) Ka = 4.5 (fixed)	IIV CL/F = 40% PropRE = 35.4%	Jalil et al.[91]
Liver 82	Paediatrics	1-CMT model, time-varying first-order elimination	Ka = 4.45/h * $CL/F = [0.001+((13.9 \times POD)/(3.97+POD))] \times (WT/60)^{0.21} \times (SIZE/SIZEmed)^{0.18} \times (HCT/HCTmed)^{-0.04} \times 0.82^{INH}$ $V/F = 347 \times (WT/60)^{0.44}$ SIZE = liver transplant size–body weight ratio INH = 1 if the patient uses inhibitors of tacrolimus, otherwise INH = 0.	IIV CL/F = 26.7% IIV V/F = 43.3% IIV F = 33% AddRE = 1.49 ng/mL PropRE = 0.25	Musuamba et al.[24]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
Liver 114	Paediatrics	2-CMT model	$CL/F = (0.01 \times 1.17^{RCYP3A5} \times 0.98^{RABCB1}) + (10.9 \times (AGE/13)^{0.16} \times 1.3^{DCYP3A5} \times 0.71^{DCYP3A4} \times 0.7^{FZLDe} \times 0.4^{FDLne} \times (TIME/144+TIME))$ $Vc/F = 79 \times (WT/10)^{0.49}$ Ka = 4.5 (fixed) Vp/F = 100 (fixed) RCYP3A5 = 1 if the recipient is a CYP3A5 expresser, otherwise 0; RACB1 = 1 if recipient is ACB1 2677G > T/A mutation carrier, otherwise 0; DCYP3A5 = 1 if the donor is a CYP3A5 expresser, otherwise 0; DCYP3A4 = 1 if the donor is CYP3A4*22 T allele carrier, otherwise 0. FZLDe = 1 if the patient use fluconazole and the donor is a CYP3A5 expresser, otherwise 0;	IIV CL/F = 27% IIV Vc/F = 36% PropRE = 10% AddRE = 2.38 ng/mL	Guy-Viterbo et al.[92]
Liver 30	Paediatrics	2-CMT model with first-order absorption and first-order elimination and a lag time	$CL/F = 12.1 \times (WT/20)^{0.75}$ $Vc/F = 31.3 \times (WT/20)$ $Vp/F = 390 \times (WT/20)$ $Q/F = 30.7 \times (WT/20)^{0.75}$ $Ka = 0.342 \times (WT/20)^{0.75}$ Tlag = 0.433	IIV Vc/F = 126.1% IIV CL/F = 55.6% IIV Q/F = 84.0% PropRE =20.3%	Kassir et al.[93]
Liver 52	Paediatrics	1-CMT model with first-order absorption	Ka = 4.48/h $CL/F = 5.72 \times POD^{0.152} \times (ALT/70)^{-0.111}$ $V/F = 131 \times POD^{0.310} \times (ALT/70)^{-0.317} \times (TP/54)^{-2.010}$	IIV CL/F = 13.5% IIV V/F = 78.1% PropRE = 7,79% AddRE = 1.54 ng/mL	Yang et al.[94]
Lung 22	Adults	1-CMT model with double γ distribution model for absorption phase and first-order elimination	For cystic/non-cystic fibrosis patient group: MAT1 = 1.10/0.92 h MAT2 = 5.14/5.47 h A_IV = 4.03/9.36/L λ = 0.64/0.8/h *r* = 0.58/0.62 Ĉ0 = 0.91/1.81 mg/L CL/F = 68.22/36.49 L/h Vc/F = 2011/444 L Coefficient, λ disposition rate constant, r fraction of the dose absorbed by the faster phase, Ĉ0 theoretical residual concentration	NA	Saint Marcoux et al.[95]
Lung	Adults		$K_{tr} = 7.06 \times 0.47^{CF}$	IIV Ktr = 46.4%	Monchaud et al.[96]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
125		2-CMT model, with Erlang model for absorption, 4 transit CMTs.	CF = 1 if patient has cystic fibrosis, otherwise CF = 0 $F = 1 \times 0.63^{CF}$ $CL/F = 17.5 \times 1.4^{CYP}$ CYP = 0 in patients with CYP3A5*3/*3 polymorphism & CYP = 1 in patients with CYP3A5*1/*3 or CYP3A5*1/*1 polymorphism Vc/F = 136 Vp/F = 529 Q/F = 41.1	IIV Vc/F = 56.0% IIV Q/F = 71.7% IIV Vp/F = 126% IIV CL/F = 61.2% IOV Ktr = 45.8% IOV Vc/F = 75.4% IOV CL/F = 46.8% AddRE = 1.6 μg/L PropRE = 6.9%	
Heart 48 (18 used in the model validation dataset)	Children	1-CMT model with first-order absorption	Ka = 3.43 (fixed) $Ke = 0.0408 \times 0.657^{FLU} \times (CRCL/122.4)^{0.85}$ $V = 233 \times (AGE/5.7)^{0.775}$ Fluconazole elimination rate = 0.0268 (5%)	OM_Ke = 0.262 OM_V = 0.329 AddRE = 3.69 μg/L	Rower et al.[97]
Haematopoietic stem cell 122	Adults	Noncompartmental approach CL = rate/Css Ou CL = F*D/(tau*Css)	CL = 5.22 L/h Total bilirubin 2–9.9 mg/dL = 0.797 Total bilirubin ≥10.0 mg/dL 0.581 SCr ≥ 2.0 mg/dL: 0.587 Graft-*vs*-host disease grade III and IV: 0.814 Presence of Veno-occlusive disease: 0.814 F = 0.28	IIV CL 33.0% IIV F 44.3% PropRE Conc = 10 μg/L: 27.5% Conc = 20 μg/L 16.8%	Jacobson P et al.[98]
Haematopoietic stem cell 22	Paediatrics	1-CMT model with first-order absorption after oral administration	$CL = 106 \times \left[1 + 18.7 \times \left(SCR^{-1} - SCR_{med}^{-1}\right)\right] \times WT^{0.75}$ mL.h^{-1}. kg$^{-0.75}$ $V = 3.97 \times WT$ $F = 15.7 \times [\ 1+(-0.002 \times (\ POD - 14))]$ % Mean weight = 24 kg	IIV CL =50% IIV V = 122% IIV F = 61% PropRE = 38.8% IIV ERR = 18%	Wallin et al.[99]
Healthy volunteers 22	Adults	2-CMT model, Erlang model with 2 transit CMT	Ka = 3.57/h $CL/F = 10.3 \times 2.06^{CYP3A}$ CYP3A = 0 for subjects with both CYP3A4*1/ *1 and CYP3A5*3/*3, otherwise =1 Vc/F = 93.3 Q/F = 26.7 Vp/F = 358	IIV Ka = 39.9% IIV CL/F = 37.4% IIV Vc/F = 44.7% Exponential error (ω1) = 12.4% AddRE(ω2) = 0.0672 ng/mL	Shi et al.[100]
Healthy volunteers 73	Adults	2-CMT model With first-order absorption, and a lag time	Ka = 0.792/h Tlag = 0.226 h $CL/F = 27.7 \times 0.503^{CYP}$ Vc/F = 37.5 L Q/F = 34.4 l/h $Vp/F = 357 \times (BSA/1.82)^{3.73} \times (RBC/4.83)^{-3.1}$ When the CYP3A5 genotype was * 1/ * 1 or	IIV Ka = 32.9% IIV Alag = 4.45% IIV CL/F = 63.3% IIV Vc/F = 62.0% IIV Q/F = 50.8% IIV Vp/F = 52.3% PropRE = 14.9%	Xue et al.[101]

(Continues)

TABLE 2 (Continued)

Organ transplanted, No. of patients	Type of population	Pharmacokinetic model	Pharmacokinetic parameters	Model variability	References
			* 1/ * 3, CYP = 0; otherwise, CYP = 1.		
Healthy volunteers 17	Adults	2-CMT, first-order absorption with lag time, and first-order elimination model	***Individual model*** $CL/F = 17.8 \times 1.26^{CYP3A5}$ V/F = 108 Ka = 3.75 K23 = 0.326 K32 = 0.069 Tlag = 0.627 ***Integrated model (interaction with MPA)*** $CL/F = 13.8 \times \left(1/e^{0.0294 \times C_{MPA}}\right) \times 1.48^{CYP3A5}$ V/F = 93 Ka = 1.78 K23 = 0.313 K32 = 0.0719 Tlag = 0.59 CYP3A5 is 1 in CYP3A5 expressers, and 0 in otherwise, and C_{MPA} is the concentrations of MPA	IIV CL/F = 26.4% IIV V/F = 30.8% IIV Ka = 93% PropRE = 0.131%	Kim et al.[102]

ABC, adenosine triphosphate-binding cassette; AddRE, additive residual random error; ALB, albumin; ALP, alkaline phosphatase (U/L); ALT, alanine aminotransferase (U/L); AST, aspartate transferase (U/L); AUC, area under the plasma concentration–time curve; BID, twice daily; BILI, bilirubin; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; C0, trough concentration; Cn, concentration at n hours postdose; CCB, antihypertensive drugs classified as calcium channel blocker use at the time of trough measurement; CL, clearance (L/h); CL/F, apparent oral clearance (L/h); CLwb/F, apparent whole blood clearance (L/h); CMIA, chemiluminescent microparticle immunoassay; CMT, compartment; Corr, correlation; CYP, cytochrome P450; DD, tacrolimus daily dose (mg/day); DOT, days since commencing tacrolimus therapy (day); ELISA, enzyme-linked immunosorbent assay; EMIT, enzyme-multiplied immunoassay technique; exp, exponential; ExpRE, exponential residual random error; F, bioavailability; FFM, fat free mass (kg); FLU, fluconazole; GRFT, graft origin; HB, haemoglobin; HCT, haematocrit (%); HF, hepatic function; hFLAG, indicator variable associated with hepatic graft; HW, graft hepatic weight; iFLAG, Indicator variable associated with intestine; IIV, interindividual variability; IOV, interoccasion variability; IS, intensive sampling; K12, transfer rate constant from the central compartment to the peripheral compartment (/h); K21, transfer rate constant from the peripheral compartment to the central compartment (/h); Ka, absorption rate constant (/h); Ke, elimination rate constant (/h); Ktr, transfer rate constant (/h); LC–MS/MS, liquid chromatography–tandem mass spectrometry; MAT1, mean absorption time associated with the first absorption phase; MAT2, mean absorption time associated with the second absorption phase; A_IV, the intravenous disposition; MEIA, microparticle enzyme immunoassay; MRP2, multidrug resistance-associated protein 2; MS, mass spectrum; MTT, mean transit time (h); n, number of transit compartments; NA, not available; NR, no reported; POD, postoperative day; PropRE, proportional residual random error; Q, inter-compartmental clearance (L/h); SCR, serum creatinine; Q/F, apparent intercompartmental clearance (L/h); Q/Fwb, apparent whole blood intercompartmental clearance (L/h); QD, once daily; RF, renal function; RBC, red blood count (10^{12}/L); TAC, tacrolimus; TBW, total body weight (kg); TFC, turbulent flow chromatography; TIME, time after transplantation; Tlag, lag time (h); TP, total protein (g/L); Vc, volume of distribution of central compartment (L); Vc/F, apparent volume of distribution of central compartment (L); Vp, volume of distribution of peripheral compartment (L); Vp/F, apparent volume of distribution of peripheral compartment (L); WT, body weight (kg); XPOD, arbitrary value of postoperative day

[a]C0 is the model estimated TAC trough level for a theoretical dose of 1000 mg (the real trough level can be calculated by dividing this value by 1000 and multiplying by the patient dose) (a_i,b_i) are the parameters of the γ distributions, r is the fraction of dose absorbed following the first γ function, F is the bioavailability, A_{IV} is the initial blood concentration obtained after a bolus IV injection, θ_{CYP3A} is the parameter representing the effect of the CYP3A covariate on the typical value of the TAC blood concentrations. Alpha is the elimination parameter.

dataset. For each new dataset, parameters were re-estimated and this resulted in a bootstrap distribution of each model parameter. Empirical 95% confidence intervals (CI) were constructed by observing the 5th and 95th percentiles of the resulting parameter distributions for those bootstrap runs that generated parameter estimates.

2.2.3 | Meta-model external evaluation

External evaluation was performed in 2 different ways: (1) available patient-level data (observed concentrations from studies not included in the model building dataset) were predicted using the final model with MAXEVAL = 0 option in NONMEM. The good predictive performance of the model is established if the model predictions are consistent with observed data; (2) comparing parameter estimates from the final meta-model to the ranges of parameters from the previously published models.

The individual- (patient-) level data were originated from 3 multicentre PK trials intended to develop population PK models and Bayesian estimators for optimized dose adjustment of immunosuppressive drugs in thoracic and renal transplant patients. The design characteristics of the 3 studies are summarized in Table 1.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.[31]

TABLE 3 Pharmacokinetic parameters estimates for the final model

Parameters (units)	Base model [estimate (RSE%)]	Final model [estimate (RSE%)]	Bootstrap analysis (n = 1000) [95%]
CL/F (L/h)	12.3 (5.5%)	22.5 (6.4%)	22.6 [19.7–25.4]
V2/F (L)	217.7(7.4%)	246.2 (9.4%)	248.7 [176.9–315.6]
Q/F (L/h)	31.18 (34.1%)	24.2 (34.3%)	25.4 [–0.45–48.9]
V3/F (L)	50.57 (20.8%)	109.9 (16.9%)	111.0 [61.1–158.8]
KA (/h)	3.69 (13.5%)	3.37 (17.7%)	5.76 [–21.1–27.8]
ALAG1 (h)	0.33 (0.1%)	0.32 (6.2%)	0.33 [0.21–0.43]
WT_CL	-	0.61 (8.6%)	0.61 [0.49–0.74]
WT_V	-	0.53 (11.4%)	0.53 [0.39–0.66]
Hepatic trans_CL	-	0.38 (10.6%)	0.38 [0.29–0.48]
Sigmoidity coefficient for time_CL	-	8.88 (17.3%)	9.08 [5.31–12.44]
Time 50% recovery	-	6.12 (5.3%)	6.12 [5.1–7.1]
Bioavailability for syrup formulation	-	0.53 (20.5%)	0.53 [0.31–0.75]
IIV on CL/F	88 (7.8%)	59.4 (10.3%)	57.9 [51.3–65.0]
IIV on V2/F	88 (16.7%)	133.2 (25.5%)	133.9 [85.0–172.1]
ε_1 (%)		24.32 (8.75%)	25.4 [15.9–30.5]
ε_2 (ng/mL)		3.22 (12.75%)	3.10 [2.01–4.09]

$$CL/F = 22.5 \times (WT/50)^{0.61} \times \left[0.39 \times \left(1 + \frac{POD^{8.88}}{POD^{8.88} + 6.12^{8.88}}\right)\right]$$

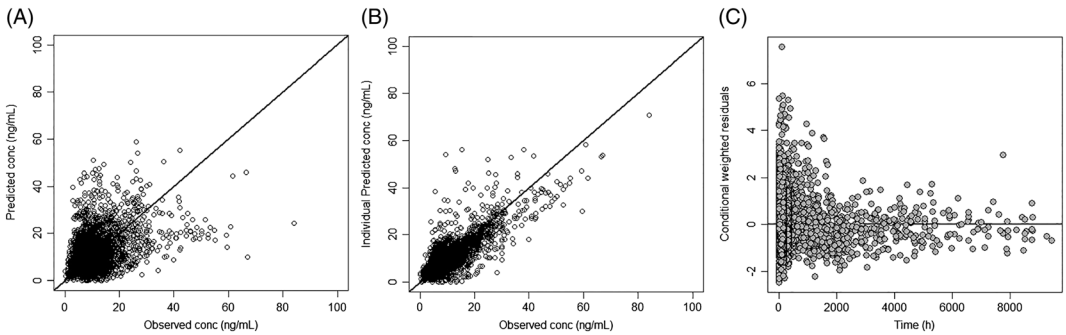

FIGURE 2 Goodness-of-fit plots of the final population pharmacokinetic model. (A) Observed *vs* population predicted concentrations; (B) observed *vs* predicted individual concentrations; (C) conditional weighted residuals *vs* time post-transplantation

3 | RESULTS

Figure 1 and Table 2 represent the PRISMA flow diagram describing the different steps for study selection and the summary table including details of the studies retained from the literature review exercise, respectively. A total of 109 publications were initially generated by PubMed search. Among these, 42 were excluded in accordance with the exclusion criteria. To the 67 selected articles, nine additional studies were added from reference scanning. A total of 76 articles were retained, in which 76 developed models were found to be relevant for meta-model building and the related parameters recorded (see Table 2).

The meta-model developed using patient-level data was structurally a 2-compartment model with first order absorption after an absorption lag time, and first-order, time varying elimination. Population values for clearance, intercompartmental clearance, central and peripheral volume were 22.5 L/h, 24.2 L/h, 246.2 L and 109.9 L, respectively. The absorption first-order rate and the lag time were fixed to 3.37/h and 0.33 hours, respectively. The transplanted organ and time after transplantation were found to influence drug apparent

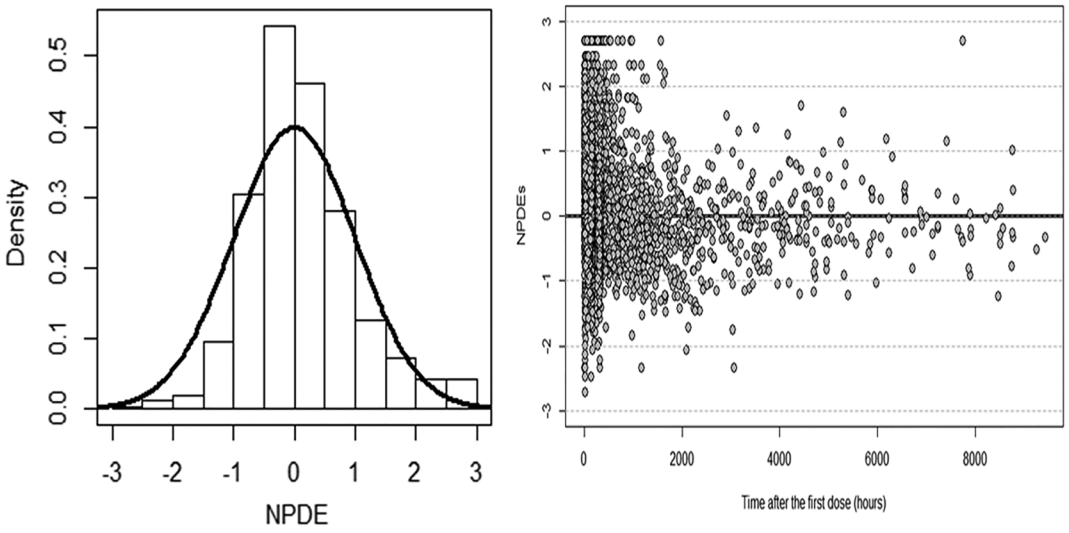

FIGURE 3 Normalised prediction distribution error plots (NPDE). (A) Distribution of NPDE. (B) NPDE *vs* time from the start of the treatment

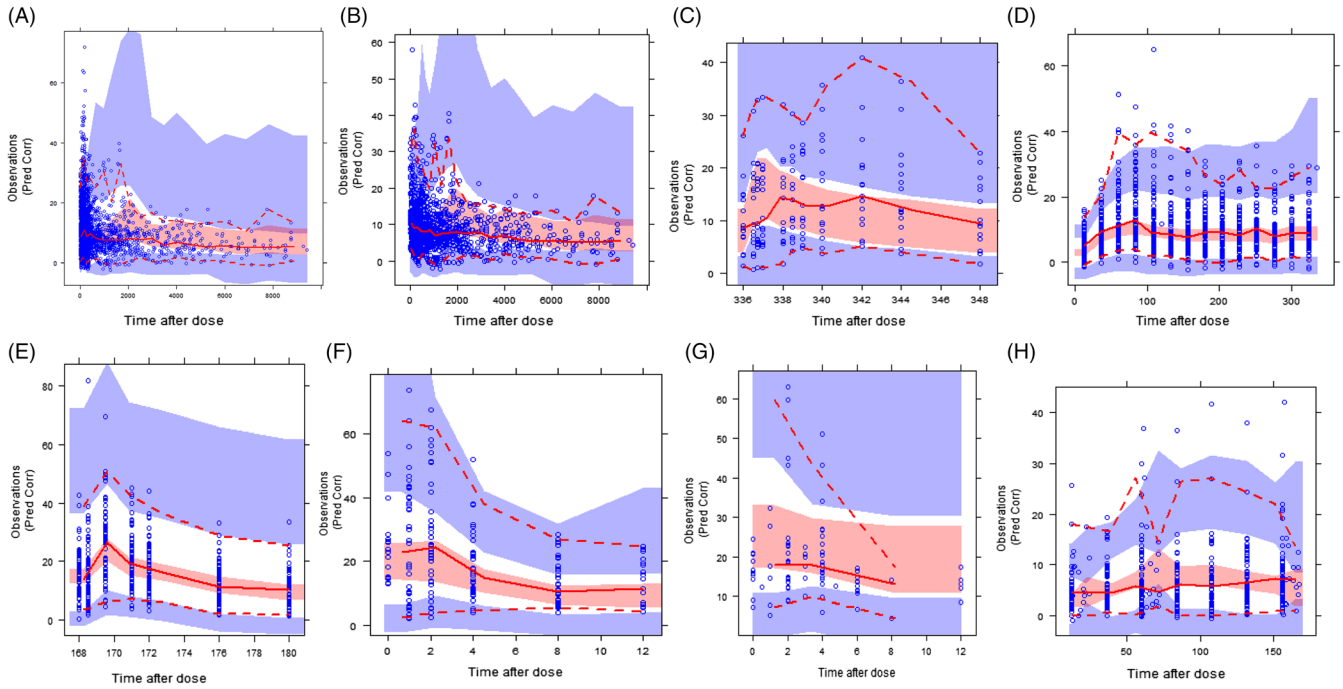

FIGURE 4 Prediction-corrected visual predictive checks (pcVPC) of the model's description of the present data for the final model (A) and stratified by database (B, C, D) for children databases, (E, F, G, H) for adult, (E) for renal transplant patients and (F) for patients on the waiting list for renal transplantation. Red solid line: Median observed concentration; red dashed lines: 5th and 95th percentiles of the observed concentrations. The red and blue shaded areas represent 95% confidence intervals of the prediction percentiles

clearance, whereas body weight influenced both the apparent volume of distribution and the apparent clearance. The final model parameters are presented in Table 3, also including bootstrap results. All parameter values were estimated with good precision as shown by bootstrap results and relative standard error values as estimated by NONMEM. The model goodness-of-fit plots for the final population PK model are shown in Figure 2 and pcVPCs in Figure 3. The final model overall displayed good predictive performances.

As the patients received different doses and the PK of TAC are linear, the VPCs were based on dose-normalized concentrations. As shown in Figure 3, they revealed good agreement between the simulated and observed concentrations at all sampling time points. The

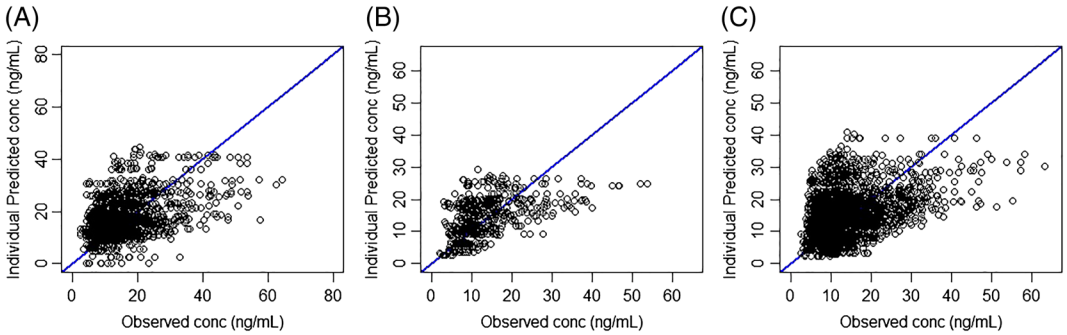

FIGURE 5 Goodness-of-fit plots of the final population pharmacokinetic model validated in 3 external patient-level datasets. (A) Observed *vs* population predicted concentrations for adult kidney transplant; (B) observed *vs* population predicted concentrations for adult heart transplant; (C) observed *vs* population predicted concentrations for adult lung transplant

TABLE 4 Comparison of parameter estimates from the meta-model and from previously published models

Patient population		Predicted by the model	Value found in the literature Mean or median [range]	References
Hepatic transplant patient	**Adults**	**D1 after transplantation:** CL/F = **8.6** L/h V/F = **356** L **Stable period:** CL/F = **17.1** L/h V/F = **356** L	**D1 after transplantation:** CL/F = **8** [7.9–10.5] (L/h) V/F = **742** [205–1201] (L) **Stable period (>1 month):** CL/F = **21.6** [18.3–148.3] (L/h) V/F = **347** [113–1199] (L)	66,67,69-71,74,75,82,83
	Children	**D1 after transplantation:** CL/F = **6.6** L/h ** V/F = **261** L ** **Stable period:** CL/F = **13.0** L/h ** V/F = **261** L **	**D1 after transplantation:** CL/F: **1.9** [0.05–0.94] (L/h) V/F: **273** [199–347] (L) **Mix period:** CL/F = **8.3 [2–17.5]** (L/h) V/F = **274.3 [131–610]** (L)	24,86
Renal transplant patient	**Adults**	CL/F = **22.5** L/h V/F = **356** L	CL/F = **23** [19–35] (L/h) * V/F = **1328** [335–3328] (L) *	40,42,47,56
	Children	CL/F = **17.2** L/h V/F = **261** L	CL/F = **21.3** [12.0–30.6] (L/h)* V/F = **749** [397–1100] (L) *	63,64
Lung transplant patients	**Adults**	CL/F = **22.5** L/h V/F = **356** L	CL/F = **27** [17.5–36.5] (L/h) *,a V/F = **554.5** [444–665] (L) *,a	95,96
Heart transplant patients	**Children**	CL/F = **17.2** L/h V/F = **261** L	CL/F = **9.5** L/h V/F = **216** L	97
Haematopoietic stem cell transplant patients	**Adults**	CL/F = **22.5** L/h V/F = **356** L	CL/F = **18.6** L/h	98b
	Children	CL/F = **17.2** L/h V/F = **261** L	CL/F = **1.15** L/h V/F = **95** L	99
Healthy volunteers	**Adults**	CL/F = **22.5** L/h V/F = **356** L	CL/F = **19** [10.3–27.7] (L/h) V/F = **422.9** [394.5–451.3] (L)	101,102

CL/F, apparent whole blood clearance; V/F: apparent volume of distribution, or the sum of the apparent volume of the central compartment and the peripheral compartment in the 2-compartment models

[a]For patient without cystic fibrosis.

[b]The volume was not estimated.

*Stable transplant patients.

**Mean body weight = 30 kg.

pcVPC gives insight into the robustness of the model in different patient populations and study types.

The normalized prediction distribution errors were distributed normally (Figure 4A) and showed no obvious trend *vs* the time from the start of the treatment (Figure 4B), suggesting that the population PK model established here could properly characterize the TDM data.

The model also displayed good results as regards the external validation as shown by good concordance between observed and predicted concentrations in Figure 5 for the external datasets and as confirmed by overall good concordance between summary level parameters as predicted by the meta-model and as reported in the previous publications (see Table 4).

4 | DISCUSSION

The aim of this study was to develop a generic model for TAC PK modelling using a meta-analysis approach, that could serve as a first step towards a prediction tool to inform PK-based optimal dosing of TAC in different populations and indications. Many PK studies have been carried out with TAC, identifying many parameters that infer on its variability. So far, there is no study in which a population PK model for TAC was built from a dataset including different types of population graft.

As a first step in this study, a search was performed of all the TAC population PK models in solid organ transplantation currently available in the scientific literature. A total of 76 relevant papers were finally retained. They included: 58 models in adults and 18 in children; 36, 31, 2, 2, 1 and 2 models in renal, liver, lung, hematopoietic stem cell and heart transplantation and in healthy volunteers, respectively. Ten of these models concerned early time periods after transplantation (so-called de novo patients), 10 stable patients and 41 models both early and late post-transplantation periods. These very variable settings were considered as a good basis for development of a generic model across populations and types of transplantation. The model developed successfully fitted data collected in adults recipients of kidney, heart and lung transplants in an external validation step, in the early as well as in the stable period after transplantation (the characteristics of these patients are summarized in Table 5) or, for data only available at summary level, the comparison was only limited to distribution of parameters, which might be less specific than the comparison at patient level.

As expected, parameter estimates were quite variable across published studies, even when the populations studied were quite similar. For example, the apparent clearance and total volume of distribution in stable adult liver transplant recipients ranged from 18.3 to 148 L/h and from 113 to 1199 L, respectively.[75,82,83] The differences observed between reported models reflect the sensitivity of model parameters to differences in study designs, such as time after transplantation, number of patients included, number of samples per patient, sampling times, availability and distribution of relevant covariates such as CYP3A5*3/*1 alleles, body weight and drug formulation.[8,11-13,22,24-26,32-106] This clearly shows the need for quantitative characterization of the different drivers of the variability of TAC PK parameters, and integrate them in a single model to be used in different settings to inform optimal dosing.

TABLE 5 Characteristics of the model-building patients

Characteristics		Number (proportions) median [range]	Missing data (%)
Transplanted organ	Liver	201	0%
	Kidney	80 (28.47%)	
Body weight (kg)		50 [5–128]	0%
Height (cm)		75 [46–164]	57%
Body mass index (kg/m^2)		16 [13–34]	57%
Body surface area (m^2)		0.59 [0.47–1.03]	57%
Age (years)		2.3 [0.3–68]	38%
Male/female		104/76	38%
Haematocrit		28 [23–41]	53%
Haemoglobin		10.2 [8.5–12.9]	80%
CYP3A5*1	Carriers	9	93%
	Noncarriers	10	
Plasma albumin (g/dL)		2.9 [1.1–4.1]	86%
Serum albumin (g/dL)		3.5 [1.1–5.9]	86%
INR		1.2 [1.1–2.6]	86%
GGT (UI/L)		59.6 [8.9–753.9]	17%
AST (UI/L)		80.6 [11–3288]	12%
ALT (UI/L)		111 [6–1874]	12%
ALP (UI/L)		77 [20–759]	54%
TBIL (mg/dL)		2.64 [0.3–24.4]	33%
DBIL (mg/dL)		0.8 [0.01–14.8]	31%

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; GGT, γ-glutamyl transferase; HCT, haematocrit; HGB, haemoglobin; INR, international normalized ratio; WBC, white blood cells; TBIL, total bilirubin

As a second step, a model was fitted to data available at the individual level. Previously published in-house data and the final model parameters were used to predict average patients in each of the previously published studies for which only level data were available: this was part of the external validation of the model. The meta-model described in this study is considered as a first step toward a generic model across populations and types of transplantations. This meta-model was intended to characterize the drug-related component and the effects of the covariates commonly collected in the published studies such as bodyweight, time after transplantation, transplanted organ and patient age. The exercise was successfully performed, demonstrating the feasibility of our approach. The model developed successfully fitted data collected in adult recipients of kidney, heart and lung transplants in external validation step, in the early as well as in the stable period after transplantation. If there was a lack of patient-level data for the other transplant population such as liver transplants, we used summary-level data to complete this external validation; however, this comparison may not be a more robust method. The model overall displayed acceptable predictive performances i.e. no

obvious bias was apparent from graphical analysis. However, as expected and as observed in other publications, the overall variability was better predicted for datasets with rich sampling than for those with very sparse sampling (e.g. with only trough blood concentrations available). For the latter, the variability displayed by the model was higher than the observed variability, which very probably reflects study design limitations (only trough concentrations available) rather than model inadequacy. Moreover, there is still quite high unexplained overall variability that may be explained by unexplored but very influent covariates such as CYP3A5 genetic polymorphism or haematocrit level.[13,48,49,59,107-109] The reason why this covariate was not included in this model is that it was not available in the individual-level datasets. The model described is thus the best we could develop with the available data using a data-driven approach. A more mechanistic approach (such as PBPK)[14,109] may help to overcome the limitation of the present model with regards to known clinically relevant covariates

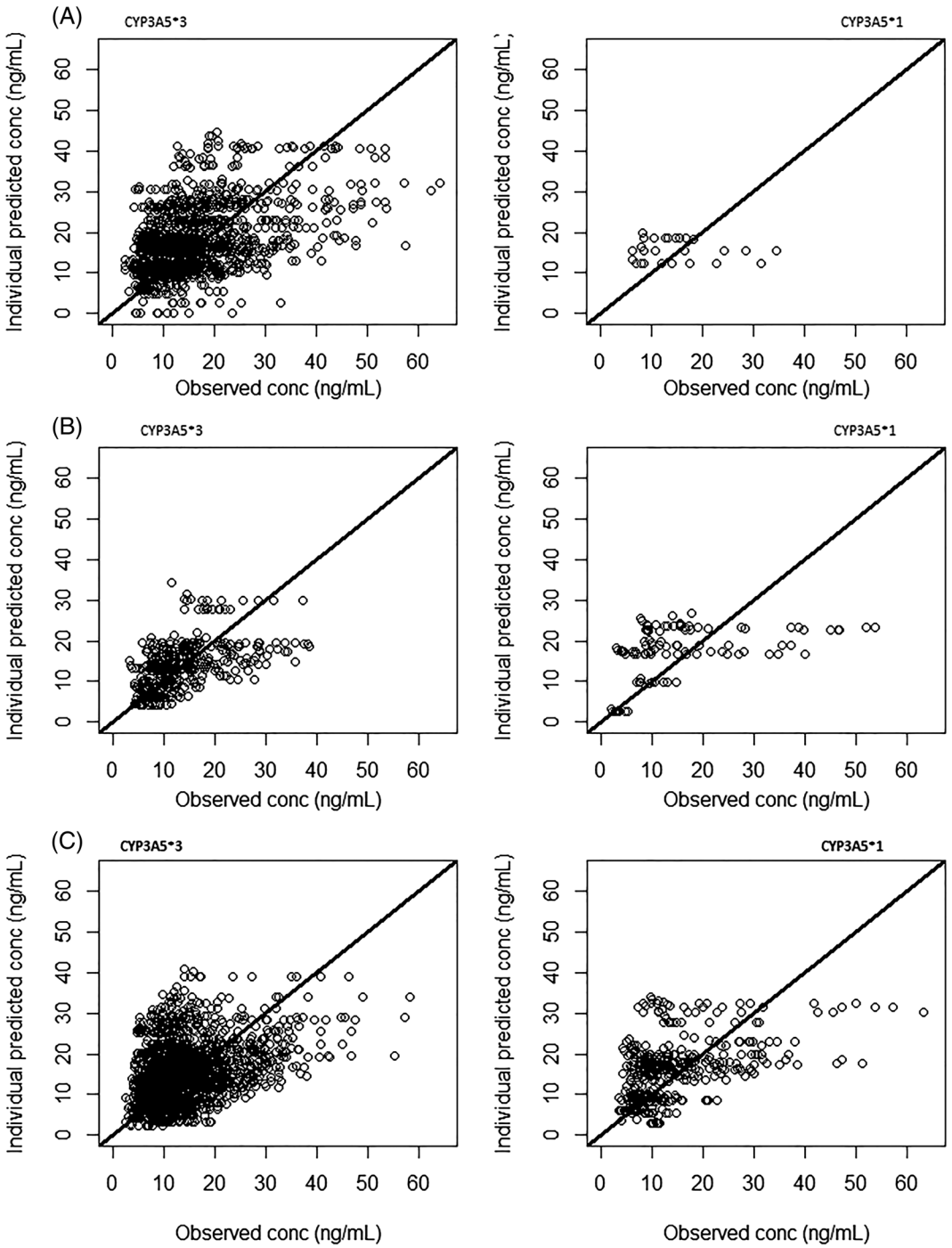

FIGURE 6 Goodness-of-fit plots of the predictions of concentrations for CYP3A5 expressors (CYP3A5*1) and nonexpressors (CYP3A5*3) in the 3 external validation patient-level datasets (A) observed *vs* individual predicted concentrations for adult kidney transplant; (B) observed *vs* individual predicted concentrations for adult heart-transplant; (C) observed *vs* individual predicted concentrations for adult lung transplant

such as genetic polymorphisms. Once the effect of these covariates is well characterized (for example using PBPK modelling), this effect can be included as a fixed parameter in the generic model to fit data from studies where this information is available. Therefore, given the absence of CY3A5 genotype in the final model (not tested as covariate during model development), the present model is not proposed as an alternative of existing CY3A5-based methods/models for individualization of tacrolimus first dose.

The model proposed herein is the first of its kind for TAC in solid organ transplantation mostly because this is the first time, to the best of our knowledge, that data from adults and children in 4 types of transplantation are jointly modelled/predicted for TAC. This opens the door to a common algorithm for dosing optimization of TAC in very different settings.

However, the model still needs optimization before its implementation in routine clinical practice since predictive performances were not completely similar across datasets, which very probably reflects differences in study design and/or in analytical methods used to measure drug concentrations across studies. This can partly explain the large residual random error associated to the meta-model developed (25.4% proportional and 3.1 ng/mL additive). Moreover, some covariates known to influence TAC PK such as the CYP3A5*3/*1 genetic polymorphism were not available in all the datasets and therefore not tested. This constitutes a limitation for this study. Given the known importance of the impact of CYP3A5 genetic polymorphism, we have made the effort to obtain the CYP3A5 polymorphism data at patient-level for the external validation dataset. The results obtained show unbiased predictions of concentrations for expressors and non-expressors (see Figure 6).

The present model is considered as a first step in the development of more robust generic model, which is going consider the other covariates most influencing the pK of TAC such as CYP 3A5 polymorphism, and which can be developed by use of tools such as PBPK modelling. It demonstrates that the common features of different models regarding both drug-related and systems-related components. The discussion has been updated accordingly. PBPK modelling is foreseen as an appropriate method for such robust model development and the results of the present meta-model could be used to feed the PBPK model, in particular if a retrograde approach is to be used.

Finally, TAC is also used in other indications including stem cell transplantation and auto-immune disease. Once refined, we believe that this generic model could also be extended to these other indications.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

T.M.N. performed the analyses and wrote the manuscript. T.T.P.D. performed the analyses. P.M. wrote the manuscript. F.T.M. performed the analyses and wrote the manuscript.

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