A Call for Advanced Pharmacokinetic and Pharmacodynamic Monitoring to Guide Calcineurin Inhibitor Dosing in Renal Transplant Recipients

Huub H. van Rossum,1,2 Rogier R. Press,2,3 Jan den Hartigh,3 and Johan W. de Fijter2*

The calcineurin inhibitors (CNIs)4 cyclosporin A and, later, tacrolimus, have revolutionized the results of organ transplantation, leading to current acute-rejection rates of 10%–20% (1). Despite substantial reductions in acute-rejection rates, however, late graft loss remains a critical issue after renal transplantation, with a progressive decline in long-term graft survival (2). The 2 major causes of graft loss are death with a functioning graft and chronic allograft nephropathy. The latter has long been considered a late-onset condition, but recent studies have shown a high prevalence of interstitial fibrosis and tubular atrophy at a median of 3 months after transplantation (3). Protocol biopsies obtained 2 years after transplantation from grafts with stable renal function have identified previous acute-rejection episodes and acute CNI-related nephrotoxicity as the most important predictors of chronic allograft nephropathy (4). Donor and recipient characteristics, as well as subclinical rejection (SCR), also play a role in disease progression.

SCR is found on protocol biopsy and is defined as tubulointerstitial infiltrates of the renal allograft without functional deterioration. In daily practice, renal function is evaluated by measuring the serum creatinine concentration, but for several reasons this variable is not an adequate marker of the glomerular filtration rate (GFR) (5). The relationship between the serum creatinine concentration and the GFR is not linear, and at a certain part of the curve only a small increment in the creatinine concentration is associated with a marked decrease in the GFR. Moreover, SCR is a patchy process in which uninvolved nephrons can hyperfiltrate and thereby maintain a typical serum creatinine concentration.

Although the causal relationship and clinical consequences of SCR are still under debate, prevention of late acute rejection after empirical reduction in the CNI dose appears to be critical (6). Recently, CNI minimization has been advocated as the preferred approach early after renal transplantation (7). Of note is that inadequate (minimal) initial dosing and inappropriate empirical tapering increase the risk of (subclinical) acute-rejection episodes and late rejection, respectively. Early minimization strategies would benefit the most from a predictive strategy instead of the current reactive strategy of monitoring drug concentration. CNI exposure could be determined during the pretransplantation workup, but a patient undergoing maintenance dialysis is different in many aspects from the early posttransplantation phase, including differences in serum albumin, hematocrit, and comedinations. Genotyping patients on the renal transplantation waiting list has the potential to improve initial CNI dosing. A potential marker for tacrolimus exposure is a polymorphism in the gene (CYP3A5,5 cytochrome P450, family 3, subfamily A, polypeptide 5) that encodes the metabolic enzyme cytochrome P450 3A5 3A5. One of alleles (*1) has been associated with increased tacrolimus clearance. Additional genetic variability could originate in the ABCB1 [ATP-binding cassette, sub-family B (MDR/TAP), member 1] gene, which encodes the efflux transporter P-glycoprotein and occurs on membranes of intestine, liver, kidney, and T cells. Variation in genes coding for the target protein calcineurin or the immunophilins may further explain the observed differences in susceptibility to CNIs (8).

We assume that drug-induced nephrotoxicity correlates best with the exposure of the amount of drug to the kidney, which in turn is determined by the area under the concentration-over-time curve (AUC) for the CNI concentration in blood. Both cyclosporin A

1 Departments of Clinical Chemistry, 2 Nephrology, and 3 Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands.
2 Address correspondence to this author at: Department of Nephrology, C3-P22, Leiden University Medical Center, Leiden, the Netherlands. E-mail jwdefijter@lumc.nl.
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5 Nonstandard abbreviations: CNI, calcineurin inhibitor; SCR, subclinical rejection; GFR, glomerular filtration rate; AUC, area under the concentration-over-time curve; TDM, therapeutic drug monitoring; C0, trough concentration; LC-MS/MS, liquid chromatography–tandem mass spectroscopy.

5 Human genes: CYP3A5, cytochrome P450 P450, family 3, subfamily A, polypeptide 5; ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1.
and tacrolimus are known to have poor and variable absorption and elimination. These characteristics, in conjunction with the narrow therapeutic window for these drugs, necessitate therapeutic drug monitoring (TDM). Although the correlation between the trough concentration (C₀) and its efficacy in preventing acute rejection or chronic nephrotoxicity is poor or nonexistent, this parameter is still used almost universally to guide CNI dosing (9).

Even when CNI C₀ concentrations are maintained within the “therapeutic range,” a large group of patients still experience acute rejection episodes, SCR, and/or nephrotoxicity, plus BK virus–associated nephropathy (5).

In general, a considerable range in AUC(0–12 h) values can be expected at a single C₀ (Fig. 1), which of course is augmented by the range of C₀s thought to be acceptable in clinical practice. Fig. 1A shows data, generated with the AxSYM fluorescence polarization immunoassay (Abbott Laboratories), for 128 renal transplant recipients in the first year after transplantation, with multiple comparisons per patient. The correlation coefficient is 0.87, but at a target C₀ interval of 150–250 µg/L, the AUC (0–12 h) ranges from 3000 to 9000 µg·h·L⁻¹, a 3-fold difference. Fig. 1B shows data, generated with Abbott Laboratories’ IMx microparticle enzyme immunoassay tacrolimus II (MEIA II) assay, for 33 renal transplant recipients on tacrolimus therapy. The correlation coefficient is 0.90 this time, but at a target interval of 5–10 µg/L, the AUC(0–12 h) values again show a 3-fold range (75–225 µg·h·L⁻¹).

Stated another way, at an AUC(0–12 h) target of 210 µg·h·L⁻¹ with a 10% range, the tacrolimus C₀ ranges from 4 to 20 µg/L, a 5-fold difference. Patients with low systemic CNI exposure compared with their C₀s could be expected to have an increased risk of developing acute, subclinical, and/or chronic rejection, whereas patients with a high AUC/C₀ ratio are likely to be overdosed, with an enhanced risk of opportunistic infections, lymphoproliferative disorders, and cancer (1). Several studies have conclusively documented that estimates of systemic drug exposure in terms of the AUC, and the absorption profile in particular, correlate better with clinical events (acute rejections, nephrotoxicity) than do C₀s (9). Remarkably, AUC monitoring has not gained much popularity, largely because of inconvenience and cost considerations.

A first prerequisite to overcome the reluctance toward AUC monitoring is a simple and flexible strategy to estimate systemic drug exposure, because “full” 12-h AUC sampling is not a realistic option in daily practice. Given that the highest between-patient variation can be identified in the first 4-h postdose, a limited sampling strategy that includes the C₀ and 1 or 2 additional samples collected within the first 4-h postdose can be used to adequately estimate systemic exposure. This so-called mini-AUC (C₀–C₂–C₃) also allows the identification of patients with typical, low, or slow absorption profiles (10, 11). The major disadvantage of a limited sampling strategy that uses a regression equation is the imperative of accurately timing blood samples. When a sample is collected 15 min later than the predefined time point, the regression equation is no longer valid. On the other hand, population pharmacokinetics including Bayesian forecasting is a TDM tool that allows...
a more-variable timing of blood sampling. Prior information consisting of disease population–specific pharmacokinetic parameters (such as drug clearance and volume of distribution) and their variation is combined with patient-specific variables (e.g., body weight, hematocrit, serum albumin concentration) to increase the likelihood of adequately predicting an individual’s drug clearance—and hence exposure—achieved with a specific dose. Optimally, these techniques also inform the clinician of the next appropriate dose to maintain or reach the desired drug exposure. This approach has been validated and successfully applied in a prospective clinical trial (12). A subsequent step to reduce costs could then be to determine the AUC on 1 or 2 occasions after transplantation and to identify the patient-specific C0 for follow-up in the outpatient setting. Within- and between-patient variation can be further reduced by applying superior laboratory methodologies, such as liquid chromatography–tandem mass spectroscopy (LC-MS/MS), instead of the nonspecific immunoassays (13). AUC and patient-specific C0-guided protocols based on LC-MS/MS drug analyses could be an approach that embraces the best of both worlds, but it still needs to be validated.

In our view, population pharmacokinetics, mini-AUCs, and the Bayesian estimator constitute the preferred CNI-monitoring strategy after transplantation. Rethinking this concept, however, also requires acknowledging that it remains a rather crude way to monitor the effect of CNIs. In whole blood, the CNIs partition predominantly into erythrocytes, with the majority of the remaining molecules staying in the plasma bound to lipoproteins. Consequently, variation in these parameters markedly influences cellular distribution (14). A straightforward approach to avoid this methodological issue could be intracellular measurement of CNI concentrations in T cells; however, for identifying patient-specific CNI susceptibility, a pharmacodynamic parameter or a response biomarker is, theoretically at least, the preferred and most accurate approach. It would bring TDM one step closer to the intracellular site of action and the corresponding individual pharmacologic sensitivity at this concentration. In addition, such a marker allows the higher-level detection of pharmacologic or immunologic drug–drug interactions (15).

Calcineurin activity assays have the important advantage that they directly measure the effect of CNIs on their target enzyme. As an alternative, downstream immunologic markers, including cytokine concentrations, production of surface activation proteins, and transcripts after lymphocyte or T cell specific stimulation, have been investigated, but these markers lack selectivity for CNIs (14). For calcineurin activity, clinical proof of concept has been demonstrated in liver and hematologic transplantation, but convincing data in renal transplantation are not yet available. A comprehensive validation is required before calcineurin activity can be used as a pharmacodynamic marker in renal transplant recipients (14). To date, these data regarding calcineurin activity are lacking, despite the fact that the first report on calcineurin activity was published more than 15 years ago.

The CNI C0 and serum creatinine monitoring are the current standard biomarkers for assessing systemic drug exposure and renal function, respectively. Serum creatinine is a notoriously unreliable marker for the GFR; changes in creatinine concentration occur late in disease progression and do not accurately represent the ongoing underlying renal damage (5). Our point is that monitoring the C0 without information on the patient’s absorption profile or the related systemic drug exposure is equally unreliable for guiding initial CNI dosing or for controlling systemic drug exposure while tapering. Until more sophisticated pharmacodynamic tools become available, advanced TDM with population pharmacokinetics constitutes the preferred CNI intervention strategy to optimize the long-term graft survival of the scarce organs available for transplantation.

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