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REVIEW ARTICLE

Therapeutic drug monitoring of tacrolimus after kidney transplantation: trough concentration or area under curve-based monitoring?

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Abstract

Measurement of pre-dose tacrolimus concentrations, also referred to as trough concentrations or C0 (in this paper the term C0 will be used), is the most frequently used parameter for therapeutic drug monitoring in patients after solid organ transplantation. C0 is relatively easy to obtain, and can be combined with other lab tests. C0 monitoring is convenient for patient and hospital staff. Adjusting the dose based on C0 assumes that the C0 has a good correlation with the overall exposure to the drug, as reflected in the area under concentration—time curve (AUC).

However, C0 may not be the panacea it is suggested to be, and there are patients who may benefit from additional measurements to more precisely assess drug exposure. Especially in patients with a low C0/dose ratio, the peak tacrolimus concentrations after oral administration may be unexpectedly high, resulting in toxicity and (as has been shown already) in poor long-term graft survival. At the other extreme, patients who only need a very low dose to reach target C0 may have a low peak and also a low AUC and may be underexposed.

In this paper, the limitations of C0 will be discussed, and the type of studies needed to provide the evidence for implementation of more sophisticated therapeutic drug monitoring. The paper focuses on treatment of adult kidney transplant recipients.

KEYWORDS
kidney, pharmacokinetics, tacrolimus, therapeutic drug monitoring, transplantation

1 | INTRODUCTION

In the last 20 years tacrolimus has become the most frequently prescribed calcineurin inhibitor (CNI) in patients who have received a kidney transplantation. Tacrolimus is a narrow therapeutic index drug with a high between-patient variability in pharmacokinetics (PK), and therapeutic drug monitoring (TDM) is widely accepted to individualize dosages to prevent rejection and toxicity. In 2019 the Immunosuppressive Drugs Scientific Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicity published a consensus report on TDM for tacrolimus to assist health care professionals in handling this immunosuppressive drug in solid organ transplantation.[1]

Other drugs for which TDM is routinely applied in transplantation are cyclosporine (CsA, the other CNI registered for kidney transplantation) and the 2 mammalian target of rapamycin-inhibitors (everolimus and sirolimus). The implementation of TDM for mycophenolic acid is more controversial, although there is sufficient evidence to support a concentration–effect relationship and there is also a randomized controlled trial demonstrating the benefit of TDM for this drug.[2,3] In solid organ transplant patients, TDM for azathioprine and for belatacept are not routinely applied.

Measurement of predose concentrations, also referred to as trough concentrations or C0 (in this paper the term C0 will be used), is the most frequently used parameter for TDM.[4] It is relatively easy to obtain, and at a once daily blood withdrawal also other lab tests (renal function, blood counts, liver enzymes and more) can be requested. C0 monitoring is convenient for patient and hospital staff. Adjusting the dose based on C0 assumes that the C0 has a good correlation with the overall exposure to the drug, as reflected in the area under concentration–time curve (AUC), and with clinical outcome. Although the C0 is an entirely PK parameter, the target range for C0 is based on investigations of the PK–pharmacodynamic relationships.[5] Patients with C0 below the target range have an increased risk of poor outcome.

For CsA, it was demonstrated that C0 did not differ between patients with and without acute rejection, while AUC did differ.[6] Because in the first few hours after oral drug intake the between-patient variability in the PK) of CsA is highest, the concept of absorption profiling emerged, using blood samples collected every hour, during the first 4 h after CsA intake.[7] Despite the potential benefits of monitoring AUC_{0-4h} this strategy was not widely accepted, largely for practical reasons including workload for hospital staff and the need for accurate timing of blood withdrawals. When it was shown that the CsA concentrations at 2 h (C2) after oral dosing postdose were a much better predictor of $AUC_{0-4\ h}$ than C0, C2 monitoring was propagated.[8] However, despite the theoretical benefits of monitoring C2, the evidence that it does result in improved clinical outcome compared to C0 monitoring is weak at best.[9]

For tacrolimus, there has been less debate on the appropriateness of C0 as the best choice for TDM. The perception of many is that C0 adequately reflects AUC, and that there is no need to monitor tacrolimus exposure through AUC, or C2 or any other time point.[10] However, C0 may not be the panacea it is suggested to be, and there are patients who may benefit from additional measurements to more precisely assess drug exposure. In this paper, we will discuss the limitations of C0, and what type of studies are needed to provide the evidence for implementation of more sophisticated TDM. The paper focuses on treatment of adult kidney transplant recipients.

2 | CORRELATION BETWEEN TACROLIMUS C0 AND AUC

Following the introduction of tacrolimus as a new drug for the prevention of acute rejection after kidney transplantation the correlation between C0 and AUC was investigated. Do note that in some of these studies R was reported, and in other studies R^2.

In 2001, Braun *et al*. published data on 21 patients in whom C0 was correlated with full 12-h AUC (samples drawn at $t = 0$, 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11, 12 h after intake) taken after the first dose (PK1), during the second week (PK2) and at 3 months (PK3) post-transplant.[11] The correlation of C0 with AUC was qualified as *good* with $R = 0.82$ in PK1, $R = 0.9$ in PK2 and $R = 0.74$ in PK3. In 2002, MacAlister showed a similar good correlation ($R^2 = 0.82$) between C0 and AUC (samples drawn at predose, 1, 2, 3, 4, 6, 8 and 12 h).[12]

Kuypers *et al*. performed a prospective PK study of tacrolimus in 100 patients during the first year after kidney transplantation (Days 7, 42, 90, 180 and 360).[13] The correlation between C0 and AUC was an R^2 of only 0.71, while a limited sampling strategy including 5 samples drawn within the first 4 h after taking the drug showed a correlation of $R^2 = 0.96$. Scholten *et al*., based on 64 AUCs obtained from 26 kidney transplant recipients, concluded that with an R^2 of 0.79 the C0 performed less well than all 2-point strategies which besides a C0 also included a 2-, 3-, or 4-h sample ($R^2 = 0.94$, 0.96 and 0.95, respectively).[14]

Wlodarczyk *et al*. compared immediate release (twice daily, $n = 34$) and prolonged release (once daily, $n = 32$) tacrolimus in a PK study, during which 3 AUCs were collected, on Day 1, Day 14 and Week 6 after transplantation, with each 24-h AUC consisting of 17 blood samples (collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20 and 24 h after dosing).[15] The authors concluded that for both formulations there was a strong correlation between AUC0–24 and C0 ($R = 0.83$ and $R = 0.94$, respectively). They also concluded that the same TDM strategy in place for tacrolimus immediate release can also be applied for tacrolimus prolonged release.

In a Japanese study the correlation between C0 and AUC in tacrolimus immediate release ($n = 25$) and prolonged release ($n = 47$) on Day 28 post-transplantation was reported as *good* but with somewhat lower R^2 values ($R^2 = 0.638$ and $R^2 = 0.575$ respectively).[16]

It seems that the reported studies show quite a bit of diversity in outcomes, with suboptimal R^2 values in several studies. A potential explanation for the differences in the correlation between C0 and AUC could be the use of different analytical assays (immunochemistry, chromatography–mass spectrometry) and their inherent analytical imprecisions. However, all studies mentioned above (except Wlodarczyk) used an immunoassay, and nevertheless there was a wide range of correlations. We do not think that the analytical assay is an important determinant for the observed variability. Whether the data were collected as part of a dedicated PK study, or collected from patients in a daily TDM service at the hospital is likely to have a stronger impact. Obviously, the studies performed in real world data have a higher relevance for clinical practice. Furthermore we need to remind ourselves of the fact that the reassuring results obtained in groups of patients may not translate in equally good correlations for individual patients.

As an alternative for C0, the C12 and C24 have been studied as predictors for AUC. Marquet *et al*. showed that for both immediate and prolonged release formulations, the AUC_{0-24h} was better correlated with C24 than C0, and for immediate release tacrolimus the AUC_{0-12h} was better correlated with C12 than C0.[17]

3 | CORRELATION BETWEEN CLINICAL OUTCOME AND TACROLIMUS C0 OR AUC

In an analysis of a dataset from 3 large randomized controlled trials, including 1304 patients, the relationship between tacrolimus exposure and the incidence of biopsy-proven acute rejection (BPAR) was studied.[18] The correlations between tacrolimus C0 and BPAR were analysed for BPARs occurring after C0 measurement but still within the first posttransplant year. The same type of analysis was also done for BPAR occurring within the month following the C0 measurement. In the multivariate analysis, only delayed graft function and induction therapy were independently correlated with BPAR, but C0 was not. In a similar type of analysis in 528 patients, however, a significant correlation between C0 and incidence of BPAR was identified, and the authors recommended to avoid C0 < 4.0 ng/mL within the first 12 months post-transplant.[19]

Also, in the DeKAF-study ($n = 1930$), C0 was found to be lower in patients who developed acute rejection.[20] In an adjusted time-varying multivariate model, each 1 ng/mL decrease in C0 was associated with a 7.2% increased risk of acute rejection in the first 6 months after kidney transplantation. There also was an additional 23% increased risk of acute rejection with each 1 ng/mL decrease in the TAC trough levels in Months 3–6.

Already 20 years ago Kuypers *et al.* designed a prospective PK study in 100 de novo kidney transplant recipients treated with tacrolimus, mycophenolate mofetil (MMF) and prednisone.[21] To investigate the concentration–effect relationship, AUCs of both MPA and tacrolimus were collected at Week 1 (full 12-h AUC) and Week 6, and Month 3 and 12 post-transplantation (AUC 0–4). In patients with an AUC below target for both tacrolimus and MMF, the incidence of acute rejection was higher (26.3%) compared with patients who were on target for both drugs (7.7%).[22]

In a cohort study including a large number of tacrolimus trough levels ($n = 80\ 470$) patients who developed de novo donor-specific antibodies (dnDSA) more often had at least 1 tacrolimus level <5 ng/mL. Furthermore in this study the minimum recorded tacrolimus trough levels were lower in recipients who developed dnDSA compared with those who did not.[23] However, a Japanese study in 584 kidney recipients could not find a relationship between the maintenance C0 and the development of dnDSA.[24] Neither did Sablik *et al.* find a difference in C0 between 59 patients diagnosed with chronic active antibody-mediated rejection compared with 189 control patients matched for age, year of transplantation and type of kidney donor.[25] The mean tacrolimus C0 was comparable for the cases (5.8 ng/mL) and control patients (6.1 ng/mL, $P = .08$).

While most studies have focused on the first 6–12 months after transplantation, our group recently performed a real-world data analysis on the concentration–effect relationship of tacrolimus and MMF in patients in the second and third year after kidney transplantation ($n = 968$).[26] An important finding of this study was that although tacrolimus C0 and AUC were both associated with incidence of BPAR, AUC predicted BPAR better than C0 and identified patients with over- or underexposure despite supposedly adequate C0. This suggests that monitoring AUC may be of additional benefit to identify patients with under- or overexposure to tacrolimus.

4 | C0/DOSE RATIO

A notoriously difficult to study outcome parameter after kidney transplantation is CNI-related nephrotoxicity. Intrarenal tacrolimus concentrations may be influenced by polymorphisms in several membrane transporter proteins (influx and/or efflux pumps), further complicating the analysis of correlations between drug exposure measurements in the blood compartment and nephrotoxicity.[27] Acute nephrotoxicity can be present as early as 1 month after transplantation, and is potentially reversible, while chronic CNI-related allograft changes such as tubulointerstitial fibrosis/tubular atrophy, glomerulosclerosis and arteriolar hyalinosis are usually irreversible and progressive.[28]

In a 24-month longitudinal study ($n = 248$) Thölking *et al.* found that the tacrolimus C0 divided by the tacrolimus dose (C0/dose ratio) could identify patients at risk for the development of CNI nephrotoxicity or BK nephropathy.[29] Patients with a C0/dose ratio below 1.05 ng/mL*1/mg, labelled as fast metabolizers, more often underwent a for-cause renal biopsy and had a worse renal function compared to patients with a higher C0/dose ratio. In a larger cohort study from the same group ($n = 558$) these findings were confirmed, with fast metabolizers having a faster decline of estimated glomerular filtration rate (eGFR) and worse graft survival at 5 years.[30,31] Also, an independent Polish group showed the impact of the C0/dose ratio on loss of eGFR over time, albeit at a different cut-off level (1.53).[32] In the TOMATO study, a retrospective study on 1029 kidney transplant patients transplanted at the Grenoble University Hospital (France) between 2004 and 2016, a multivariate analysis confirmed the prognostic value of the C0/dose ratio (cut-off 1.05 ng/mL*1/mg) at 3 months post-transplantation on death-censored graft survival.[33] In this study, the investigators corrected for use of corticosteroids and for CYP3A5 genotype status.

A potential explanation for the prognostic value of this ratio is that patients with a lower C0/dose ratio are treated with higher dosages, and therefore have higher C2 tacrolimus blood concentrations (19.2 ± 8.7 *vs.* 12.2 ± 5.2 ng/mL respectively; $P = .001$) and higher degrees of nephrotoxicity despite comparable trough levels (6.3 ± 2.4 *vs.* 6.6 ± 2.2 ng/mL, respectively; $P = .669$).[30] At least partly, this is related to the faster metabolism of tacrolimus in patients expressing the CYP3A5 enzyme, as shown in a study that linked pathology results from routine surveillance renal biopsies taken at 3 months post-transplant to PK and pharmacogenetic data.[34] CNI-related nephrotoxicity was more frequent (prevalence 25%) in patients with tacrolimus dose requirements exceeding 0.2 mg/kg/day than in patients with dose requirements between 0.10 and 0.20 mg/kg/day (16.2% CNI-related nephrotoxicity) and patients who needed <0.10 mg/kg/day (only 4.2% CNI-related nephrotoxicity). Patients who developed CNI-related nephrotoxicity more often carried the CYP3A5*1 allele (32.4% *vs.* 15.2%, $P = .01$), known to be associated with faster metabolism of tacrolimus.

The C0/dose ratio of tacrolimus does seem to identify a group of patients with increased risk of poor outcome after kidney

transplantation. The higher tacrolimus peak concentrations in the first few hours after drug intake go unnoticed when TDM is focused on C0 monitoring only.[35] These data support the potential added value of AUC monitoring. This assumption is supported by the data from a Belgian study in 53 patients who were divided into those taking a low (≤0.15 mg/kg) or high (>0.15 mg/kg) once-daily tacrolimus dose.[36] Although the C0 was similar between the 2 groups, the mean AUC was substantially higher in the high-dose group (320 ± 96 *vs.* 255 ± 81 h μg/L, $P < .001$). Also, this study showed that AUC may be too high in patients who have a C0 that is on target, if they are treated with a high tacrolimus dose.

Possibly, the accumulation of tacrolimus metabolites in plasma and renal tubular cells plays a role in the pathophysiology of CNI-related nephrotoxicity. Up to 15 metabolites of tacrolimus are formed during its metabolism (https://www.pharmgkb.org/pathway/PA165986114), with the most prevalent being 13-O-demethyl-tacrolimus.[37,38] This metabolite is approximately 1/10 as active as tacrolimus, while a minor metabolite, 31-O-demethyl-tacrolimus, has been found to have an immunosuppressive activity comparable to tacrolimus.[39] The remaining metabolites have all been found to have weak or negligible pharmacologic activity.[40] In patients with faster metabolization of tacrolimus the metabolites will be present in higher concentrations. Evidence comes from a study by Zheng *et al*., who found a 2.0- to 2.7-fold higher metabolite/parent AUC ratio in CYP3A5 expressers, who are known to have fast metabolism.[41]

5 | DISCUSSION

In 2005, in a position paper on TDM in solid organ transplantation Kuypers stated that: "… the practical ease of classic trough concentration monitoring and the excellent short-term results obtained in renal transplantation nowadays make it difficult to convince clinicians that a more laborious and extensive method of drug monitoring might prove necessary in order to improve long-term patient and graft survival".[42] What has changed since then is that the feasibility of monitoring AUCs in large numbers of patients is now much better.[43] Microsampling techniques such as dried blood spot (DBS) analysis for the quantitative determination of small molecule drugs and drug metabolites is now possible, thanks to the availability of highly sensitive analytical techniques.[44] Following extensive training patients can collect these samples at home. DBS can be collected as a nonvolumetric drop of blood onto a filter paper, or the blood sample may be deposited volumetrically using a capillary or microsampler tip.[45] A number of microsampling devices to quantitatively collect capillary dried blood are commercially available already or under development.[46] Clinical validation studies have shown that results from DBS are interchangeable with those obtained with the standard matrix used for TDM, which for tacrolimus is whole blood.[47]

In which patients AUC monitoring should be done is a matter of debate. One could argue that the patients with a low C0/dose ratio are the most likely to benefit, as they may have high peak concentrations and high tacrolimus AUC despite a C0 within the target range. Measurement of AUC may show that their dose can be lowered, and that for them a lower target C0 is more appropriate. The main benefit would be a better renal function, as CNI-related nephrotoxicity may be reduced. It is not likely that incidence of rejection or development of dnDSA is affected, as these patients were initially overexposed, and even after a dose reduction they will remain on adequate immunosuppression. Prospective studies could focus on patients in maintenance treatment, in whom a C0/dose ratio below a certain threshold is observed. To show the benefit of AUC monitoring 50% of the patients would be randomized to continued follow-up based on C0 monitoring, while in the other 50% the AUC-based monitoring strategy is implemented. The eGFR slope would serve as a reasonably likely surrogate endpoint for risk of graft loss, and a follow-up of several years will be necessary to demonstrate a difference between the 2 groups. As up to 25% of the patients in the low C0/dose group may suffer from CNI nephrotoxicity, the sample size of the study will remain acceptable. If patients would be identified within a few weeks of transplantation, then incidence of BK-viraemia could also be included as an endpoint.

Tables 1 and 2 show the target AUC and corresponding C0 ranges defined for patients at various time points after transplantation, assuming maintenance therapy consisting of tacrolimus and MMF, with or without low dose prednisolone, following basiliximab induction therapy. The target AUC ranges and corresponding C0 target ranges are in line with the exposure targets for adult renal allograft recipients defined by the online expert system Immunosuppressant

TABLE 1 Target area under concentration–time curve up to 12 h ($AUC_{0\text{-}12h}$) with corresponding trough concentration (C0) concentrations used in our transplant centre defined for patients at various time points after transplantation, assuming maintenance therapy consisting of tacrolimus and mycophenolate mofetil (MPA), with or without low dose prednisolone (PRED), following basiliximab induction therapy.

Tacrolimus	Time after transplantation	Target $AUC_{0\text{-}12h}$	Corresponding target range C0
(Prograft, Adport)	<6 weeks (triple therapy MPA + PRED)	160 μg*h/L	8–10 μg/L
	>6 weeks (triple therapy MPA + PRED)	120 μg*h/L	5–7 μg/L
	>6 months (triple therapy MPA + PRED)	80 μg*h/L	3–5 μg/L #

Note: # C0 levels <5 μg/L should only be accepted when corresponding $AUC_{0\text{-}12\,h}$ is >75 μg/L (see Meziyerh *et al*.). Recommendations for these targets are based on: <6 weeks: Ekberg *et al*.[48] and Moes *et al*.[49]; >6 weeks: Moes *et al*. (in preparation); >6 months: Meziyerh *et al*.[26]

TABLE 2 Target area under concentration–time curve up to 24 h ($AUC_{0\text{-}24h}$) with corresponding trough concentration (C0) concentrations used in our transplant centre defined for patients at various time points after transplantation, assuming maintenance therapy consisting of tacrolimus and mycophenolate mofetil (MPA), with or without low dose prednisolone (PRED), following basiliximab induction therapy.

Tacrolimus	Time after transplantation	Target $AUC_{0\text{-}24h}$	Corresponding target range C0
(Advagraf, Dailiport)	<6 weeks (triple therapy MPA + PRED)	320 μg*h/L	9–11 μg/L
	>6 weeks (triple therapy MPA + PRED)	240 μg*h/L	7–8 μg/L
	>6 months (triple therapy MPA + PRED)	160 μg*h/L	4–6 μg/L #

Note: # C0 levels <5 μg/L should only be accepted when corresponding $AUC_{0\text{-}24\ h}$ is >150 μg/L (see Meziyerh *et al.*[26]).

Bayesian Dose Adjustment (ISBA; https://abis.chu-limoges.fr).[50] In a large population of kidney recipients on tacrolimus maintenance therapy this group recently showed that the individual AUC/C0 ratio is stable over time with a low intrapatient variability, and can be used to individualize the C0 targets based on population AUC targets.[51]

Patients with a remarkably low C0/dose ratio probably have a high Cmax and are likely to be overexposed, but patients at the other end of the range with a high C0/dose ratio most likely have a low Cmax following intake of a low dose. In them the AUC may be lower than expected, and they may have a higher risk of rejection or development of dnDSA. Dose increases, and somewhat higher C0 target levels, may bring their tacrolimus exposure closer to the median of the population. Again, a randomized trial approach may be preferred in patients with a high C0/dose ratio. Sample size is likely to be substantially higher as the incidence of both rejection and development of dnDSA in long-term follow-up are quite low. The evidence that the patients with a high C0/dose are indeed at an increased risk of poor outcome is less strong than for patients with a low C0/dose ratio, and we suggest focusing on the latter group first.

Potentially all newly transplanted patients could be included in a study, with the argument that also in patients with C0 in the target range clinical events including rejection, infection and nephrotoxicity occur. The frequently observed intrapatient variability in C0 may be less if AUC is monitored. AUC targeted treatment would then be compared to C0 based TDM, with or without model informed precision dosing.[52]

Another possibility would be to switch patients with a low C0/dose ratio to a prolonged release formulation or to dose the drug more frequently, in smaller doses, to avoid high peak concentrations. If it is indeed the high peak concentration that plays an important role in the nephrotoxicity, then this might be successful. However, if accumulation of tacrolimus metabolites in renal tubular cells is the pathophysiological mechanism behind CNI-induced nephrotoxicity, then avoiding high C2 but maintaining the same AUC will not work.[41]

Also, CNI withdrawal or CNI tapering would be a possible intervention, for example, by aiming for low-dose tacrolimus combined with everolimus and aim for a TRANSFORM-like treatment regimen.[53] Now that belatacept availability has been restored, also substituting tacrolimus for belatacept is an option.[54] The prospective, randomized, open-label phase 3b study published in 2021 showed that after switching to belatacept renal function improved, at the cost of a numerically higher BPAR rate but with a lower incidence of dnDSA.[55] Whether or not the improvement of renal function in this study was highest in patients with a low C0/dose ratio has not been studied yet.

Admittedly, repetitive collection of tacrolimus AUCs for TDM will take an effort, from both patients and health care providers. With adequate training patients can learn to sample these AUCs themselves, using the DBS technology or microsampling devices. Based on the AUCs for a proportion of patients a different individualized C0 target concentration can be defined. This will lead to more patients reaching the appropriate tacrolimus exposure, potentially improving both efficacy and safety of tacrolimus treatment. If we are able to increase the lifespan of transplanted kidneys, this will have an immediate effect on the waiting lists, and on quality of life of our patients. We do believe it is worth the effort to attempt to further improve the use of this *old* drug.

AUTHOR CONTRIBUTIONS

Teun van Gelder wrote the first draft of this manuscript, and Dirk Jan Moes provided the data shown in Table 1 and Table 2. All authors were involved in writing and review of this manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

In the last 3 years T.v.G. has received lecture fees and consulting fees from Roche Diagnostics, Thermo Fisher, Vitaeris, Otsuka, CSL Behring, Astellas and Aurinia Pharma. In all cases money has been transferred to hospital accounts, and none has been paid to his personal bank accounts. T.v.G. does not have employment or stock ownership at any of these companies, and neither does he have patents or patent applications.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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