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ORIGINAL ARTICLE

Tacrolimus 4-hour monitoring in liver transplant patients is non-inferior to trough monitoring: The randomized controlled FK04 trial

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Abstract

Background: After liver transplantation (LT), tacrolimus and ciclosporin treatment can lead to, partially concentration-dependent, chronic kidney disease. Monitoring ciclosporin with two-hour levels reduced overexposure and led to better renal function than trough-monitoring (C0). For tacrolimus, a 4-hour level (C4) can give a reasonable approximation of total drug exposure. We evaluated whether monitoring tacrolimus in stable patients after LT by C4 was superior to C0 regarding renal function, rejection and metabolic parameters.

Methods: This open label randomized controlled trial compared C4 monitoring of tacrolimus BID (Prograft) to trough (C0) monitoring in stable LT recipients. The target range for C4 of 7.8–16 ng/ml was calculated to be comparable with target C0 of 4–8 ng/ml. Primary endpoint was the effect on renal function and secondary endpoints were the occurrence of treated biopsy-proven acute rejection, blood pressure and metabolic parameters, during 3 months of follow-up.

Results: Fifty patients were randomized to C0 ($n = 25$) or C4 ($n = 25$) monitoring. There was no difference in renal function between the C0 and the C4 group ($p = .98$ and $p = .13$ for CG and MDRD at 3 months). Also, the amount of proteinuria was similar ($p = .59$). None of the patients suffered from graft loss or was treated for rejection. Metabolic parameters did not differ between the two groups.

Conclusion: Tacrolimus 4-hour monitoring in stable LT patients is not superior to trough monitoring, regarding the effect on renal function, but is safe for use to facilitate tacrolimus monitoring in an afternoon outpatient clinic.

KEYWORDS
calcineurin inhibitor, graft survival, liver transplantation, renal function, therapeutic drug monitoring

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1 | INTRODUCTION

Chronic kidney disease (CKD) is a common complication after liver transplantation (LT) with an incidence ranging between 20% and 80%.[1–5]

CKD following LT increases cardiovascular burden, can lead to renal replacement therapy and can affect both quality of life and patient survival.[6–8] The main risk factors for post LT CKD have been identified to be preoperative glomerular filtration rate, hemoglobin, hypertension, and postoperative average serum levels of calcineurin inhibitors (CNIs). CNIs, including ciclosporin and tacrolimus, are the backbone of immunosuppression after solid organ transplantation. Besides their very potent effect (rates of acute cellular rejection after LT currently are below 20%,[9] an important adverse effect can be renal injury, which is partially dose-dependent.[10–13]

Tacrolimus, like ciclosporin, has a narrow therapeutic window and is characterized by a profound inter-patient variability. Therefore, therapeutic drug monitoring is warranted. Tacrolimus trough (C0) level correlates reasonably well both with the twenty-four-hour Area under the Concentration-Time Curve (24 h AUC)[14–17] and clinical outcome.[18,19] A number of studies in different types of organ transplantation have used less intensive 12 h or shortened 6 h AUCs and demonstrated that for tacrolimus C0 was a reasonable approximation of AUC,[20–24] although there are some publications reporting a much lower correlation between C0 and the AUC.[25,26]

Although we have developed pharmacokinetic models with a derived limited sampling formula and derived limited sampling models with Bayesian estimation of the AUC for both tacrolimus BID (Prograf) as well as tacrolimus QD (Advagraf) dosing after LT,[27,28] for practical purposes C0 is still widely used. Monitoring ciclosporin after LT with two-hour levels reduced overexposure and led to better renal function than trough-monitoring (C0).[29] After LT there was an excellent correlation between AUC and a single time point measurement of tacrolimus concentration four hours after dosing (C4) when used in the limited sampling model or with a limited sampling formula.[28] This inspired us to design the current randomized controlled study in which C4 monitoring is compared to C0 monitoring of tacrolimus BID (Prograft) in stable LT recipients, with renal function as the primary endpoint. We hypothesized that C4 monitoring was superior to C0 monitoring regarding renal function.

2 | PATIENTS AND METHODS

2.1 | Patients and study design

The FK04 study was a single center, randomized controlled open label study, which was initiated by and performed in the Leiden University Medical Center, Leiden, the Netherlands.

Stable LT recipients between 18 and 75 years old, more than 6 months after LT were included. Patients were excluded if they underwent multi-organ transplantation, were pregnant or breast-feeding, had a systemic infection (except viral hepatitis), were allergic/intolerant to macrolide antibiotics or tacrolimus, had a gastrointestinal disorder or diarrhea. Patients with known CKD (serum creatinine > 200 μmol/L), patients who required parallel therapy with immunosuppressive antibody preparations, who participated in another clinical trial, who were known with substance abuse or psychiatric disorders, or were unlikely to comply with the study visits were also excluded.

At randomization all patients used similar tacrolimus BID (Prograf, Astellas Pharma B.V, Leiden, the Netherlands). If patients used ciclosporin after LT, they were first converted to tacrolimus BID (Prograf) and entered the study as a separate stratum, after a 3-month period in which the dose was stabilized and not changed in the last month.

Patients were randomized 1:1 to C0 or C4 monitoring. Randomization took place by drawing blinded treatment allocation envelopes. The C0 group continued the standard regimen with trough levels 4–8 ng/ml (equivalent to AUC 90–140 ng*h/ml), the other group was dosed on a C4 level 7.8–16.0, but preferably 7.8–12.2 ng/ml, which is equivalent to a C4 AUC level of 90–185 and 90–140, respectively (using limited sampling formulas from our previous publication).[28] Treating physicians of patients dosed on C0 levels were blinded for C4 levels, while physicians of patients dosed on C4 levels were blinded for C0 levels, and all were blinded for AUCs. The total duration of the study was 12 weeks, with study visits at baseline and in weeks 4, 8, and 12.

The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol and amendments were approved by the Institutional Review Board and Independent Ethics Committee. All patients provided written informed consent before enrolment.

2.2 | Therapeutic drug monitoring

Determination of tacrolimus blood levels was performed using a previously validated LC–MS/MS assay capable of determining tacrolimus, sirolimus, everolimus, and cyclosporine simultaneously.[27] All parameters were in accordance with the bioanalytical method validation guideline of the European Medicines Agency.[30] $AUC_{0\text{-}12}$ MAP Bayesian estimation was performed using MW/Pharm version 3.83 (Mediware, Groningen, the Netherlands), based on models for tacrolimus C0, C1, C2, C3 and C4 yielding the estimated AUC from time zero to 12 h (AUC0–12).[31]

All concomitant immunosuppressive medications used in combination with tacrolimus at start of study were maintained at a constant dose throughout the duration of this study. If changes were required, the reason was recorded. In case of medical need, patients could be converted back to their original immunosuppressive regimen.

2.3 | Visits and evaluation

Baseline measurements consisted of complete physical examination, vital signs, tacrolimus trough level, laboratory assessments (including

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complete blood count, serum creatinine, electrolytes, liver enzymes and function, blood glucose and lipid panel) and 24 h urine analysis. Thereafter, study visits were scheduled at 4, 8, and 12 weeks after randomization. Additional visits could be made if necessary. During each visit vital signs, laboratory determinations as previously mentioned and C0 or C4 levels of tacrolimus were obtained. Abbreviated AUC's were sampled at baseline and at the end of the study.

2.4 | Endpoints

The primary endpoint of this study was renal function (calculated by BSA-adjusted Cockcroft and Gault and MDRD) at 12 weeks after randomization between C0 and C4 based tacrolimus monitoring. Secondary endpoints included arterial blood pressure, lipid- and fasting glucose levels, and number and dose of antihypertensive-and lipid-lowering medication. Safety secondary endpoints measured throughout the study included patient- and graft survival, treated biopsy-proven acute rejection (tBPAR) and all recorded adverse effects. In case of increase of liver enzymes ASAT, ALAT, ALP, or GGT a liver biopsy had to be performed to exclude tBPAR, otherwise not. At baseline (randomization) and at 12 weeks an abbreviated AUC for tacrolimus was performed for comparisons and correlation with C0 and C4.

2.5 | Statistical analysis

Power analysis was performed using an α of 5% as the critical p-value for superiority of C4 over C0 monitoring and a power with a 1-beta of 80%. The sample size calculated to detect a difference in serum creatinine > 13.4 umol/L (comparable to the difference between C2 and C0 monitoring of ciclosporin) between the parallel groups on tacrolimus with C0 versus C4 monitoring was 47. To compensate for patient drop-out, the aim for inclusion was $n = 50$. The study was designed as RCT with intention-to-treat analysis and results were verified using per-protocol analysis. All patients who were randomized and had received at least one dose of study medication were included in the safety analysis.

Categorical data were reported as frequency (percentage), and continuous data were reported as mean with standard deviation (SD). Correlation was by Passing-Bablok regression analysis.

For comparison of the two monitoring methods (C0 vs. C4) regarding renal function, rejection, blood pressure and metabolic parameters, the t-test was used. A $p < .05$ was considered statistically significant. SPSS Statistics 25 (IBM, Chicago, IL, USA) was used for statistical analysis.

3 | RESULTS

3.1 | Patients

Fifty patients after LT and on a stable CNI based regime were included in the study (Figure S1). Eight patients (16%) had been converted from ciclosporin to tacrolimus BID and for 3 months maintained on C0 4–8 ng/ml before randomization. The remaining 42 patients (84%) were already treated with tacrolimus BID with these levels. Patients were evenly randomized (25/25) between the C0 and C4 group. All patients (100%) completed the study. Therefore per-protocol analysis was similar to intention-to-treat analysis. The median time to transplant in the C0 group was: 52.7 (SD ± 45.3) months. This was slightly—but not significantly—longer than in the C4 group: 32.4 (SD ± 29.9) months ($p = .07$). Baseline renal function, lipid levels, and blood pressure were similar between the two groups, although the patients in the C0 group were significantly younger and used less prednisolone (Table 1). For patients using prednisolone, the dose was 5 mg, whereas if patients used mycophenolate mofetil (MMF) the dose ranged between 1000 mg and 2000 mg/day. The number of patients using MMF and doses did not differ between groups.

3.2 | Primary endpoint

During the 12 weeks follow-up after randomization, renal function estimated by Cockcroft-Gault (CG) and MDRD remained stable within the C0 and C4 group.

At the end of the study, there was no difference in renal function between the C0 and the C4 group ($p = .98$ and $p = .13$ for CG and MDRD). Also, the degree of proteinuria was similar ($p = .59$) (Table 2).

3.3 | Secondary endpoints

3.3.1 | Metabolic parameters

Blood pressure did not differ between groups throughout the study, nor did serum fasting glucose and triglycerides (Table 2). Serum total cholesterol was significantly lower in the C0 than in the C4 group ($p = .02$). The number of antihypertensive- and lipid-lowering medications were similar (Table S1).

3.3.2 | Survival and graft rejection

Patient survival at the end of the study was 100% in both groups. Graft loss was observed in none of the patients during the study. Two patients (one in the C0 and one in the C4 group) lost their graft 3 and 6 years after study closure from unrelated causes. None of the 50 patients had a clinical suspicion of rejection based on absence of changes in liver enzymes, therefore no liver biopsies had to be performed to further exclude tBPAR.

3.3.3 | Tacrolimus pharmacokinetics

Tacrolimus dosage was adjusted during the study, based on C0 or C4 levels according to protocol. The correlation for C4 levels and AUC was

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TABLE 1 Baseline characteristics

	C0 group		C4 group		
	Mean	SD	Mean	SD	*p* value
Age	47.6	±13.1	55.6	±9.0	.02*
Renal function, MDRD (ml/min/1,73 m^2)	83.5	±44.1	68.6	±22.9	.14
Renal function, Cockcroft-Gault (ml/m^2)	102.8	±35.2	89.7	±27.2	.16
Serum creatinine (mmol/L)	95.8	±25.1	105.7	±29.6	.21
Blood pressure systolic (mm Hg)	136	±16.2	140	±13.6	.45
Blood pressure diastolic (mm Hg)	87	±10.0	88	±6.4	.72
Total cholesterol (mmol/L)	4.7	±1.2	5.2	±1.2	.16
Triglycerides (mmol/L)	1.6	±.9	1.6	±.7	.83
Glucose (mmol/L)	7.0	±2.9	6.3	±2.4	.37
Gender (male %)	76		72		.75
Concomitant use of MMF (%)	64		60		.78
Concomitant use of prednisolone (%)	28		56		.046*

Abbreviation: SD, standard deviation.
*= statistically significant.

TABLE 2 Primary and secondary endpoints

	C0 group		C4 group		
	Mean	SD	Mean	SD	*p* value
Renal function, MDRD (ml/min/1,73 m^2)	85.4	±44.1	69.5	±25.9	.13
Renal function, Cockcroft-Gault (ml/m^2)	91.6	±47.0	91.3	±28.6	.98
Proteinuria (g/24 h)	.23	±.26	.20	±.14	.59
Blood pressure systolic (mm Hg)	134	±17.2	141	±19.2	.19
Blood pressure diastolic (mm Hg)	84	±8.1	86	±13.1	.51
Total cholesterol (mmol/L)	4.5	±.9	5.2	±1.1	.02*
Triglycerides (mmol/L)	1.5	±1.1	1.8	±.7	.26
Glucose (mmol/L)	6.6	±3.0	6.3	±2.1	.75

Abbreviation: SD, standard deviation.
*= statistically significant.

better than the correlation between C0 and AUC (R^2 = 0.802 vs. .588) (Figure 1).

At the end of the study, 23 patients in the C0 group (92%) and 17 patients in the C4 group (68%) had tacrolimus levels within the target range (p = .04).

The AUC 0–12 h at start (C0 mean 107,5; C4 mean 104,4) and end (C0 mean 98,0; C4 mean 99,2) of the study were comparable between the two groups (p = .77 and p = .89).

4 | DISCUSSION

This RCT demonstrates that C4 monitoring of tacrolimus BID is not superior to C0 monitoring in stable adult LT recipients, with a similar outcome regarding renal function, metabolic parameters and safety endpoints.

Since the therapeutic window of tacrolimus is narrow, inadequate dosing and monitoring can lead to under- or overexposure, which can promote rejection or adverse effects including renal dysfunction, respectively.

Tacrolimus trough level monitoring corresponds reasonably well with the 24 h AUC.[14–17] A downside of trough level monitoring is a limited flexibility whilst managing outpatients, requiring outpatient visits during the morning. It was shown before that, unlike ciclosporin, 2 h (C2) monitoring in tacrolimus did not correlate well with AUC[20,32] and therefore has no clinical value. In a previous study in stable patients after LT we found C4 to reasonably correlate to AUC.[28] Our current results also demonstrate a better correlation of AUC with C4 than with C0 levels.

The present study shows that C4 monitoring is not superior to C monitoring regarding the effect on renal function, but that it is safe to use, with no rejection or other differences in potential CNI induced

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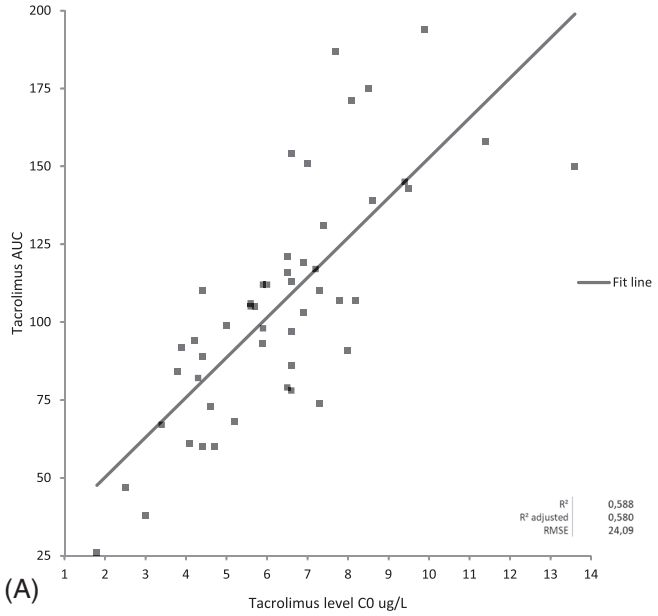

FIGURE 1 Correlation plots of tacrolimus C0 (Figure A) and C4 (Figure B) levels versus AUC, showing a better correlation for C4 than C0 ($R^2 = 0.802$ vs. .588).

side effects like hypertension, hyperglycemia or dyslipidemia. The difference in endpoint total cholesterol between the two groups can be attributed to improved cholesterol levels in the C0 group, rather than worsening of lipid levels in the C4 group.

C4 monitoring offers an easier scheduling for the outpatient clinic, by making afternoon visits possible. One of the limitations of C4 monitoring is that samples must be obtained within a quarter of an hour before or after the C4 moment, because the target range has been based on a limited sampling formula and not a Bayesian limited sample model. Since we complied strictly with these time limits, this does not explain the lower number of C4 patients within the target range of AUC comparable to a trough level of 4–8 nl/L. A possible explanation is that it was sometimes difficult to keep the C4 between 7.8 and 12.2 ng/L in the 12 weeks after randomization, possibly due to some more variability for C4 than for C0, and due to monitoring with a monthly interval.

Tacrolimus dose was adjusted in 24% of the patients in the C0 group versus 48% in the C4 group. This is probably a response to the fact that more patients in the C4 group were out of therapeutic range. There appears to be more variation in peak levels than in trough levels, which was expected. This could indicate some "over-correction" with C4 monitoring, at least more correction than with C0 monitoring if aiming for the same AUC, but it could also indicate some "under-correction" with C0 monitoring.

The concomitant use of prednisolone was higher in the C4 group, but this did not lead to unwittingly acceptance of lower tacrolimus levels, since the AUC levels of tacrolimus did not differ between groups throughout the study. Median AUC levels were below target in both groups without rejection, possibly due to the use of concomitant immunosuppressive therapy and a study population with a longer period after LT, where lower AUCs often do not lead to rejection.

A limitation of the study is a possible variation in C0 or C4 times. Blood sampling for the C0 or C4 measurements was performed in the outpatient clinic. Patients in the study were instructed to have the trough level drawn exactly 12 h after the last tacrolimus dose and the C4 level exactly 4 h after the morning dose. Despite this instruction, we cannot rule out some variation in C0 and C4 times, but this was not more than 15 min earlier or later. Exact times were not registered.

Bayesian limited sampling models have been proven to be more accurate than trough or C4 monitoring of tacrolimus[27] and with the development of dried blood spot tests, even home-based monitoring is possible.[33] Although these improvements in therapeutic drug monitoring are very promising, resources and availability of these tests are still limited in most centers, and not all patients are able to handle dried blood spot home tests.

In conclusion, C4 monitoring of tacrolimus in stable patients after LT is safe but not superior to trough level monitoring. For an afternoon outpatient LT clinic, C4 monitoring provides a patient-friendly alternative to C0 monitoring. For clinical purpose, we recommend a C4 level between 8 and 12 ng/ml. A higher level (12–16 ng/ml) could be used in the first 3 months after transplantation especially if no co-medication like MMF is given.

AUTHOR CONTRIBUTIONS

Bart van Hoek and Babs M. de Klerk participated in the research design and in the performance of the research. Dirk J. A. R. Moes and Bastian N. Ruijter participated in the data analysis. Bastian N. Ruijter, Maarten E. Tushuizen, Dirk J. A. R. Moes and Bart van Hoek participated in the writing of the paper.

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CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. *Transplantation*. 1998;66(1):59-66.
2. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349(10):931-940.
3. Gonwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTX) using calcineurin-based immunotherapy: risk of development and treatment. *Transplantation*. 2001;72(12):1934-1939.
4. Wyatt CM, Arons RR. The burden of acute and renal failure in non-renal solid organ transplantation. *Transplantation*. 2004;78(9):1351-1355.
5. Fraley DS, Burr R, Bernardini J, Angus D, Kramer DJ, Johnson JP, Impact of acute renal failure on mortality in end-stage liver disease with or without transplantation. *Kidney Int*. 1998;54(2):518-524.
6. Gainza FJ, Valdivieso A, Quintanilla N, et al. Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. *Transplant Proc*. 2002;34(1):250-251.
7. Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. *Liver Transpl*. 2003;9(7):741-747.
8. Paramesh AS, Roayaie S, Doan Y, et al. Post-liver transplant acute renal failure: factors predicting development of end-stage renal disease. *Clin Transplant*. 2004;18(1):94-99.
9. Rodríguez-Perálvarez M, Germani G, Papastergiou V, et al. Early tacrolimus exposure after liver transplantation: relationship with moderate/severe acute rejection and long-term outcome. *J Hepatol*. 2013;58(2):262-270.
10. Kuypers DR, Claes K, Evenepoel P, Maes B, Vanrenterghem Y. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. *Clin Pharmacol Ther*. 2004;75(5):434-447.
11. Morard I, Mentha G, Spahr L, et al. Long-term renal function after liver transplantation is related to calcineurin inhibitors blood levels. *Clin Transplant*. 2006;20(1):96-101.
12. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa GL. Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (neoral) in organ transplantation. *Drugs*. 2001;61(13):1957-2016.
13. Al Aly Z, Abbas S, Moore E, Diallo O, Hauptman PJ, Bastani B. The natural history of renal function following orthotopic heart transplant. *Clin Transplant*. 2005;19(5):683-689.
14. Hardinger KL, Park JM, Schnitzler MA, Koch MJ, Miller BW, Brennan DC. Pharmacokinetics of tacrolimus in kidney transplant recipients: twice daily versus once daily dosing. *Am J Transplant*. 2004;4(4):621-625.
15. Alloway R, Steinberg S, Khalil K, et al. Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37(2):867-870.
16. Jusko WJ, Piekoszewski W, Klintmalm GB, et al. Pharmacokinetics of tacrolimus in liver transplant patients. *Clin Pharmacol Ther*. 1995;57:281-290.
17. Florman S, Alloway R, Kalayoglu M, et al. Conversion of stable liver transplant recipients from a twice-daily Prograf-based regimen to a once-daily modified release tacrolimus-based regimen. *Transplant Proc*. 2005;37(2):1211-1213.
18. Undre NA, Van Hooff J, Christiaans M, et al. Low systemic exposure to tacrolimus correlates with acute rejection. *Transplant Proc*. 1999;31(1-2):296-298.
19. Schwartz M, Holst B, Facklam D, Buell D. FK 506 in liver transplantation: correlation of whole blood levels with efficacy and toxicity. *Transplant Proc*. 1995;27(1):1107.
20. Jorgensen K, Povlsen J, Madsen S, et al. C2 (2-h) levels are not superior to trough levels as estimates of the area under the curve in tacrolimus-treated renal-transplant patients. *Nephrol Dial Transplant*. 2002;17(8):1487-1490.
21. Wang CH, Ko WJ, Chou NK, Wang SS. Therapeutic drug monitoring of tacrolimus in cardiac transplant recipients: a comparison with cyclosporine Neoral. *Transplant Proc*. 2004;36(8):2386-2387.
22. Braun F, Schutz E, Peters B, et al. Pharmacokinetics of tacrolimus primary immunosuppression in kidney transplant recipients. *Transplant Proc*. 2001;33(3):2127-2128.
23. Kimikawa M, Kamoya K, Toma H, Teraoka S. Effective oral administration of tacrolimus in renal transplant recipients. *Clin Transplant*. 2001;15(5):324-329.
24. Mardigyan V, Tchervenkov J, Metrakos P, Barkun J, Deschenes M, Cantarovich M, Best single time points as surrogates to the tacrolimus and mycophenolic acid area under the curve in adult liver transplant patients beyond 12 months of transplantation. *Clin Ther*. 2005;27(4):463-469
25. Cantarovich M, Fridell J, Barkun J, et al. Optimal time points for the prediction of the area-under-the-curve in liver transplant patients receiving tacrolimus. *Transplant Proc*. 1998;30(4):1460-1461.
26. Mardigyan V, Giannetti N, Cecere R, Besner JG, Cantarovich M. Best single time points to predict the area-under-the-curve in long-term heart transplant patients taking mycophenolate mofetil in combination with cyclosporine or tacrolimus. *J Heart Lung Transplant*. 2005;24(10):1614-1618.
27. Moes DJ, van der Bent SA, Swen JJ, et al. Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients. *Eur J Clin Pharmacol*. 2016;72(2):163-174.
28. Langers P, Press RR, den Hartigh J, et al. Flexible limited sampling model for monitoring tacrolimus in stable patients having undergone liver transplantation with samples 4 to 6 hours after dosing is superior to trough concentration. *Ther Drug Monit*. 2008;30(4):456-461.
29. Langers P, Cremers SC, den Hartigh J, et al. Switching monitoring of emulsified cyclosporine from trough level to 2-hour level in stable liver transplant patients. *Liver Transpl*. 2004;10(2):183-189.
30. European Medicines Agency – Guideline Bioanalytical Method Validation: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf
31. Scholten EM, Cremers SC, Schoemaker RC, et al. AUC-guided dosing of tacrolimus prevents progressive systemic overexposure in renal transplant recipients. *Kidney Int*. 2005;67(6):2440-2447.
32. Dansirikul C, Staatz CE, Duffell SB, Taylor PJ, Lynch SV, Tett SE. Sampling times for monitoring tacrolimus in stable adult liver transplant recipients. *Ther Drug Monit*. 2004;26(6):593-599.
33. Zwart TC, Gokoel SR, van der Boog PJ, et al. Therapeutic drug monitoring of tacrolimus and mycophenolic acid in outpatient renal transplant

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recipients using a volumetric dried blood spot sampling device. *Br J Clin Pharmacol*. 2018;84(12):2889-2902.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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