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Immunosuppressive therapy is pivotal for sustained allograft and patient survival after renal transplantation. However, optimally balanced immunosuppressive therapy is challenged by between-patient and within-patient pharmacokinetic (PK) variability. This could warrant the application of personalised dosing strategies to optimise individual patient outcomes. Pharmacometrics, the science that investigates the xenobiotic–biotic interplay using computer-aided mathematical modelling, provides options to describe and quantify this PK variability and enables identification of patient characteristics affecting immunosuppressant PK and treatment outcomes. Here, we review and critically appraise the available pharmacometric model-informed dosing solutions for the typical immunosuppressants in modern renal transplantation, to guide their initial and subsequent dosing.

Keywords: Kidney transplantation; Immunosuppressive therapy; Personalised medicine; Model-informed precision dosing; Pharmacometrics; Population pharmacokinetic modelling

Introduction

Immunosuppressive therapy is vital for the prevention of allograft rejection after renal transplantation. Induction therapy is initiated just before transplantation, typically comprising a short course of **basiliximab**, **antithymocyte globulin** (ATG) or **alemtuzumab** (see Glossary).[1] Simultaneously, life-long maintenance immunosuppression is begun, often comprising a combination of a calcineurin inhibitor (**tacrolimus** or cyclosporine), antimetabolite [**mycophenolic acid** (MPA) or azathioprine], with or without prednisolone.[1] Other maintenance regimens can include a mammalian target of rapamycin (mTOR) inhibitor (**everolimus** or **sirolimus**) or **belatacept**.[1]

The delicate balance between over- and underimmunosuppression poses a persistent challenge in the clinical management of renal transplant recipients. Underimmunosuppression can give rise to allograft rejection, whereas overimmunosuppression poses a risk for infection, toxicity, and malignancies.[1] Therefore, appropriate dosing algorithms are key to achieving sustained allograft and patient survival. However, the efficacy and safety of immunosuppressant therapy are challenged by narrow therapeutic indices and considerable between-subject and time-varying within-subject PK variability. This is particularly well established for the calcineurin inhibitors, antimetabolites and mTOR inhibitors.[2,3] These phenomena have driven the development of personalised dosing strategies for these agents, for which most centres rely on classical therapeutic drug monitoring (TDM).[2–4] By contrast, alemtuzumab, basiliximab, ATG, and belatacept are typically applied as a fixed or weight-adjusted dose, owing to broad therapeutic indices, limited PK variability, or sparse evidence to support alternative dosing strategies.[5–7]

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Pharmacometrics encompasses the computer-aided mathematical modelling of the **population PK** and/or pharmacodynamic (PD) characteristics of an agent of interest, provides options to quantify its PK variability, and enables identification of clinical characteristics that affect its PK and treatment outcomes (Box 1).[8] In particular, for the immunosuppressive agents that are typically personalised by TDM, pharmacometrics can allow for clinically feasible area under the concentration–time curve (AUC)-guided monitoring using Bayesian forecasting with limited sampling (Box 1), to yield a more reliable exposure marker compared with the conventionally used trough concentration (C_0). This is especially valuable for agents displaying unreliable C_0–AUC relationships, including MPA,[4] and, to a lesser extent, tacrolimus[3] and everolimus.[2] In addition, pharmacometrics can aid in accelerating the initial dose titration through *a priori* model-informed precision dosing (MIPD) relying on baseline covariate information, and/or increase subsequent C_0 or AUC target attainment through *a posteriori* MIPD based on previous PK assessments and updated covariate information over time (Box 1).[9] Alternatively, pharmacometrics can be used to evaluate dosing algorithms for induction immunosuppressive agents that are applied as a fixed dose and, if necessary, aid to personalise these therapies utilising *a priori* MIPD (Box 1).[9] Herewith, pharmacometrics can aid to achieve optimally balanced immunosuppressive therapy, ensuring efficacious allograft rejection prophylaxis with limited risk for infection, toxicity, and malignancies. Whereas pharmacometrics has reached the clinic in various medical disciplines, its widespread application is hampered by limited clinical modelling expertise, limited model generalisability and harmonisation, and an abiding absence of conclusive evidence that it does in fact improves outcomes.[10] Nevertheless, considerable progress has been made, which provides a valuable source of evidence to aid and inform future clinical pharmacometrics endeavours in the renal transplantation setting.

Here, we identify (Box 2), grade (Box 2, Fig. 1), summarise (Box 2, Figs. 2–4), and critically discuss the available pharmacometric models and pharmacometric model-guided dosing approaches for the immunosuppressive agents that constitute the modern immunosuppressive regimen for the typical adult renal transplant recipient, including tacrolimus, MPA, everolimus, sirolimus, belatacept, alemtuzumab, basiliximab, and ATG, to optimise and guide their initial and subsequent dosing.

Induction immunosuppressive therapy

Alemtuzumab

Alemtuzumab, under an off-label construction, is generally applied as a fixed dose, administered intravenously or subcutaneously just before transplantation and, if divided over two gifts, the day thereafter.[7] No clear exposure–effect relationship has been established for alemtuzumab and its between-subject PK variability in renal transplant recipients is unknown.[7] However, clinical experience indicates considerable between-subject variability in lymphocyte reconstitution after alemtuzumab induction, possibly suggestive for substantial PK variability and an exposure–effect relationship. Pharmacometrics could be used to evaluate the adequacy of the current dosing algorithm for alemtuzumab and, if indicated, aid to personalise alemtuzumab therapy utilising *a priori* MIPD.

No population PK studies for alemtuzumab in renal transplantation were identified. Although perhaps not suitable for unambiguous translation to renal transplantation because of divergent CD52 expression and concomitant immunosuppressive therapy and their interrelation with alemtuzumab PK,[7] evidence from previously published population PK studies in paediatric hematopoietic stem cell transplantation,[11] chronic lymphocytic leukaemia,[12] and multiple sclerosis[13] could inform future model development in renal transplantation. These studies used two-compartmental model structures with linear,[13] nonlinear,[12] or combined linear and nonlinear clearance.[11] Substantial between-subject variability in alemtuzumab clearance (mean, 64.7%; range, 32–104%) and distribution (mean, 57.7%; range, 26–84%) was apparent.[11–13] Of note, these studies described intravenous alemtuzumab PK. However, some centres apply alemtuzumab subcutaneously, which is likely associated with higher PK variability owing to its additional absorption phase. Lymphocyte count[12,13] and body composition[11,13] were found to affect alemtuzumab PK in these populations and, thus, comprise important covariates to also explore in the renal transplantation setting.

Overall, clinical experience and the abovementioned population PK studies bring into question the current fixed-dosing algorithm for alemtuzumab. Hence, a thorough evaluation of alemtuzumab PK in renal transplant recipients is warranted.

Antithymocyte globulin

ATG is typically applied as a weight-adjusted and/or T cell count-guided dose divided over two to five gifts administered just before and on the first days after transplantation, relying on empirical considerations from decades of clinical experience.[6,14] Evidence for its PK variability and exposure–effect relationship is limited.[6,14] However, substantial between-subject variability in immune cell reconstitution after ATG induction is apparent, which has raised concerns about the current dosing approach.[6,14] Pharmacometrics could be used to evaluate the adequacy of the current dosing algorithm for ATG and, if necessary, aid to personalise ATG therapy utilising *a priori* MIPD.

One population PK study was identified for horse-derived ATG (Table S2 in the supplemental information online),[15] and none for rabbit-derived ATG. Ternant et al. included 14 renal transplant recipients who received intravenous horse-derived ATG (Lymphoglobuline®) therapy, administered as an initial infusion of 10 mg/kg/day followed by T cell count-guided subsequent infusions.[15]

Ternant et al. developed a two-compartmental model with first-order elimination and a combined constant and time-varying central distribution volume (Table S3 in the supplemental information online).[15] ATG clearance, intercompartmental clearance, constant and time-varying central distribution volumes, and the peripheral distribution volume were 0.41 l/day, 0.53 l/day, 2.0 l, 538 l/day, and 8.0 l, respectively (Fig. 2, Table 1).[15] Distribution and elimination half-lives were 1.3 days and 25.5 days, respectively. Moderate between-subject variability was identified for clearance (21%), intercompartmental clearance (18%), constant (40%), and time-varying (40%) central distribu-

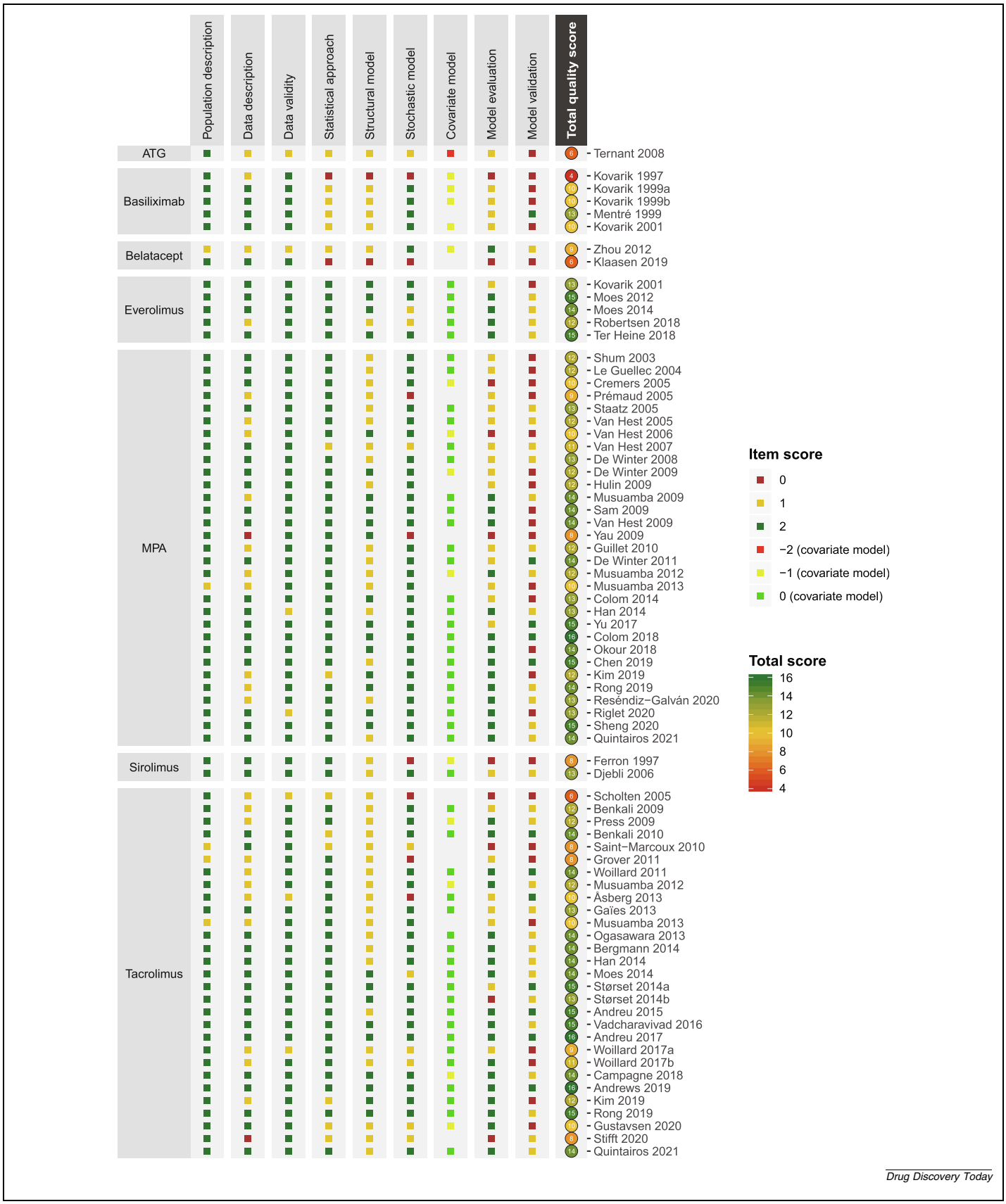

FIGURE 1

Quality assessment summary for all population pharmacokinetic studies.

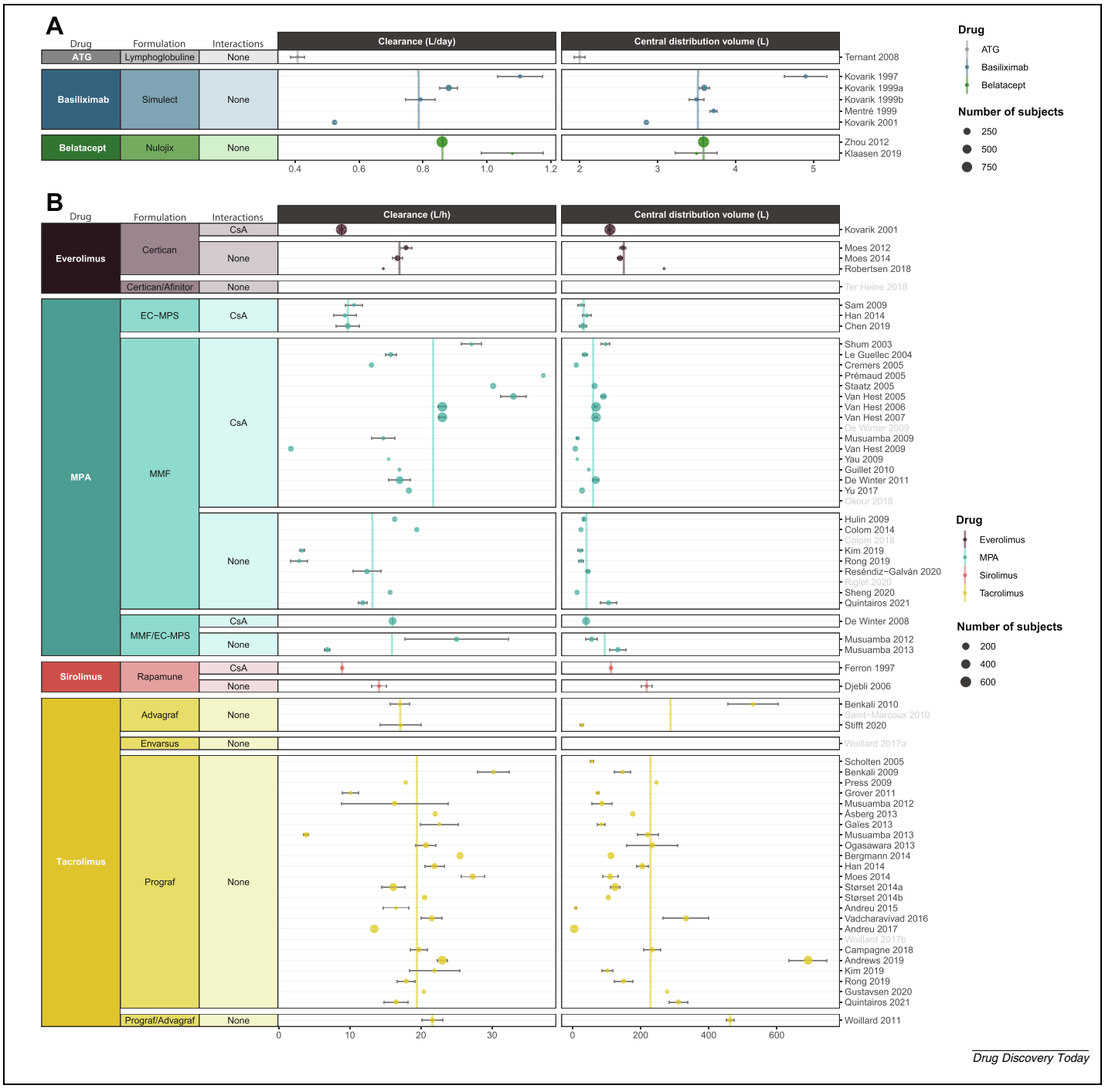

FIGURE 2

Population estimates for clearance and central distribution volume from population pharmacokinetic studies of (a) antithymocyte globulin (ATG), basiliximab, and belatacept, and (b) everolimus, mycophenolic acid (MPA), sirolimus, and tacrolimus. The solid dots and whiskers represent parameter estimates and their standard errors, sized according to the number of subjects in the development cohort. Vertical solid lines indicate the mean parameter estimate for each drug, formulation and interacting co-medication, weighted according to the number of subjects included in each study. Abbreviations: CsA, cyclosporine A; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

tion volumes, peripheral distribution volume (28%), and the distribution (35%) and elimination (29%) half-lives.[15]

Age, total bodyweight, gender and *FCGR3A* genetic variants did not affect ATG pharmacokinetics (Fig. 3).[15]

The study by Ternant et al. was of low quality, with a quality score of 6 (Fig. 1). Important information on the data description, data validity, and the modelling methodology was missing. In addition, no internal or external validation was performed.

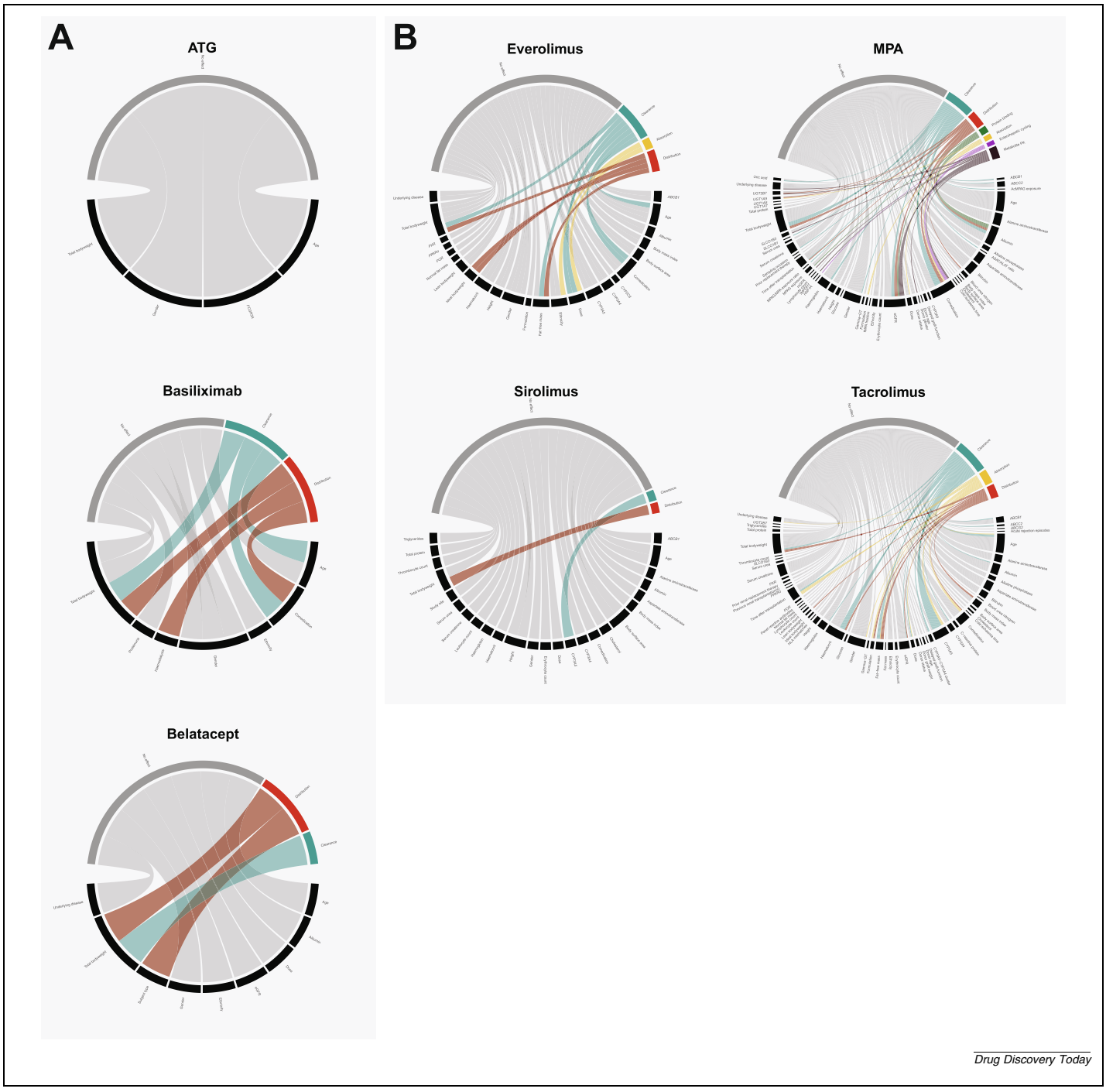

FIGURE 3

Associations between evaluated covariates and model parameters for (a) induction therapies and (b) maintenance therapies. Each line represents a study that evaluated a given covariate. Studies that reported influential covariates are linked to the corresponding model parameter(s) and shaded accordingly. Studies that reported non-influential covariates are designated as 'no effect' and shaded grey. Abbreviations: ATG antithymocyte globulin; MPA, mycophenolic acid.

Thus, evidence for the population PK of ATG in renal transplantation is limited and of low quality. Whereas the available study for horse-derived ATG indicated limited between-subject variability in ATG PK and did not identify any influential covariates, the absence of confirmatory population PK studies warrants further evaluation of horse- and especially rabbit-derived ATG PK in renal transplantation.

Basiliximab

Basiliximab is generally applied as a fixed dose divided over two gifts, administered just before transplantation and 4 days thereafter.[5] It displays limited PK variability, an exposure–effect relationship, and a wide therapeutic index.[16] Although considerable between-subject variability in CD25 receptor saturation duration is observed, this does not affect treatment out-

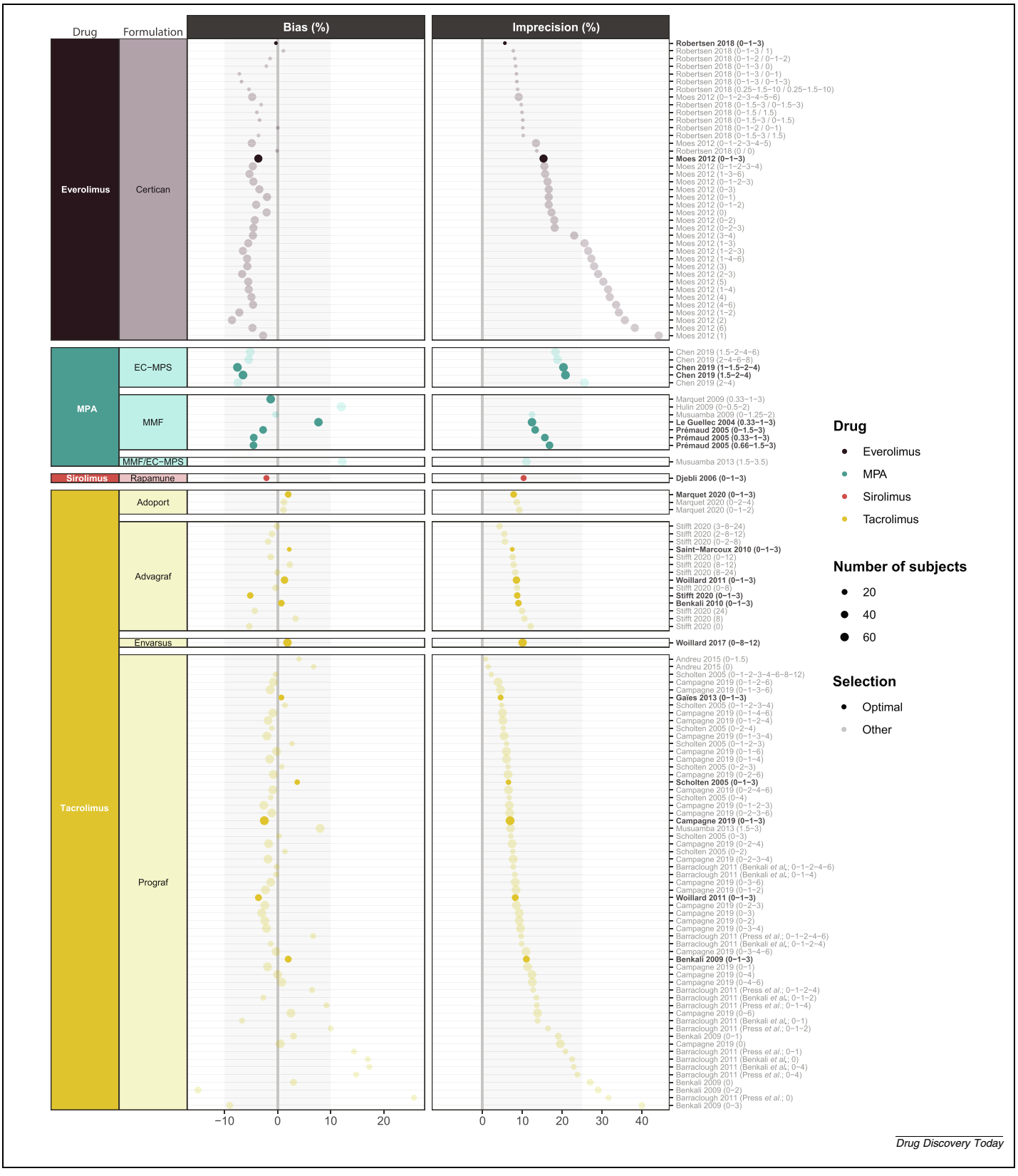

FIGURE 4

Predictive performances in terms of bias [mean percentage prediction error (MPPE)] and imprecision [root mean squared prediction error (RMSE) or mean absolute prediction error (MAPE)] of the Bayesian estimators for each drug formulation, sized according to the number of subjects in the development cohorts, and sorted to ascending imprecision. The grey-shaded areas represent the maximum tolerable bias and imprecision, whereas solid-grey lines represent the lines of equality. The Bayesian estimators displaying the most optimal trade-off between clinical pragmatism and predictive performance are highlighted. Abbreviations: EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

TABLE 1

Clearances and central distribution volumes for all immunosuppressive agents.[a]

Drug	Formulation	Interactions	No. of studies	No. of subjects	Parameter	Mean[b]	Range	Refs
ATG	Lymphoglobuline	None	1	14	CL (l/day)	0.41		15
			1	14	V_c (l)	2.00		15
Basiliximab	Simulect	None	4	336	CL (l/day)	0.79	0.52–1.10	16–18,20
			5	382	V_c (l)	3.52	2.86–4.90	16–20
Belatacept	Nulojix	None	2	929	CL (l/day)	0.86	0.86–1.08	22–23
			2	929	V_c (l)	3.59	3.50–3.59	22–23
Everolimus	Certican	None	3	160	CL (l/h)	17.0	14.7–17.9	26,28–29
			3	160	V_c (l)	151	140–269	26,28–29
		CsA	1	673	CL (l/h)	8.82		27
			1	673	V_c (l)	110		27
MPA	MMF	None	7	385	CL (l/h)	13.2	2.87–19.4	44,50,54–57,59
			7	385	V_c (l)	41.1	13.2–106	44,50,54–57,59
		CsA	14	1892	CL (l/h)	21.7	1.70–37.2	35–42,45–49,51
			13	1847	V_c (l)	60.6	8.00–97.7	35–37,39–42,45–49,51
	MMF/EC-MPS	None	2	130	CL (l/h)	15.9	6.83–25.0	64–65
			2	130	V_c (l)	94.5	56.0–133	64–65
		CsA	1	259	CL (l/h)	16.0		63
			1	259	V_c (l)	40.0		63
	EC-MPS	CsA	3	154	CL (l/h)	9.72	9.30–10.6	60–62
			3	154	V_c (l)	32.7	25.9–42.0	60–62
Sirolimus	Rapamune	None	1	22	CL (l/h)	14.1		72
			1	22	Vc (l)	218		72
		CsA	1	36	CL (l/H)	8.91		71
			1	36	Vc (l)	113		71
Tacrolimus	Advagraf	None	2	56	CL (l/h)	17.1	17.0–17.2	95,97
			2	56	V_c (l)	288	28.2–530	95,97
	Advagraf/Prograf	None	1	49	CL (l/h)	21.6		99
			1	49	V_c (l)	463		99
	Prograf	None	22	2085	CL (l/h)	19.4	3.85–30.2	28,59,64–65,77–89,91–94
			23	2102	V_c (l)	229	5.02–692	28,59,64–65,76–89,91–94

[a] Abbreviations: CL, clearance; CsA, cyclosporine A; V_c, central distribution volume.

[b] Mean parameter estimate, weighted according to the number of subjects included in each population pharmacokinetic study contributing to the calculation of the mean parameter estimate.

comes.[16] Pharmacometrics could be used to re-evaluate the adequacy of the current dosing algorithm for basiliximab and, if deemed necessary, aid to personalise basiliximab therapy utilising *a priori* MIPD.

Five population PK studies were identified for basiliximab (Table S2 in the supplemental information online).[16–20] These included 30–169 renal transplant recipients up to 12 weeks after transplantation.[16–20] These patients received cumulative basiliximab dosages of 40–60 mg, administered as a single infusion before transplantation or as two or three consecutive infusions given just before surgery and 4–10 days thereafter. Concomitant maintenance immunosuppressive therapy comprised cyclosporine and prednisolone, with either azathioprine or mycophenolate mofetil (MMF).

All models comprised two-compartmental structures with first-order elimination (Table S3 in the supplemental information online).[16–20]) Mean weighted basiliximab clearance and central distribution volume were 0.79 l/day (range, 0.52–1.10) and 3.52 l (range, 2.86–4.90), respectively (Fig. 2, Table 1, Box 2. Moderate between-subject variability in basiliximab clearance (mean, 36.7%; range, 34.8–41.4%)[16–19] and distribution (mean, 31.2%; range, 18.6–41.1%)[16–19] were reported.

One study reported basiliximab clearance to decrease with age, and clearance and distribution to increase with total bodyweight, albeit both explained <6% of its between-subject PK variability.[16] Others found no such effects for age[18] or total bodyweight (Fig. 3).[17,18] One study reported haemodialysis to increase distribution,[16] whereas another reported concomitant antimetabolite therapy to decrease basiliximab clearance by 22–51%.[20] Gender,[16–18] ethnicity,[16] or proteinuria[16] did not affect basiliximab PK.

The population PK studies for basiliximab were of low to moderate quality, with quality scores of 4–13 (Fig. 1). In particular, limited model evaluation and validation were conducted. All studies relied solely on goodness-of-fit plots, and only Mentré et al. evaluated their model in an independent cohort.[19]

So, considerable evidence of low to moderate quality is available on the population PK of basiliximab in renal transplantation. These studies indicated limited between-subject variability in basiliximab PK and no particularly influential covariates, supportive of a fixed-dosing strategy. However, they do show shortcomings when held against current standards in pharmacometrics. Considering the vast scale at which basiliximab is applied in renal transplantation, this might justify a re-evaluation.

Maintenance immunosuppressive therapy

Belatacept

Belatacept is typically administered by means of recurrent weight-adjusted intravenous infusions.[21] It displays limited between-subject PK variability, but only limited evidence on its therapeutic index and exposure-effect relationship is available.[21] Pharmacometrics could aid evaluation of the adequacy of the current dosing algorithm and, if necessary, aid personalisation belatacept therapy using *a posteriori* MIPD and/or accelerate its initial dose titration with *a priori* MIPD.

Two population PK models were identified for belatacept (Table S2 in the supplemental information online).[22,23] Zhou et al. developed a model in 924 renal transplant recipients 0–12 months after transplantation,[22] whereas Klaasen et al. included five patients 23–60 months after transplantation.[23] These subjects received recurrent belatacept (Nulojix®) infusions of 5–10 mg/kg bodyweight under concomitant MMF and prednisolone.[22,23]

Zhou et al. developed a two-compartmental model with zero-order intravenous infusion and first-order elimination (Table S3 in the supplemental information online).[22] Klaasen et al. applied a three-compartmental model, but provided only limited information on their modelling methodology.[23] Mean weighted belatacept clearance and central distribution volume were 0.86 l/day (range, 0.86–1.08) and 3.59 l (range, 3.50–3.59), respectively (Fig. 2, Table 1). Between-subject variability for clearance (21.4%) and the central (17.7%) and peripheral (28.8%) distribution volumes was limited.[22]

Belatacept clearance and its central and peripheral distribution volumes increased with baseline total bodyweight, and intercompartmental clearance with baseline and time-varying total bodyweight (Fig. 3).[22] Belatacept dose, age, ethnicity, gender, serum albumin, renal function, and diabetes mellitus did not affect belatacept PK.[22]

The population PK studies for belatacept were of low quality, with quality scores of 6–9 (Fig. 1). In particular, Klaasen et al. provided limited information on their model development, parameterisation, and evaluation.[23] Zhou et al. did adequately evaluate and validate their model internally, but their population and PK data description were limited.[22] Neither study included an external validation.

Thus, limited, low-quality evidence is available on the population PK of belatacept in renal transplantation. Although the findings by Zhou et al. support a weight-adjusted dosing strategy, the abiding absence of confirmatory studies and the report by Klaasen et al. provide limited assurance of the adequacy of this approach. Hence, a call for a thorough evaluation of the current linear weight-adjusted dosing algorithm for belatacept appears justified.

Everolimus

Everolimus displays substantial PK variability, a narrow therapeutic index, and an exposure–effect relationship.[2,24,25] Hence, everolimus therapy is personalised, typically by C_0-guided TDM.[2] The everolimus C_0 is informative for its $AUC_{0–12}$ (R^2 = 0.78),[26] rendering it a reliable marker for exposure assessment. Unfortunately, maintaining everolimus C_0 target attainment can be challenging.[25] In addition, patient subpopulations can display variable C_0–AUC relationships, for whom the C_0 is less informative. This could render patients exposed to subtherapeutic everolimus exposure, which is associated with an increased allograft rejection risk.[24] By contrast, supratherapeutic everolimus exposure can occur, which can give rise to infections and toxicity, including anaemia, thrombocytopenia, hypertriglyceridaemia, hypercholesterolaemia, and non-infectious pneumonia.[2] Pharmacometrics could aid optimisation of everolimus therapy by enabling pragmatic $AUC_{0–12}$ monitoring using Bayesian forecasting with limited sampling, increasing C_0 or $AUC_{0–12}$ target attainment through *a posteriori* MIPD, and/or accelerating its initial dose titration with *a priori* MIPD.

Five population PK studies were identified for everolimus (Table S2 in the supplemental information online).[26–30] These studies included 12–673 renal transplant recipients 0–38 years after transplantation, who received 0.75–3.0 mg everolimus twice daily, with concomitant prednisolone, tacrolimus, or cyclosporine and prednisolone, or MMF and prednisolone.

Everolimus PK was described using two-compartmental[26,28–30] or one-compartmental[27] model structures (Table S3 in the supplemental information online). None of the studies included intravenous data, and all fixed bioavailability to 100%.[26–30] Absorption was described using standard first-order,[27] time-lagged first-order,[26,28] Erlang,[30] or double-gamma absorption.[29] All models included first-order elimination. Mean weighted apparent clearances for everolimus without or with cyclosporine were 17.0 l/h (range, 14.7–17.9) and 8.82 l/h, and central distribution volumes 151 l (range, 140–269) and 110 l, respectively (Fig. 2, Table 1. Everolimus absorption displayed extensive between-subject (mean, 110%; range, 109–111%)[26,28] and within-subject variability (mean, 124%; range, 110–136%).[26,28,30] Between-subject variabilities in clearance (mean, 31.8%; range, 26.2–43.2%)[26–30] and distribution (mean, 35.0%; range, 27.7–40.6%)[26–30] were less pronounced. Of note, Ter Heine et al. used semi-mechanistical modelling, utilising a stirred liver model and erythrocyte-binding kinetics to describe everolimus plasma PK.[30] Alternatively, Robertsen et al. included a peripheral blood mononuclear cell (PBMC) compartment to capture everolimus PBMC PK, relying on paired whole-blood and PBMC observations.[29]

Four studies reported body composition to affect everolimus distribution, using ideal bodyweight,[26,28] total bodyweight,[27] or fat-free mass (Fig. 3).[30] Two studies found clearance to increase with total bodyweight and fat-free mass,[27,30] whereas others observed no such effects. Two studies reported concomitant high-dose prednisolone (>20 mg/day) to yield 31% higher clearance,[30] and 19% lower clearance in patients receiving azithromycin or erythromycin.[27] Of note, the straightforward immunosuppressant regimens in these studies rendered evaluation of influences of cyclosporine impossible. However, cyclosporine affects everolimus PK notoriously.[2] In addition, Kovarik et al. reported everolimus PK to differ between ethnicities, with black subjects showing 20% higher clearance than nonblack subjects, and clearance to decrease with age,[27] but others found no such effects for age[26,28,29] or ethnicity.[26,28] Three studies observed dose-dependent everolimus bioavailability[27] or clearance.[26,28] However, these effects were likely induced by TDM,

in which patients with high clearance receive higher dosages.[26] Most studies found no effects of haematocrit[26,28,29] and/or serum albumin.[26,29] Contrarily, Ter Heine et al. accounted for everolimus erythrocyte-partitioning using a saturable binding model.[30] This model relies on binding constants from *in vitro* experiments and paired observations of everolimus whole-blood concentrations and haematocrit to estimate everolimus plasma PK.[30] Pharmacogenetic variants in *CYP3A5*,[26,28,29] *CYP3A4*,[28,29] *POR*,[29] *ABCB1*,[26,29] *CYP2C8*,[26] *PXR*,[26] and *PPARα*[29] did not affect everolimus PK. Similarly, gender[26–29] and underlying diseases[26,28] were not associated with everolimus PK.

The population PK studies for everolimus were of high quality, with quality scores of 12–15 (Fig. 1). However, model validation was limited, with one study using no validation[27] and the other four studies relying solely on internal validation techniques.[26,28–30] Of note, the model by Ter Heine et al. was evaluated externally in a separate study based on 4123 everolimus concentrations from 173 renal transplant recipients.[31] Zwart et al. demonstrated that, with *a posteriori* Bayesian forecasting relying on one previous C_0 or $AUC_{0–12}$, the model predicted a subsequent C_0 or $AUC_{0–12}$ with biases of <15% and <10% and imprecisions of ≤30% and <15%, respectively.[31]

Moes and Robertsen et al. evaluated **Bayesian estimators** intended for everolimus $AUC_{0–12}$ prediction (Fig. 4; Table S4 in the supplemental information online).[26,29] Moes et al. demonstrated adequate predictive performance (MPPE, –3.63%; RMSE, 15.3%) (Box 2) with a Bayesian estimator based on C_0, and the concentrations at 1 h and 3 h after everolimus intake. Robertsen et al. reported considerably higher predictive performance with this sampling schedule (MPPE, –0.31%; RMSE, 5.60%). Although this schedule showed promising results, its validation was limited. Moes et al. evaluated its predictive performance only in their development cohort, whereas Robertsen et al. used a validation cohort of only two patients.

So, considerable high-quality evidence is available on the population PK of everolimus in renal transplantation. Several *a posteriori* MIPD models are available that rely on previous PK assessments and covariate information, with body composition and concomitant prednisolone therapy being particularly influential factors to consider when individualising everolimus therapy. The model by Ter Heine et al.[30] has undergone thorough external validation and, thus, appears preferable to consider for clinical application, provided additional local validation before implementation. In addition, a few Bayesian estimators for enabling pragmatic everolimus $AUC_{0–12}$ assessment have been developed and have shown promising predictive abilities, but require additional external validation before being considering for routine clinical application. Lastly, alternative everolimus monitoring approaches based on intracellular PK and estimated plasma PK have been proposed, which warrant further investigation.

Mycophenolic acid

MPA displays substantial PK variability, a narrow therapeutic index, and an increasingly clear exposure–effect relationship.[4] This has driven the personalisation of MPA therapy, with the consensus shifting toward AUC-guided TDM.[4,32,33] The MPA C_0 is uninformative for its AUC (R^2 = 0.16–0.45),[34] rendering it an unreliable marker for exposure assessment. Unfortunately, MPA AUC target attainment is often disappointing. This could render patients exposed to subtherapeutic MPA exposure, which is associated with an increased risk for allograft rejection. By contrast, supratherapeutic MPA exposure can occur, which can give rise to infections and toxicity, including gastrointestinal toxicity, haematological toxicity, and malignancies.[33] Pharmacometrics could aid optimisation of MPA therapy by enabling pragmatic AUC monitoring using Bayesian forecasting with limited sampling, increasing AUC target attainment through *a posteriori* MIPD, and/or accelerating its initial dose titration with *a priori* MIPD.

Thirty-one population PK studies were identified for MPA, of which 24 focussed on MMF,[35–59] three on enteric-coated mycophenolate sodium (EC-MPS),[60–62] and three on both formulations (Table S2 in the supplemental information online).[63–65] These studies included 14–468 renal transplant recipients, 0–21 years after transplantation, who received MPA therapy with concomitant cyclosporine, tacrolimus, everolimus, or sirolimus, with or without prednisolone.

MPA PK was modelled using a variety of model structures (Table S3 in the supplemental information online), owing predominantly to its complicated absorption profile, which includes enterohepatic cycling (EHC) of its main metabolite, MPA glucuronide (MPAG). Most studies used standard two-compartmental model structures,[35,36,38–42,44,48,49,51,54,56,59,61–65] with one also proposing a one-compartmental model.[38] Six used two-compartmental models for MPA, combined with metabolite compartments to describe the PK of either MPAG[37,45,47] or MPAG and a second metabolite, MPA acyl-glucuronide (AcMPAG),[50,55,60] coupled to additional intestinal compartments to capture EHC. Given that MPA displays extensive protein binding, six others parameterised their models with the free MPA fraction (fMPA), relying on protein-binding kinetics.[43,46,52,53,57,58] These included two fMPA compartments, combined with a MPAG,[46] EHC,[52] PBMC,[58] or MPAG and EHC[43,57] compartment(s). One study described a one-compartmental fMPA model, coupled to MPAG, AcMPAG, and EHC compartments.[53] MPA/fMPA absorption was modelled using time-lagged first-order,[35,40–43,45,47,49,50,52,54,57,59,61–63] standard first-order,[37,39,51,53,55,56,60,65] time-lagged zero-order,[46] standard zero-order,[36,48,58] Erlang,[64] or single-gamma[38] or double-gamma absorption.[38,44] In most studies, MPA/fMPA elimination was modelled using first-order elimination,[35–38,40–51,53,55–59,61–65] whereas some used zero-order[52,54,60] or bi-exponential elimination.[39] Mean weighted apparent clearances for MMF without or with concomitant cyclosporine were 13.2 l/h (range, 2.87–19.4) and 21.7 l/h (range, 1.70–37.2), and central distribution volumes 41.1 l (range, 13.2–106) and 60.6 l (range, 8.00–97.7), respectively (Fig. 2, Table 1). For EC-MPS, mean weighted apparent clearance and central distribution volume were 9.72 l/h (range, 9.30–10.6) and 32.7 l (range, 25.9–42.0) under concomitant cyclosporine therapy (Fig. 2, Table 1. Between-subject variabilities in MPA/fMPA absorption (mean, 107%; range, 10.9–296%)[36,37,39–44,46,49,51,53,54,57,58,61–65] and distribution (mean, 79.1%; range, 3.2–161%)[35–37,40–46,48–57,59–63,65] were considerable, but moderate for clearance (mean, 48.0%; range, 19.9–246%).[35–37,39–43,46,48–65] Similarly, within-subject variabilities in MPA/fMPA absorption (mean,

110%; range, 60.0–184%)[35,40–42,45,46,48,49,51,58] and distribution (mean, 64.2%; range, 13.7–138%)[35,40–42,45,49,51,52] were considerable, but limited for clearance (mean, 22.4%; range, 3.80–47.0%).[35,39–42,45,46,48,49,51,52,58]

Cyclosporine notoriously inhibits MPAG EHC, yielding markedly higher MPA clearance in patients on concomitant cyclosporine.[32] Most studies reported cyclosporine to affect MPA PK (Fig. 3).[37,39–43,45,46,49,50,52,53,62] Three studies found no significant effect of cyclosporine, possibly owing to limited sample size[60] or the absence of EHC compartments.[51,63] Total bodyweight was used to describe MPA PK in several studies,[36,45,48,51,57,59] but others found no effect of body composition.[35,37,39–42,46,50,52,54–56,58,60–62,64] Consistent with the general consensus that MPA is predominantly excreted renally,[33] renal function as assessed by either estimated or measured GFR was found to affect MPA/fMPA clearance,[40,41,53,58] distribution,[40–42,58] protein binding,[46,52] and/or metabolite PK.[37,43,45,46,50,57,60] However, others found no such effects.[36,39,54–56,59,61,62,64] Clearance increased with serum creatinine in one study,[51] but others found no relation with MPA PK.[35,36,39,54–57,61,62,64] Five studies that modelled fMPA reported protein binding to increase with serum albumin,[43,46,48,57,58] whereas a similar study found no such relationship.[52] In four models without protein binding, serum albumin was reported to reduce MPA clearance or distribution directly,[39–42] but others reported no relationship.[45,50,51,54,60–62] Both studies that evaluated MPA PK across formulations reported divergent absorption between EC-MPS and MMF.[63,64] Evidence for other covariates is limited and, in some cases, contradictory. Pharmacogenetic variation in *UGT1A9* has been related to MPA absorption[61] and distribution,[56] whereas *UGT2B7* variants were reported to affect MPA distribution[51] and its metabolisation to AcMPAG.[55] However, others found no associations between *UGT1A9*,[51] *UGT1A8*,[56] *UGT1A7*,[61] or *UGT2B7*[56,61] variants and MPA PK. One study reported an association between *SLCO1B1* and MPA clearance.[61] Another study found *SLCOB13* to affect MPAG distribution[55], but three others found no association with MPA PK.[56,57,61] One study reported *ABCC2* variants to affect MPA PK,[64] but this was not replicated in five other studies.[50,52,56,58,61] One study reported an association of *ABCB1* with MPA PK,[58] whereas another did not.[64] Albeit physiologically unlikely, one study reported MPAG clearance to vary between genetic variants of *IMPDH1*.[53] These authors also reported *HNF1A* variants to affect MPAG EHC,[53] which has not been replicated. One study reported MPA bioavailability to decrease with increasing dose,[49] but four others reported no dose dependencies in MPA PK.[40–42,59] Most studies found no relation of MPA PK with gender,[35,36,39–42,45,46,48,50–52,54–57,59,61,62,64] haemoglobin,[37,40,45,46,50,52,56,57,61,62] blood urea nitrogen,[51,61,62] uric acid,[51,62] time after transplantation,[35,39,50,52,54,56,57,62] or underlying disease,[39–42,46,59,60] whereas one,[40] two,[41,42] one,[56] one,[56] one,[49] and one[53] studies did report such effects, respectively. Age,[35–37,39–42,45,46,48,50–52,54–62,64] alanine aminotransferase,[36,40–42,45,46,50–52,57,60–62,64] alkaline phosphatase,[41,42,51,61,64] aspartate aminotransferase,[36,40,45,46,50–52,57,60–62,64] bilirubin,[36,40–42,45,46,50–52,60–62,64] cholesterol,[61] cold ischaemia time,[59] delayed graft function,[41,42,46] donor age,[59] donor status,[35,39,56,59] erythrocyte count,[41,42,62] ethnicity,[40–42,45,60,64] gamma-glutamyltransferase,[51,64] glucose,[56] haematocrit,[51,52,55,56,61,62,64] lymphocyte count,[59] pretransplant renal replacement therapy,[59] serum urea,[56,64] or total plasma protein[61,64] did not affect MPA PK.

The population PK studies for MPA were of variable quality, with quality scores of 8–16 (Fig. 1). In particular, model validation and evaluation were limited, with only 12.9% of studies evaluating their model in a validation subgroup or external cohort and only 45.2% of studies providing at least goodness-of-fit plots, simulation-based diagnostics, and parameter estimate precision. De Winter et al. evaluated their model in an external cohort (N = 289) using a goodness-of-fit plot, Colom et al. conducted a fit-for-purpose validation in a small external cohort (N = 39), and Yu and Chen et al. used a data-split to validate their model.[49,51,52,62] Of note, several of these population PK models were evaluated externally in a separate study.[66] Zhang et al. evaluated the models by Cremers et al.,[37] Staatz et al.,[39] De Winter et al.,[43] Colom et al.,[50] Yu et al.,[51] and Colom et al.,[52] based on single-occasion ten-point MPA curves from 45 renal transplant recipients.[66] Substantial variability in the *a priori* predictive performances was apparent, with the models by Cremers et al.[37] and De Winter et al.[43] showing slightly preferable results with biases less than ±20% and imprecisions less than 30%.[66] An additional fit-for-use validation based on recurrent PK assessments would provide important additional information on the *a posteriori* predictive performances of these models.

Le Guellec et al.,[36] Hulin et al.,[44] Musuamba et al.,[45,65] and Chen et al.[62] also evaluated Bayesian estimators intended for MPA $AUC_{0\text{-}12}$ estimation (Fig. 4, Table S4 in the supplemental information online). In addition, Prémaud et al. developed Bayesian estimators for their population PK model,[38] in a separate study based on 10- or 11-point MPA curves from 44 renal transplant recipients.[67] Marquet et al. also applied the model and a selection of Bayesian estimators by Prémaud et al.[38,67] in a separate study based on 894 MPA concentrations from 64 solid organ transplant recipients.[68] Most studies relied on internal validation techniques to evaluate the predictive performance of their Bayesian estimators,[36,45,62,65,67] whereas Hulin et al. did conduct an external validation (N = 73).[44] For MMF, most Bayesian estimators comprised 3-point schedules within 2–3 h post-dose, showing biases of –8.16–12.20%[36,44,45,67,68] and imprecisions of 11.0–20.5%.[36,45,67] For EC-MPS, a 3-point schedule within 4 h post-dose showed adequate performance (MPPE, –6.52%; RMSE, 20.8%), which was further improved with a 4-point schedule up to 6 h post-dose (MPPE, –5.15%; RMSE, 18.3%).[62] Musuamba et al. proposed a 2-point schedule for either MMF or EC-MPS, with 12.2% bias and 11.0% imprecision.[65]

Thus, evidence of variable quality is available for the population PK of MPA. Modelling MPA absorption has posed a persistent challenge and necessitates the use of advanced model structures and extended sampling. Various population PK models intended for MMF and EC-MPS MIPD have been proposed, for which information on concomitant cyclosporine therapy, renal function, and serum albumin was found to be most informative for guiding personalised MPA therapy. Given that only a few of these models have been evaluated externally, their clinical application should be considered carefully and preceded by thorough local validation. For MMF, the model by Colom et al.[52] did show adequate predictive abilities in a small *a posteriori* fit-

for-use validation, rendering this model preferable when considering *a posteriori* MIPD for MMF. Additionally, the models by Cremers et al.[37] and De Winter et al.[43] have been shown to be somewhat preferable when considering strictly *a priori* MIPD to optimise the initial dose titration for MMF. None of the EC-MPS models has been thoroughly validated externally. In addition, several Bayesian estimators to enable clinically feasible MMF or EC-MPS $AUC_{0\text{-}12}$ monitoring have been proposed. Bayesian estimation based on three samples within 3 h after administration rendered adequate estimation reliability for the MMF $AUC_{0\text{-}12}$, whereas 3–4 samples up to 4 h are required for EC-MPS. Of note, clinical application of these Bayesian estimators should be considered carefully, because most authors relied strictly on internal validation techniques.

Sirolimus

Sirolimus displays substantial PK variability, a narrow therapeutic index, and a clear exposure–effect relationship.[2] Hence, sirolimus therapy is personalised, typically using C_0-guided TDM.[2] The sirolimus C_0 is particularly informative for its AUC (R^2 = 0.83),[69] rendering it a reliable marker for exposure assessment. Unfortunately, sirolimus C_0 target attainment is often disappointing.[70] This can result in patients being exposed to subtherapeutic sirolimus exposure, which has been associated with an increased risk for allograft rejection.[2] By contrast, supratherapeutic sirolimus exposure can occur, which is associated with infections and toxicity, including anaemia, leukopenia, thrombocytopenia, hypertriglyceridaemia, and non-infectious pneumonia.[2] Pharmacometrics could aid optimisation of sirolimus therapy by increasing C_0 target attainment through *a posteriori* MIPD, and/or accelerating initial dose titration with *a priori* MIPD.

Two population PK studies were identified for sirolimus (Table S2 in the supplemental information online).[71,72] Ferron et al. included 36 renal transplant recipients, who received 3–15 mg sirolimus/m^2 body surface area once daily, with concomitant cyclosporine and prednisolone with or without azathioprine.[71] Djebli et al. included 22 patients 0–3 months after transplantation who received 10–15 mg sirolimus once daily for the first 10 days after transplantation with subsequent TDM-guided dose adaptation, under concomitant MMF and prednisolone.[72]

Sirolimus PK was described using two-compartmental model structures, using time-lagged first-order[71] or Erlang[72] absorption, and first-order elimination (Table S3 in the supplemental information online). Neither study included intravenous data, and both fixed bioavailability to 100%. Mean weighted apparent clearances for sirolimus without and with concomitant cyclosporine were 17.0 l/h and 8.91 l/h, and central distribution volumes 211 l and 113 l, respectively (Fig. 2, Table 1. Sirolimus displayed moderate between-subject PK variability in absorption (mean, 42.0%; range, 41.3–42.7%), distribution (mean, 43.8%; range, 38.2–49.3%), and clearance (mean, 42.3%; range, 31.8–52.7%).[71,72] Neither model included within-subject PK variability.

Sirolimus intercompartmental clearance and peripheral distribution volume were reported to increase with total bodyweight in one study,[71] but not in the other (Fig. 3).[72] Djebli et al. demonstrated *CYP3A5* variants to explain 8.8% of the between-subject variability in sirolimus clearance, with homozygotes for the non-functional *CYP3A5**3 variant (rs776746) showing 50% lower clearance compared with *CYP3A5* expressors (*CYP3A5**1/*3 or *CYP3A5**1/*1).[72] Genetic polymorphisms in *CYP3A4* and *ABCB1*,[72] age,[71,72] gender,[72] body mass index,[72] body surface area,[71,72] height,[71,72] comedication,[71] sirolimus dose,[71] alanine aminotransferase,[72] aspartate aminotransferase,[72] serum creatinine,[72] serum urea,[72] serum albumin,[72] erythrocyte count,[72] haematocrit,[72] haemoglobin,[72] total protein,[72] total cholesterol,[72] triglycerides,[72] thrombocyte count,[72] or leukocyte count[72] did not affect sirolimus PK. Of note, the straightforward immunosuppressant regimens in these studies rendered evaluation of the influences of cyclosporine impossible. However, cyclosporine affects sirolimus PK notoriously.[2]

The population PK studies for sirolimus were of variable quality, with quality scores of 8–13 (Fig. 1). Model evaluation and validation were limited for the model by Ferron et al. By contrast, Djebli et al. provided parameter estimate precision, goodness-of-fit plots, and internal validation, but conducted no external validation.

Djebli et al. developed Bayesian estimators for sirolimus $AUC_{0\text{-}24}$ estimation (Fig. 4, Table S4 in the supplemental information online). A Bayesian estimator based on C_0 and the concentrations at 1 h and 3 h post-dose showed the best predictive ability, with –2.1% bias and 10.3% imprecision. Of note, these authors relied solely on internal validation techniques for evaluating the predictive performance of their Bayesian estimators.

So, limited evidence of variable quality is available on the population PK of sirolimus in renal transplantation. The available population PK models and a Bayesian estimator based on C_0 and the concentrations at 1 h and 3 h post administration show promising predictive abilities, but additional confirmatory and validation studies are warranted before considering these for routine clinical application.

Tacrolimus

Tacrolimus displays substantial PK variability, a narrow therapeutic index, and a clear exposure–effect relationship.[3] Hence, tacrolimus therapy is personalised, typically using C_0-guided TDM.[3] The tacrolimus C_0 is informative for its AUC (R^2 = 0.63–0.76),[73,74] rendering it a reliable marker for exposure assessment. Unfortunately, tacrolimus C_0 target attainment is often disappointing.[75] In addition, patient subpopulations display variable C_0–AUC relationships, for whom the C_0 is less informative.[3] This can result in patients being exposed to subtherapeutic tacrolimus exposure, which has been associated with an increased risk for allograft rejection.[3] By contrast, supratherapeutic tacrolimus exposure can occur, which is associated with infections and toxicity, including nephrotoxicity, neurotoxicity, cardiovascular toxicity, and malignancies.[3] Pharmacometrics could aid the optimisation of tacrolimus therapy by enabling pragmatic AUC monitoring using Bayesian forecasting with limited sampling, increasing C_0 or AUC target attainment through *a posteriori* MIPD, and/or accelerating its initial dose titration with *a priori* MIPD.

Twenty-nine population PK studies were identified for tacrolimus, of which 24 focussed on Prograf®,[28,55,59,64,65,76–94] three and

one studies on Advagraf®[95–97] and Envarsus®,[98] and one on both Prograf® and Advagraf® (Table S2).[99] These studies included 12–337 renal transplant recipients 0–17 years after transplantation, who received tacrolimus once daily or twice daily with concomitant prednisolone, mycophenolic acid, or both.

Tacrolimus PK was modelled using two-compartmental,[28,55,59,64,65,76–79,81–83,85–87,89,91–95,97,99]) one-compartmental,[84,88,90,96,98] or three-compartmental model structures (Table S3 in the supplemental information online).[80] None of the studies included intravenous data, and bioavailability was fixed to either 100%[55,59,64,65,77,79,81–85,87–99] or 23%.[28,76,78] Alternatively, two studies used a relative bioavailability parameter.[80,86] Absorption was modelled using time-lagged first-order,[28,55,59,64,65,76,79,80,82–86,89,91–94,97] Erlang,[77,81,87,95,99] or standard first-order absorption.[78,88] Three nonparametric studies described absorption using double-gamma distributions.[90,96,98] All models included first-order elimination. Mean weighted apparent tacrolimus clearances for Prograf® and Advagraf® were 19.4 l/h (range, 3.85–30.2) and 17.1 l/h (range, 17.0–17.2), and central distribution volumes of 229 l (range, 5.02–692) and 288 l (range, 28.2–530), respectively (Fig. 2, Table 1. Tacrolimus displayed pronounced between-subject variability in absorption (mean, 62.4%; range, 11.7–199%)[64,65,77,79,81,83,84,87,91,93,95,97,99] and distribution (mean, 59.7%; range, 7.7–157%),[28,55,59,64,65,77–79,81–86,88,91–93,95,97,99] whereas between-subject variability in clearance (mean, 44.1%; range, 19.5–185%)[28,55,59,64,65,77–79,81–89,91–93,95,97,99] was less pronounced. Similarly, within-subject variability in absorption (mean, 60.8%; range, 24–120%)[77,85,86,99] and distribution (mean, 88.5%; range, 68.0–127%)[77,83,99] were substantial, whereas within-subject variability in clearance (mean, 27.8%; range, 13.6–36.8%)[77,83,87,89,92,99] was limited. Of note, Andrews et al. also slightly adjusted their *a posteriori* MIPD model to derive a population PK model intended specifically for *a priori* MIPD.[92] Their *a priori* MIPD model relies on *CYP3A5* and *CYP3A4* genotype information, age, and body surface area to predict the optimal individual tacrolimus starting dose.[92]

The influence of genetic polymorphisms in *CYP3A5* on tacrolimus clearance is particularly well established, with *CYP3A5* nonexpressors, homozygous for the nonfunctional *CYP3A5**3 variant (rs776746), showing lower clearance and ~50% higher dosage requirements compared with *CYP3A5* expressors (*CYP3A5**1/*3 or *CYP3A5**1/*1).[3,100] All studies that evaluated *CYP3A5* rs776746 included it as covariate on clearance (Fig. 3).[28,55,64,78,80,82–85,91,92,95,99] Additionally, *CYP3A4* polymorphisms can explain PK in *CYP3A5* nonexpressors, in whom tacrolimus is predominantly metabolised by CYP3A4.[100] Thus, a *CYP3A5-CYP3A4* cluster approach appears most informative to guide tacrolimus therapy.[3] Three studies found a *CYP3A5-CYP3A4* cluster[89,90] or a combination of *CYP3A5* and *CYP3A4*[92] to best explain between-subject variability in tacrolimus PK, but others reported no added value of including *CYP3A4**22 (rs35599367) in addition to *CYP3A5**3.[28,78,82] Studies on other pharmacogenetic variants have yielded conflicting results. One study showed *ABCB1* variants to affect tacrolimus clearance,[64] whereas six others found no such association.[78,82,84,90–92] Two studies evaluated *ABCC2* variants, with one supporting[82] and one refuting[64] relationships with tacrolimus PK. *POR*,[90,92] *PXR*,[77,78] *PPARα*,[90] or *ABCG2*[82] variants did not affect tacrolimus PK. Prednisolone, a CYP3A inducer, was found to decrease tacrolimus bioavailability or distribution in four studies.[28,78,83,85] However, others found no effects of prednisolone or other comedication on tacrolimus PK.[80,82,84,86,88,91–93,95,99] Of note, none of the studies evaluated influences of strong CYP3A inhibitors, likely because these are generally avoided in patients receiving tacrolimus.[3] Furthermore, tacrolimus clearance gradually decreases over the first weeks after renal transplantation. Studies have partly linked this phenomenon to erythrocyte partitioning by tacrolimus, because the haematocrit drops profoundly during transplantation and gradually returns to baseline over the following weeks. Some authors used empirical approaches to capture this behaviour, including time-varying haematocrit,[64,77,92,99] time after transplantation,[84] or a combination of both[83] as covariates. Others have used mechanistic modelling, incorporating *in vitro* binding constants in an erythrocyte-binding model to describe tacrolimus plasma PK, relying on paired haematocrit and tacrolimus whole-blood observations.[80,85,86,94] These authors also identified independent effects of time after transplantation on tacrolimus bioavailability or absorption.[80,85,86,94] Others found no effect of haematocrit[28,55,78,81,82,84,87,89,91,95,98] and/or time after transplantation.[79,82,88,91–93,98,99] Body composition was used to describe tacrolimus PK in several studies, using either total[59,81,83,91] or lean[92] bodyweight, fat-free mass,[85,86] or a combination of fat-free mass and body mass index.[80,94] However, others found no effect of body composition on tacrolimus PK.[28,55,64,77–79,82,84,87–90,93,95,99] Two studies suggested dose-dependent tacrolimus clearance,[78,79] but this has not been confirmed in other studies.[28,59] As also highlighted by Press et al.,[78] any apparent dose dependency is likely induced by TDM, because subjects with higher tacrolimus clearance receive higher dosages. Most studies reported no influences of age,[28,55,59,64,77–81,83–85,87,90,91,93,95,98,99] although three studies reported tacrolimus clearance to decrease with age[82,89,92] and one found its bioavailability to increase with age.[86] One study reported lower bioavailability in females,[86] but most studies found no influences of gender.[28,55,59,64,77–80,82,84–85,87,89–93,95,99] In addition, one study reported slower tacrolimus absorption in patients with diabetes mellitus,[82] whereas others found no effects of diabetes mellitus or other underlying diseases.[28,59,84,91,92] One study reported higher tacrolimus clearance with increasing serum albumin,[92] but others reported no such association.[78,80–88,91,93] In addition, one study found tacrolimus clearance to decrease with increasing haemoglobin,[88] but this has not been replicated.[77,82,84,87,89,91,95,99] Consistent with the general consensus that tacrolimus is predominantly cleared hepatically, most studies found no effects of renal function as assessed with estimated GFR,[55,59,64,82,83,87–93] albeit one study suggested tacrolimus clearance to decrease with increasing eGFR.[93] One study demonstrated food intake and circadian variation to affect tacrolimus PK.[94] Although consistent with the general consensus on these covariates from nonpharmacometric studies, no other population PK studies evaluated these, likely owing to the clinical impracticality of extended blood collection and dietary restric-

tions. Acute rejection episodes,[86] aspartate aminotransferase,[64,80–87,89,92] alanine aminotransferase,[64,80–82,84–87,89] alkaline phosphatase,[64,80,83,85,86] bilirubin,[80,82–87,92] gamma-glutamyltransferase,[64,83] cholesterol,[78,91] cold ischaemia time,[59] C-reactive protein,[80,86,92] donor age,[59,83] donor status (living/deceased),[59,83,84] graft weight,[84] delayed graft function,[92] ethnicity,[28,64,82,83,91,92] erythrocyte count,[77,87,89] thrombocyte count,[91] leukocyte count,[77,91] lymphocyte count,[59] glucose,[82,91] human leukocyte antigen mismatches,[92] panel reactive antibodies,[92] prior renal transplantation(s),[92] prior renal replacement therapy,[59,92] serum creatinine,[55,64,77,81–86,91–93,95,99] serum urea,[64,83] blood urea nitrogen,[82] total serum protein,[64,84,92] or triglycerides,[91] did not affect tacrolimus PK.

The population PK studies for tacrolimus were of variable quality, with quality scores of 6–16 (Fig. 1). Model validation was limited, with only 24.1% of studies evaluating their models in an external cohort or validation subgroup. Additionally, only 62.1% provided at least goodness-of-fit plots, simulation-based diagnostics, and parameter estimate precision. Åsberg et al., Størset et al., Andreu et al., and Andreu et al.[80,85,87,89] conducted external *a priori* or *a posteriori* fit-for-use validations in 59–91 subjects relying on C_0 assessments exclusively, whereas Andrews et al. externally evaluated the appropriateness of their model across the entire tacrolimus PK profile ($N = 304$).[92] Benkali et al.[95] and Woillard et al.[99] used a data-split, and Benkali et al.[77] and Gaïes et al.[81] relied on resampling techniques for model validation. Of note, several of these models have been evaluated externally in separate studies. Størset et al. confirmed their model appropriateness[85] in a study based on 1999 tacrolimus concentrations from 79 renal transplant recipients.[101] Additionally, Zhao et al. evaluated the models by Press et al.,[78] Grover et al.,[79] Woillard et al.,[99] Musuamba et al.,[64] Gaïes et al.,[81] Ogasawara et al.,[82] Han et al.,[84] Størset et al.,[85] and Andreu et al.,[87] in a study based on 609 C_0 from 52 renal transplant recipients.[102] Evaluation of the *a priori* predictive performances of these models confirmed the need for previous PK information to guide model predictions, with all models showing P_{30} values <50%.[102] With *a posteriori* Bayesian forecasting relying on one previous PK observation, these models showed biases of –58–0% and imprecisions of 22–59%, which improved slightly with the inclusion of one or two additional observations.[102] Overall, the model by Størset et al.[85] showed slightly preferable results.[102] Similarly, Hu et al. evaluated the models by Han et al.[84] and Vadcharavivad et al.,[88] in a study based on 1715 C_0 assessments from 174 renal transplant recipients.[103] With *a posteriori* Bayesian forecasting relying on one previous PK observation, these models showed biases of –43.6 to –9.63% and imprecisions of 28.7–53.4%, which improved slightly with one to three additional observations.[103]

Scholten et al.,[76] Benkali et al.,[77,95] Saint-Marcoux et al.,[96] Woillard et al.,[99] Gaïes et al.,[81] Musuamba et al.,[65] Han et al.,[84] Andreu et al.,[87] and Woillard et al.[98] also developed Bayesian estimators, intended for tacrolimus $AUC_{0–12}$ or $AUC_{0–24}$ estimation (Fig. 4, Table S4). Additionally, Barraclough et al. used the models by Press et al.[78] and Benkali et al.[77] to evaluate Bayesian estimators based on 13-point tacrolimus curves from 20 renal transplant recipients.[104] In addition, Campagne et al. used their model[91] to evaluate Bayesian estimators in a separate study based on 9-point tacrolimus curves from 67 renal transplant recipients.[105] Gustavsen et al. used the model by Åsberg et al.[80] to evaluate Bayesian estimators based on 14-point tacrolimus curves from 27 renal transplant recipients[106] and then applied these with their own model in another study.[94] These authors expressed the predictive performance of their Bayesian estimators using alternative agreement statistics, showing adequate predictive abilities but thwarting a direct comparison with the other studies. Last, Marquet et al. evaluated Bayesian estimators in a study based on 9-point generic tacrolimus (Adoport®) curves from 29 renal transplant recipients,[108] with a nonparametric PK model based on previous models.[96,98] For validation, Scholten et al.[76] and Stifft et al.[97] evaluated the predictive performances of their Bayesian estimators in external cohorts of 26 and 24 subjects, respectively. Benkali et al.,[95] Woillard et al.,[98,99] and Musuamba et al.,[65] applied a data-split, and Benkali et al.[77] and Marquet et al.[108] relied on resampling-based validation techniques. In addition, Op den Buijs et al. externally evaluated the Bayesian estimator by Scholten et al.[76] in a study based on 9-point tacrolimus curves from 37 renal transplant recipients.[107] Overall, a schedule based on C_0 and the concentrations at 1 h and 3 h post-dose appears to comprise an optimal trade-off between predictive performance and clinical feasibility across several studies on Prograf®, Advagraf®, and Adoport®, showing $AUC_{0–12}$ or $AUC_{0–24}$ predictions with −5.2–3.7% bias and 4.5–11% imprecision.[76,77,81,91,95–97,99,108] For Envarsus®, Woillard et al. proposed a schedule based on C_0 and the concentrations at 8 h and 12 h post-dose for $AUC_{0–24}$ prediction, with 0.3–3.4% bias and 6.9–13% imprecision.[98]

Thus, substantial evidence of variable quality is available for the population PK of tacrolimus. Various population PK models intended for *a priori* and *a posteriori* MIPD of Prograf® and, to a lesser extent, Advagraf® have been proposed, whereas evidence for Envarsus® remains limited. Overall, genetic polymorphisms in *CYP3A5* and, to a lesser extent, *CYP3A4* were shown to be particularly informative to guide personalised tacrolimus therapy, whereas body composition, haematocrit, and time after transplantation were also considered important covariates. Given that only a few of these models have been evaluated externally, their clinical application should be considered carefully and preceded by thorough local validation. Overall, the model by Størset et al.[85] has shown particularly consistent predictive abilities for Prograf® across several studies, whereas none of the models for Advagraf® has undergone external validation. Additionally, several Bayesian estimators for pragmatic tacrolimus $AUC_{0–12}$ and $AUC_{0–24}$ estimation have been proposed. For Prograf® and Advagraf®, substantial experience has been established for a schedule based on C_0 and the concentrations at 1 h and 3 h after administration, which can be applied in the clinic after local validation. For Envarsus®, a schedule based on C_0 and the concentrations at 8 h and 12 h after administration has been suggested, but requires additional validation. Last, alternative tacrolimus monitoring strategies have been proposed, using haematocrit-corrected whole-blood PK or estimated plasma PK, which warrant further investigation.

Discussion

The renal transplantation field has experienced a continuing increase in pharmacometrics solutions aimed at optimising the initial and subsequent dosing of immunosuppressive therapy. These efforts have focussed predominantly on the maintenance regimens, in particular tacrolimus and MPA. Population PK models for tacrolimus have been more-or-less straightforward, although recent semi-mechanistical modelling efforts to capture erythrocyte partitioning and models incorporating pharmacogenetic information have been particularly successful. By contrast, the complex absorption profile of MPA has driven the development of advanced multicompartmental models, with various success in characterising MPA PK. Less substantial evidence is available for everolimus, sirolimus, and belatacept. For induction therapies, pharmacometric studies have supported fixed-dosing approaches for basiliximab, whereas the evidence is limited for ATG and alemtuzumab. Of note, large variability in model quality was discernible across all agents. Model evaluation and particularly model validation were superficial or lacking for most models, with only a handful of models and Bayesian estimators for tacrolimus and MPA, and, to a lesser extent, everolimus, showing persistent predictive abilities across several studies. Whereas model validation might have limited added value for exploratory population PK analyses, it comprises a pivotal element for MIPD implementation. Specifically, model appropriateness and its *a priori* and/or *a posteriori* predictive performance should be evaluated in a representative independent cohort.[9] Moreover, it is advisable to conduct such a fit-for-purpose validation locally and adjust the model parameters accordingly before model implementation, because model performance can vary across institutions.[9] In addition, model validation can be applied in an iterative fashion, evaluating and updating the model over time as more local PK information becomes available.[9]

Although numerous population PK models are available, the clinical application of pharmacometrics remains limited. One factor curtailing its clinical application is the abiding absence of conclusive evidence that computer-aided immunosuppressant dosing does yield improved target attainment, and ultimately, superior clinical outcomes compared with conventional TDM, albeit efforts to provide this evidence have yielded encouraging results regarding the former.[75,109–111] In this context, results from an online pharmacometric tool have been particularly reassuring, demonstrating improved tacrolimus target attainment with computer-aided dosing.[74,112] In addition, model development is not seldomly conducted in a predominantly self-contained manner, with little attention for previous evidence and limited efforts at demonstrating model validity and clinical utility. Lastly, clinical implementation can be hampered by the absence of adequate supportive platforms. Routine clinical pharmacometrics demands high-throughput capacity with short turnaround times, necessitating application in automated, highly standardised, and end user-friendly IT solutions, integrated with local electronic medical record (EMR) software to ensure updated PK and covariate information. Regarding the latter aspect, Kantasiripitak et al. identified 28 IT solutions that can be used for MIPD purposes.[113] These authors evaluated ten of these MIPD tools on eight categories: user-friendliness and utilisation, user support, computational aspects, population models, quality and validation, output and report generation, privacy and data security, and costs. Overall, all tools performed well on all aspects, with mean category scores ranging from 7.2 to 8.5 out of a maximal score of 10.[113] When ranked according to the percentage of their total fulfilment of all categories, the following descending order of tool performances was established: InsightRX Nova (83%), MwPharm++ (82%), DoseMeRx (78%), PrecisePK (77%), ID-ODS (74%), AutoKinetics (68%), NextDose (66%), Tucuxi (57%), TDMx (56%), and BestDose (54%).[113] Of these, InsightRx Nova, DoseMeRx, and NextDose offer ready-to-use immunosuppressive drug modules for clinical application. However, considerations for MIPD tool selection might vary among centres, depending on the local situation and intended MIPD application.

The ultimate success of a pharmacometrics approach in optimising treatment outcomes also depends on the informativeness of the applied markers. Historically, the C_0 has provided a convenient marker for tacrolimus, everolimus, and sirolimus monitoring, but encompasses only a surrogate measure for their AUC. Bayesian estimators have proven helpful to enable clinically feasible AUC-guided TDM, which could provide a more informative marker, especially for those patient subpopulations that display unreliable or highly variable C_0–AUC relationships. Particularly for patients taking combination immunosuppressive regimens, blood draw alignment across Bayesian estimators might then help to minimise sampling intensity for simultaneous immunosuppressant monitoring. Moreover, combining synchronized Bayesian estimators with remote blood collection by means of microsampling could allow for more frequent and more flexible AUC-based monitoring with minimal patient discomfort. Dried blood spots and volumetric absorptive microsampling tips have gained particular interest as alternative sampling matrices for enabling remote immunosuppressant monitoring.[3,4] In this context, development of diagnostic tools to identify those patients who would benefit most from AUC-based MIPD over standard C_0-based MIPD might also help to achieve more efficient monitoring strategies. Application of alternative markers could also aid in optimising patient outcomes. Whereas computer-aided dosing likely aids to increase C_0 or AUC target attainment, its added value on treatment outcomes remains limited when patients with on-target PK exposure might still develop allograft rejection or toxicity. Efforts to find more informative markers have focussed mainly on intracellular immunosuppressant PK assessment and pharmacodynamic monitoring, as alternatives to conventional whole blood or plasma PK assessment.[3,4,24] In addition, the combined PK exposure of combination immunosuppressive treatment regimens is likely more informative for treatment outcome. However, because widespread routine application of intracellular PK[114] and pharmacodynamic monitoring remain distant prospects, monitoring estimated plasma PK might constitute the most promising approach to further optimise immunosuppressive therapy currently available. Nevertheless, these advances require further investigation, validation, and evidence that they

do yield a more informative marker for outcomes after renal transplantation.

Although beyond the scope of this review, it is important to acknowledge that evidence from similar populations or related modelling approaches is also available. These include a substantial number of population PK models for tacrolimus and sirolimus that have been developed based on C_0 assessments, exclusively. Whereas such one-compartmental models can be used for *a priori* and *a posteriori* MIPD for these agents, their application is strictly limited to C_0-based approaches. Similarly, some authors have proposed two-compartmental models for tacrolimus, sirolimus, and MPA, using solely C_0 PK assessments with fixation of all absorption-related parameters to literature values. Although this might pose a justifiable strategy for some centres, thorough local validation across the entire PK profile is advisable before considering these models for routine AUC-based MIPD. By contrast, population PK models that have been developed using richly sampled PK curves covering the entire dosing interval could be used for *a priori* and *a posteriori* C_0- and AUC-based MIPD, allowing for more versatile and more widespread application. Additional evidence from other populations and modelling approaches includes population PK models in paediatric renal transplantation, population PK metamodels across transplantation populations,[115–117] more complex physiology-based PK approaches,[118,119] and even artificial intelligence solutions.[120,121]

Concluding remarks

In conclusion, pharmacometrics has gradually evolved from a theoretical promise to a clinically feasible means of personalising and optimising immunosuppressive therapy in renal transplantation. Building on the available evidence, developing harmonised models, finding informative and easily accessible markers, and realising reliable, user-friendly supportive platforms comprise key factors to further aid its implementation in routine clinical care.

Box 1 . Population PK modelling.**Model components.**

Population PK models comprise mathematical components, including a structural, stochastic, and often a covariate model. The structural model describes the course of a dependent variable over an independent variable, usually a drug concentration over time. Dependent of its structural design, models can include various flow parameters, volume parameters, and constants. Together, these capture drug absorption, distribution, metabolism, and/or elimination. Population PK models incorporate 'fixed' and 'random' effects, which are defined in the stochastic model.

The fixed effects, or 'thetas', describe the population parameters, defining the typical drug behaviour in the population. The random effects, or 'etas', account for the divergence of individual parameter values from the typical population values. The variance of eta, or 'omega', summarises the between- and within-subject variability for each parameter across the population. The stochastic model describes the residual unexplained variability, or 'epsilon', which captures the differences between the observed and model-predicted data and is summarised by its variance, 'sigma'. Last, population PK models can include a covariate model to investigate whether certain patient characteristics explain PK variability.

Model development, evaluation, and validation.

Population PK models are typically developed using nonlinear mixed-effects modelling software. It encompasses finding the best fit for the concentration–time data, using a stepwise modelling approach. The design and selection of candidate models are typically guided by previous evidence, biological plausibility, model stability, predictive performance, and comparative statistics. Various model evaluation techniques are available, of which goodness-of-fit plots and visual predictive checks (VPCs) are most commonly applied. Goodness-of-fit plots are generally used to compare model predictions and observations, and inspect trends in prediction errors. VPCs comprise a graphical depiction of model-simulated concentration–time data plotted over the observed concentration–time data, allowing for visual inspection of their concordance. Ultimately, internal and external evaluation techniques can be used to demonstrate model validity. Internal validation techniques, aimed specifically at evaluating the robustness of model parameters, typically rely on resampling of the concentration–time data of the development cohort. By contrast, external validation techniques aim to establish the predictive ability and generalisability of the model, relying on concentration–time data from an independent cohort.

Model application.

Population PK models can serve various clinical purposes. Exploratory population PK analyses are often aimed at describing the PK characteristics of an agent of interest, quantifying its PK variability, and informing dosing strategies. By contrast, population PK models can be used for MIPD purposes, aimed at guiding individual dosing decisions. Population PK models aimed at *a priori* MIPD can guide dosing decision for single-dosed drugs or initial doses of chronically prescribed agents, relying strictly on baseline clinical information. Alternatively, population PK models intended for *a posteriori* MIPD can guide dosing decisions for recurrent dosing occasions, relying on collected PK and covariate information from previous dosing instances. In addition, population PK models can be used to enable pragmatic AUC-based exposure assessment, relying on a limited number of PK observations early after drug intake and *a posteriori* Bayesian forecasting to predict the full AUC.

Box 2 . Methods.**Literature search.**

The PubMed, Embase, Web of Science, Cochrane Library and Emcare databases were explored from inception up to and including March 31, 2021. The search queries included 'alemtuzumab', 'antithymocyte globulin', 'basiliximab', 'belatacept', 'everolimus', 'mycophenolate', 'sirolimus', 'tacrolimus', 'pharmacometrics', 'pharmacokinetics', 'nonlinear mixed-effects modelling', 'Bayesian estimation', and related terms (Supporting Information S1 in the supplemental information online). Initial article selection was performed based on title and abstract, and final selection by full-text assessment. English primary articles on the development or validation of population PK models with or without Bayesian estimators for the selected immunosuppressants in adult renal transplant recipients were eligible for inclusion. Any non-English articles, articles on paediatric renal transplantation, or other fields of transplantation or nonpharmacometric approaches, were excluded. Additionally, articles describing the development or validation of population PK models using exclusively C_0 were excluded. Reference lists of selected articles were screened for additional articles, and a selection of miscellaneous articles was added to supply background information. The search generated 684 unique articles, of which 88 were included in this review (Fig. S1 in the supplemental information online).

Quality assessment.

Population PK study quality was assessed using a systematic approach. Studies were evaluated on nine quality items: 'population description', 'data description', 'data validity', 'statistical approach', 'structural model', 'stochastic model', 'covariate model', 'model evaluation', and 'model validation', as derived from the European Medicines Agency (EMA) guideline on reporting the results of population PK analyses.[122] The EMA requirements for each item were translated into a scoring algorithm (Table S1 in the supplemental information online). The resultant score ranges from 0 to 16, providing an indication of the concordance of the study with 'good pharmacometric modelling practices' (Fig. 1).

Data extraction.

Information was extracted systematically. For study characteristics, the drug, formulation, dose, concomitant immunosuppressive therapy, sample size, number of PK observations, sampling schedule, bioanalytical assay(s), and post-transplant time were collected. For models, the software, model structure, parameter estimates, evaluated covariates, and model evaluation techniques were collected. For Bayesian estimators, sampling schemes, reference exposure measures, prediction bias (MPPE or MPE), prediction imprecision (root mean squared prediction error; RMSE, or mean absolute prediction error; MAPE), Pearson's correlation coefficient (R^2), percentage of predictions exceeding ±15–20% (P_{15}–P_{20}) of the reference exposure, and evaluation technique(s) were collected.

Statistics and software.

To compare parameter estimates across studies, clearance and central distribution volume were selected as primary PK model parameters. These were standardised and converted to means, weighted according to the development cohort sample size. If possible, uncertainty measures were standardised to standard errors. Stratification to formulation and concomitant cyclosporine was applied, because these can affect immunosuppressant PK. Owing to model heterogeneity across studies, parameters other than clearances and central distribution volumes are referred to as nonweighted means and/or ranges. Additionally, we compared Bayesian estimator predictive performances. The MPPE and RMSE (or MAPE) were selected for prediction bias and imprecision, respectively. The maximal tolerable bias and imprecision were set at ±10% and 25%, respectively. Visualisation and statistics were performed in R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio 1.2.5019 (RStudio Inc., Boston, USA).

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Declarations of interest

The authors declare no conflicts of interests in relation to this work.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2021.06.001.

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Glossary

Alemtuzumab: a humanised monoclonal antibody targeting CD52 on lymphocytes, yielding profound immune cell depletion. Alemtuzumab is applied as induction and anti-rejection immunosuppressive therapy in renal transplantation by means of an off-label construction.

Antithymocyte globulin: rabbit- or horse-derived polyclonal antilymphocyte antibodies, yielding profound immune cell depletion upon administration. Antithymocyte globulin is applied as induction and antirejection immunosuppressive therapy in renal transplantation.

Basiliximab: a humanised monoclonal antibody targeted at CD25 on the interleukin-2 (IL-2) receptor on T cell progenitors, preventing IL-2-induced T cell proliferation. Basiliximab is applied as induction immunosuppressive therapy in renal transplantation.

Bayesian estimator: a certain combination of consecutive PK observations used as input in a population PK model to predict a full area under the concentration–time curve, the gold standard marker for the total amount of drug in the body.

Belatacept: a fusion protein of human cytotoxic T lymphocyte-associated protein 4 extracellular domain and a modified human immunoglobulin 1 Fc, targeted at CD80/CD86 on antigen-presenting cells to block T cell activation. Belatacept is applied as maintenance immunosuppressive therapy in renal transplantation.

Everolimus: a mTOR inhibitor, yielding cell cycle arrest resulting in the inhibition of lymphocyte proliferation. Everolimus is applied as maintenance immunosuppressive therapy in renal transplantation.

Mycophenolic acid (MPA): an inhibitor of inosine-5-monophosphate dehydrogenase type 2, which converts inosine monophosphate to guanosine monophosphate in lymphocytes, inhibiting the formation of key factors for DNA and RNA synthesis. MPA is applied as maintenance immunosuppressive therapy in renal transplantation.

Pharmacometrics: the science of describing the xenobiotic–biotic interplay in its broadest sense using computer-aided mathematical modelling.

Population pharmacokinetic (PK) model: a mathematical model which describes the typical PK behaviour of a drug in a specific population, and characterises the between-subject and within-subject variability in that PK behaviour across the population.

Sirolimus: a mTOR inhibitor, yielding cell cycle arrest resulting in the inhibition of lymphocyte proliferation. Sirolimus is applied as maintenance immunosuppressive therapy in renal transplantation.

Tacrolimus: a calcineurin inhibitor interacting with transcription factor dephosphorylation, inhibiting the production of key factors for T helper cell activation and proliferation. Tacrolimus is applied as maintenance immunosuppressive therapy in renal transplantation.