PHARMACOKINETICS AND DISPOSITION

Evaluation of limited sampling strategies for tacrolimus

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Abstract

Objective In literature, a great diversity of limited sampling strategies (LSS) have been recommended for tacrolimus monitoring, however proper validation of these strategies to accurately predict the area under the time concentration curve (AUC0–12) is limited. The aim of this study was to determine whether these LSS might be useful for AUC prediction of other patient populations.

Methods The LSS from literature studied were based on regression equations or on Bayesian fitting using MWPHARM 3.50 (Mediware, Groningen, the Netherlands). The performance was evaluated on 24 of these LSS in our population of 37 renal transplant patients with known AUCs. The results were also compared with the predictability of the regression equation based on the trough concentrations C0 and C12 of these 37 patients. Criterion was an absolute prediction error (APE) that differed less than 15% from the complete AUC0–12 calculated by the trapezoidal rule.

Results Thirteen of the 18 (72%) LSS based on regression analysis were capable of predicting at least 90% of the 37 individual AUC0–12 within an APE of 15%. Additionally, all but three LSS examined gave a better prediction of the complete AUC0–12 in comparison with the trough concentrations C0 or C12 (mean 62%). All six LSS based on Bayesian fitting predicted <90% of the 37 complete AUC0–12 correctly (mean 67%).

Conclusions The present study indicated that implementation of LSS based on regression analysis could produce satisfactory predictions although careful evaluation is necessary.

Keywords Tacrolimus · Limited sampling strategy · Trough level · AUC0–12

Introduction

The calcineurin-inhibitor tacrolimus, used widely after organ transplantation, has a narrow therapeutic index and highly variable pharmacokinetic characteristics. Close monitoring of the drug concentration is required to achieve an optimum efficiency by minimizing the risk of subtherapeutic and toxic blood concentrations. Efficacy and side effects of tacrolimus are highly correlated with the area under the time concentration curve (AUC0–12) [1]. Elevated tacrolimus concentrations may lead to severe side effects such as nephrotoxicity, neurotoxicity and hyperglycaemia [2–4], while subtherapeutic tacrolimus concentrations increase the risk of transplant rejection enormously [5–7].

The most exact way to monitor the total tacrolimus exposure is by creating 12-h pharmacokinetic profiles, which implies that the tacrolimus concentration should be measured at at least six different time points. The AUC0–12 can then be calculated according to the trapezoidal rule using the tacrolimus concentrations measured at different
time points. Since recording a complete 12-h pharmacokinetic profile for every patient is not feasible in clinical practice, traditionally many transplant centres have used tacrolimus trough (C₀) concentrations to estimate the tacrolimus exposure. Although tacrolimus C₀ concentrations are generally considered to be a good indication of the total systemic drug exposure [1, 8], its usefulness in differentiating graft rejection episodes from nephrotoxicity has been questioned [6, 9–11]. Recently, the correlation between individual tacrolimus concentrations and AUC₀–12 has been studied in kidney [12–18], liver [19], heart [20, 21] and lung [22] transplant recipients. In these studies, a poor association was found between the tacrolimus C₀ for tacrolimus, there seems to be a growing interest for non-

predictive value of whether the LSS described in literature could be used in other populations. Predictive value of the different LSS with an independent transplant population is an absolute prerequisite. The question was of the different LSS with an independent transplant population. Ting et al. [23] recently reported that validation strategies have not been validated with an independent population. Most of these studies recommend different LSS, but these strategies have not been validated with an independent population. Ting et al. [23] recently reported that validation of the different LSS with an independent transplant population is an absolute prerequisite. The question was whether the LSS described in literature could be used in other centres with different populations. Predictive value of LSS from literature was evaluated using our own renal post-transplant group of 37 patients with known AUCs. Also the predictive value of trough levels (C₀ and C₁₂) determined in our own population was investigated.

Materials and methods

Patient population

In total, 37 Caucasian renal transplant recipients for whom a complete 12-h time tacrolimus concentration curve had been determined in a past clinical trial were included in this study (Table 1). The transplant recipients underwent a renal transplantation at least 1 year ago. Patients taking medication known to interact with tacrolimus, who suffered from gastro-intestinal or liver disease, pre-transplantation diabetes mellitus or other disorders that could have altered the absorption of tacrolimus were excluded from this study as illustrated in Table 1.

Prior to the blood sample collection, there was no tacrolimus dose change for at least 1 week. After overnight fasting, the blood samples were collected immediately before (C₀) and 0.5 (C₀.₅), 1 (C₁), 2 (C₂), 3 (C₃), 4 (C₄), 5 (C₅), 7.5 (C₇.₅) and 12 (C₁₂) h after the morning tacrolimus administration. Patients were not allowed to take food until 1 h after ingesting the tacrolimus dose and were advised to avoid grapefruit intake to prevent alterations in the tacrolimus metabolism. Demographic as well

| Table 1 Demographic characteristics of renal-transplant recipients |
|---------------------------------------------------------------|
| Demographic characteristics                  | Patients |
| (n=37)                                    |          |
| Gender (male/female)                        | 24/13    |
| Age (years, mean±SD)                       | 51.3±10.9|
| Length (cm, mean±SD)                       | 174±8.4  |
| Weight (kg, mean±SD)                       | 77.4±13.5|
| Body mass index (kg/m², mean±SD)           | 25.6±3.42|
| Primary kidney disease (n)                  |          |
| Glomerulonephritis                         | 1        |
| Chronic pyelonephritis                     | 2        |
| IgA nephropathy                            | 4        |
| Hypertensive nephropathy                    | 7        |
| Diabetes mellitus nephropathy               | 0        |
| Polycystic kidney disease                  | 8        |
| Unknown                                    | 4        |
| Other                                       | 11       |
| Transplantation number (n)                 |          |
| First                                       | 30       |
| Second                                      | 6        |
| Third or more                               | 1        |

| Tacrolimus mono therapy (n)                 | 29       |
| Tacrolimus dose (mg kg⁻¹ day⁻¹, mean±SD)    | 0.054±0.029|
| C₀ (ng/mL, mean±SD)                         | 6.59±1.39 |
| AUC₀–12 (ng·h/mL, mean±SD)                 | 122.5±31.1|
| Cₚmax (ng/mL, mean±SD)                     | 20.9±6.5  |
| Tₚmax (h, mean±SD)                         | 1.24±0.43 |

| Use of azothioprine/MMF/rapamycine/steroids |          |
| Time since transplantation (days, mean and range) | 1,542 (453–4,128) |

| Haemoglobin (mmol/L, ref. M: 8.2–11.0, F: 7.3–9.7) | 8.52±0.83 |
| Haematocrit fraction (ref. M: 0.41–0.52, F: 0.36–0.48) | 0.41±0.04 |
| ALAT (units/L, ref. M: <45, F: <35) | 24±13 |
| ASAT (units/L, ref. M: <35, F: <30) | 17±10 |
| Serum albumin (g/L, ref. 34–45) | 37.0±3.84 |
| Serum creatinine (μmol/L, ref. M: 71–110, F: 53–97) | 128±29 |
| Creatinine clearance (Cockcroft-Gault; mL/min, ref. 90–140) | 58.4±26.6 |

Ref. are the reference values applied in the Clinical Chemistry and Haematology Laboratory of the University Hospital in Maastricht. M Male, F female, MMF mycophenolate mofetil
as clinical data were determined at the time of recording the 12-h time tacrolimus concentration curve. The study was performed in accordance with the Declaration of Helsinki and its amendments. The protocol was approved by the local Medical Ethics Committee and written informed consent for participation in this study was obtained from all patients.

Determination of tacrolimus concentrations

The tacrolimus blood concentrations were determined in ethylene diamine tetra-acetic acid (EDTA) whole blood, using a method based on high-pressure liquid chromatography tandem mass spectrometry (HPLC-MS/MS). The assay is linear from 1 to 300 μg/l. Intra-assay precision and accuracy were 3.4, 2.2, and 3.0% and 102, 94 and 94% respectively at 3.04, 6.23 and 13.0 μg/l (n=6). Inter-assay precision and accuracy were 8.2, 5.2, and 4.6% and 102, 94 and 93% (n=9) respectively. Lower limit of quantification was 1.0 μg/l. The laboratory participates in the International Tacrolimus Proficiency Testing Scheme.

Limited sampling strategies investigated

In our opinion, a suitable limited sampling strategy for tacrolimus should consist of two or three time concentration points within a short time post-dose (≤4 h) including a trough level. We selected 24 LLS from the literature [12, 15, 16, 18, 20, 22]. Eighteen of these strategies were based on regression analysis [12, 16, 18, 20, 22], and six other strategies were based on Bayesian fitting [15]. Also strategies based on the tacrolimus C0 and C12 concentrations were developed for our own renal transplant patient population and compared with above-mentioned LSS.

Pharmacokinetics and statistical analysis

The area under the tacrolimus time concentration curve (AUC0–12) was calculated from the time versus tacrolimus concentration plot using the linear trapezoidal rule in MWPharm 3.50 (Mediware, Groningen, The Netherlands). The predicted AUC0–12 (AUCpred), calculated with the 24 different LSS, were validated by determining the predictive performance as described by Sheiner and Beal [24]. The percentage of the prediction error (PE) and the percentage of the absolute prediction error (APE) are parameters often used for validation in LSS [12, 14–16, 18, 20, 22]. Given the high pharmacokinetic variability, an APE of less than 15% was considered clinically acceptable [16, 25, 26].

Prediction bias was measured as a percentage of the prediction error [PE (%)] using the following formula:

\[
PE(\%) = 100 \times \frac{(AUC_{\text{pred}} - AUC_{\text{actual}})}{AUC_{\text{actual}}}
\]

Prediction precision was measured as a percentage of the APE using the following formula:

\[
APE(\%) = 100 \times \frac{|(AUC_{\text{pred}} - AUC_{\text{actual}})|}{AUC_{\text{actual}}}
\]

The variance in the strength of association between the AUCpred and the AUCactual was reflected by the linear regression coefficient of multiple determination (R2). All values are expressed as mean±SD. All statistical analyses were performed with use of SPSS 12.0 software for windows (Chicago, IL, USA).

Results

Evaluation of predictive performances of the limited sampling strategies

Table 2 shows an overview of the studies describing the LSS evaluated in the present study. The regression equations and the R2 found by the investigators for the evaluated LSS are summarised in Table 3. Table 4 describes the R2, which represents the association between AUCpred and AUCactual and the calculated PE and APE of the 24 evaluated LSS for our 37 pharmacokinetic profiles. Thirteen of the 18 LSS (72%) based on regression analysis had a predictivity of >90%. Additionally, all except three of the LSS examined gave a better prediction of the complete AUC0–12 in comparison with LSS based on a trough concentration C0 and C12 (mean 62%). Predictivity of all six LSS based on Bayesian fitting was <90% (mean 66.8%). Additionally, Fig. 1 illustrates an overview of the performances of the 26 LSS evaluated in our well-characterized population of renal transplant recipients.

Discussion

Our results confirm the results of several other studies [12, 14–16, 18, 20, 22] that trough concentrations C0 and C12 have a lower predictive value for the complete 12-h AUC than almost all other studied LSS. The predictivity of LSS based on Bayesian estimation of the AUCactual was lower than the LSS based on regression analysis. Therefore a trough level and one or two time points in the early phase (≤4 h) post-dose seem not to be sufficient for a Bayesian estimation strategy to fit correctly most of the AUC0–12 and thus predict the complete AUC0–12 reliably. The differences in variability and shape between the curves of post-transplant recipients combined with just two or three sample points might have been caused by the large differences found between the AUCpred calculated according to the Bayesian estimation strategy and the complete AUCactual.
Limited sample strategies derived from the linear trapezoidal rule and the complete 12-h AUC.

In contrast to most studies that describe LSS for tacrolimus in literature, we used an HPLC-MS/MS assay to determine the tacrolimus concentration. Because there seems to be a fixed difference of about 15% between the immunoassay and the HPLC-MS/MS, the prediction will change proportionally, and the predictivity of the LSS will be the same. Also potential interfering drug-drug interactions will have an equal influence on the different

Table 2 Overview of the characteristics of transplant patients included in the studies that described limited sampling strategies

| Study                | Transplanted organ | Number of patients | Number of AUC_{0-12} curves for validation (Ib/NIc) | Analytical method | Time since transplantation | Inclusion criteria |
|----------------------|--------------------|--------------------|--------------------------------------------------|-------------------|---------------------------|--------------------|
| Wong et al. [16]     | Kidney             | 18                 | 0/18                                             | Imx II            | 2.5 years                 | 1,2                |
| Aumente Rubio et al. [20] | Heart             | 22                 | 0/25                                             | Imx               | <1 year                    |                    |
| Pisitkun et al. [18] | Kidney             | 15                 | 0/15                                             | Imx II            | 8.7 months                | 1,2,3              |
| Armendariz et al. [12] | Kidney             | 22                 | 13/14                                            | Imx               | Unknown                    |                    |
| Scholten et al. [15] | Kidney             | 43                 | 64/20                                            | Imx               | Differs                   | 2                  |
| Ragette et al. [22]  | Lung               | 15                 | 0/31                                             | Imx               | 7.3 months                |                    |

Number of transplant patients used in the included study for both developing and validating the limited sampling strategies.

Number of AUC_{0-12} used for developing the limited sampling strategies.

Number of independent (I) and dependent (NI) AUC_{0-12} used in the study to validate the created limited sampling strategies.

The analytical method used to determine the whole blood tacrolimus concentration.

The mean time after transplantation.

The inclusion criteria used for the transplant patients in the different studies. I Tacrolimus administrated when patients were in the fasting state, 2 patients selected for using no interfering medication with tacrolimus, 3 patients selected with a normal liver function test.

Twenty-two pharmacokinetic profiles were obtained within 2 weeks after transplantation, and 42 pharmacokinetic profiles were obtained between 6 and 52 weeks after transplantation.

Table 3 Overview of limited sampling strategies and their reported coefficients of correlation (R^2) with the complete tacrolimus AUC_{0-12}

| Equation | Time points | Regression equations | R^2  | Ref   |
|----------|-------------|----------------------|------|-------|
| 1        | C_0         | 14.550 + 13.387 × C_0 | 0.54 |       |
| 2        | C_{12}      | 15.892 + 17.852 × C_{12} | 0.79 |       |
| 3        | C_0, C_2, C_4 | 13.3 + 1.2 × C_0 + 2.4 × C_2 + 5.6 × C_4 | 0.93 | [16]  |
| 4        | C_2, C_4    | 16.2 + 2.4 × C_2 + 5.9 × C_4 | 0.93 | [16]  |
| 5        | C_0, C_2, C_4 | 0.98 + 4.17 × C_0 + 2.29 × C_2 + 5.3 × C_4 | 0.97 | [20]  |
| 6        | C_0, C_4    | 3.75 + 5.52 × C_0 + 6.97 × C_4 | 0.95 | [20]  |
| 7        | C_0, C_1, C_2 | −5.496 + 7.189 × C_0 + 2.357 × C_1 + 2.131 × C_2 | 0.93 | [18]  |
| 8        | C_0, C_1, C_4 | 3.85 + 3.688 × C_0 + 1.355 × C_1 + 6.649 × C_4 | 0.97 | [18]  |
| 9        | C_0, C_2, C_4 | −6.103 + 2.383 × C_0 + 1.911 × C_2 + 7.582 × C_4 | 0.97 | [18]  |
| 10       | C_1, C_2, C_4 | 1.304 + 0.465 × C_1 + 1.636 × C_2 + 8.256 × C_4 | 0.96 | [18]  |
| 11       | C_0, C_1    | 9.345 + 8.408 × C_0 + 3.23 × C_1 | 0.91 | [18]  |
| 12       | C_0, C_4    | 8.231 + 2.316 × C_0 + 9.636 × C_4 | 0.95 | [18]  |
| 13       | C_1, C_4    | 13.114 + 0.873 × C_1 + 9.291 × C_4 | 0.95 | [18]  |
| 14       | C_2, C_4    | −0.192 + 1.888 × C_2 + 8.783 × C_4 | 0.96 | [18]  |
| 15       | C_0, C_1, C_4 | 4.5 × C_0 + 2 × C_1 + 5.5 × C_4 | 0.97 | [18]  |
| 16       | C_0, C_2, C_4 | 5 × C_0 + 2 × C_2 + 5 × C_4 | 0.96 | [18]  |
| 17       | C_0, C_1, C_4 | 8.90 + 4.0 × C_0 + 1.77 × C_1 + 5.47 × C_4 | 0.97 | [12]  |
| 18       | C_0, C_1, C_3 | Bayesian estimation of the actual AUC_{0-12} | 0.97 | [15]  |
| 19       | C_0, C_2, C_3 | Bayesian estimation of the actual AUC_{0-12} | 0.96 | [15]  |
| 20       | C_0, C_2, C_4 | Bayesian estimation of the actual AUC_{0-12} | 0.97 | [15]  |
| 21       | C_0, C_3    | Bayesian estimation of the actual AUC_{0-12} | 0.96 | [15]  |
| 22       | C_0, C_4    | Bayesian estimation of the actual AUC_{0-12} | 0.95 | [15]  |
| 23       | C_0, C_2    | Bayesian estimation of the actual AUC_{0-12} | 0.95 | [15]  |
| 24       | C_0, C_2, C_4 | 5.87 + 4.50 × C_0 + 1.05 × C_2 + 5.87 × C_4 | 0.98 | [22]  |
| 25       | C_0, C_4    | 1.16 + 4.41 × C_0 + 7.71 × C_4 | 0.96 | [22]  |
| 26       | C_2, C_4    | 24.36 + 0.97 × C_2 + 7.94 × C_4 | 0.94 | [22]  |

Limited sample strategies derived from the linear trapezoidal rule and the complete 12-h AUC.

Limited sampling strategies that are able to predict 90% of complete AUC_{0-12} of the renal transplant recipients within the absolute prediction error (APE) of 15%.

Limited sample strategies derived from the linear trapezoidal rule and the actual AUC_{0-12}.
Table 4 Evaluation of predictive performance of limited sampling strategies to estimate the complete AUC_{0-12} in the 37 renal transplant recipients

| Equation | Time points | $R^2$ | Mean PE (%) | Mean APE (%) | ≤15%a |
|----------|-------------|-------|-------------|--------------|-------|
| 23. b    | \(C_0, C_4**\) | 0.760 | \(-14.9 \pm 13.8 (-46.0-33.2)\) | \(17.9 \pm 9.43 (1.12-46.0)\) | 13 (35%) |
| 22. b    | \(C_0, C_3**\) | 0.779 | \(-11.5 \pm 14.0 (-41.9-33.1)\) | \(15.7 \pm 8.83 (2.0-41.9)\) | 21 (57%) |
| 1.       | \(C_0\)     | 0.536 | \(2.11 \pm 14.8 (-27.1-24.4)\) | \(12.3 \pm 8.22 (0.7-27.1)\) | 22 (59%) |
| 11.      | \(C_0, C_1\) | 0.703 | \(6.58 \pm 14.8 (-26.5-43.7)\) | \(12.6 \pm 10.1 (0.1-43.7)\) | 24 (65%) |
| 2.       | \(C_{12}\)  | 0.80  | \(9.56 \pm 11.6 (-12.7-29.9)\) | \(12.0 \pm 8.97 (0.3-29.9)\) | 24 (65%) |
| 19. b    | \(C_0, C_2, C_4**\) | 0.502 | \(-4.44 \pm 17.4 (-45.3-50.6)\) | \(13.7 \pm 11.4 (0.4-50.6)\) | 25 (68%) |
| 20. b    | \(C_0, C_2, C_4**\) | 0.537 | \(-5.11 \pm 16.3 (-43.1-50.3)\) | \(12.9 \pm 10.4 (0.2-50.3)\) | 28 (76%) |
| 18. b    | \(C_0, C_1, C_4**\) | 0.525 | \(9.95 \pm 19.4 (-29.7-88.8)\) | \(13.1 \pm 17.4 (0.4-88.8)\) | 30 (81%) |
| 25.      | \(C_0, C_4\) | 0.911 | \(-7.83 \pm 6.36 (-21.3-2.4)\) | \(8.08 \pm 6.02 (0.1-21.3)\) | 30 (81%) |
| 7.       | \(C_0, C_1, C_2\) | 0.869 | \(2.35 \pm 9.96 (-17.2-27.3)\) | \(8.03 \pm 6.22 (0.0-27.3)\) | 31 (84%) |
| 6.       | \(C_0, C_4\) | 0.896 | \(-5.97 \pm 6.71 (-20.1-4.7)\) | \(6.63 \pm 6.04 (0.6-20.1)\) | 31 (84%) |
| 21. b    | \(C_0, C_2**\) | 0.802 | \(-3.69 \pm 10.2 (-19.6-18.6)\) | \(9.10 \pm 5.67 (0.4-19.6)\) | 31 (84%) |
| 17.      | \(C_0, C_1, C_4\) | 0.943 | \(5.91 \pm 7.06 (-8.8-26.3)\) | \(7.02 \pm 5.93 (0.2-26.3)\) | 33 (89%) |
| 15. c    | \(C_0, C_1, C_2\) | 0.934 | \(5.00 \pm 7.28 (-9.8-25.8)\) | \(6.81 \pm 5.57 (0.2-25.8)\) | 34 (92%) |
| 14.      | \(C_2, C_4\) | 0.964 | \(2.28 \pm 6.58 (-17.1-16.1)\) | \(5.45 \pm 4.24 (0.7-17.1)\) | 35 (95%) |
| 24.      | \(C_0, C_2, C_4\) | 0.941 | \(-4.81 \pm 5.26 (-17.3-2.8)\) | \(5.32 \pm 4.73 (0.1-17.3)\) | 35 (95%) |
| 13.      | \(C_1, C_4\) | 0.973 | \(3.37 \pm 5.21 (-5.2-17.7)\) | \(4.87 \pm 3.80 (0.2-17.7)\) | 36 (97%) |
| 8.       | \(C_0, C_2, C_4\) | 0.967 | \(6.30 \pm 4.84 (-5.9-17.8)\) | \(6.68 \pm 4.28 (0.3-17.8)\) | 36 (97%) |
| 9.       | \(C_2, C_4\) | 0.962 | \(1.01 \pm 6.37 (-16.7-14.7)\) | \(4.71 \pm 4.22 (0.3-16.7)\) | 36 (97%) |
| 26.      | \(C_2, C_4\) | 0.959 | \(3.38 \pm 5.24 (-7.6-15.5)\) | \(5.20 \pm 3.37 (0.0-15.5)\) | 36 (97%) |
| 10.      | \(C_1, C_2, C_4\) | 0.976 | \(3.07 \pm 5.40 (-14.9-13.2)\) | \(4.99 \pm 3.64 (0.1-14.9)\) | 37 (100%) |
| 16. c    | \(C_0, C_2, C_4\) | 0.953 | \(-1.58 \pm 5.29 (-14.9-10.1)\) | \(4.00 \pm 3.75 (0.0-14.9)\) | 37 (100%) |
| 12.      | \(C_0, C_4\) | 0.930 | \(3.55 \pm 6.30 (-9.8-14.3)\) | \(6.29 \pm 3.46 (0.1-14.3)\) | 37 (100%) |
| 4.       | \(C_2, C_4\) | 0.963 | \(-1.66 \pm 4.99 (-12.0-14.3)\) | \(4.13 \pm 3.20 (0.2-14.3)\) | 37 (100%) |
| 5.       | \(C_0, C_2, C_4\) | 0.959 | \(1.33 \pm 5.24 (-11.8-14.0)\) | \(4.22 \pm 3.32 (0.5-14.0)\) | 37 (100%) |
| 3.       | \(C_2, C_4\) | 0.965 | \(-0.20 \pm 4.79 (-10.4-13.7)\) | \(3.64 \pm 3.06 (0.2-13.7)\) | 37 (100%) |

a Number and percentage of calculated AUC_{0-12} with a prediction error within 15%.
b Bayesian estimation of the actual AUC_{0-12}.
c Limited sample strategies derived from the linear trapezoidal rule and the actual AUC_{0-12}.

tacrolimus concentrations, which consequently has no effect on the predictivity of the different LSS.
Ting et al. [23] recently suggested that LSS should only be applied on transplant patient populations that are comparable with the transplant patient population that was used to develop the LSS. However, the renal transplant patient group examined in the present study was not exactly comparable with the transplant patient populations in which the equations for the LSS were developed. For example Aumente Rubio et al. [20] and Ragette et al. [22] used heart and lung transplant recipients respectively to develop and validate their LSS. Despite the fact that the LSS were developed with the pharmacokinetic profiles of patients who underwent a different kind of transplantation, Eqs. (5), (24) and (26) were able to predict at least 90% of the AUC_{0-12} within an APE of 15%, which suggests that these LSS are more robust than expected by Ting et al. [23]. Even though LSS gave a better reflection of the tacrolimus exposure, they are currently not often applied by clinical transplant practitioners, possibly for logistical and financial reasons.
In conclusion, after validating several LSS from the literature, the present study indicates that all but three LSS gave a better prediction of the complete AUC\textsubscript{0–12} than the trough concentrations C\textsubscript{0} or C\textsubscript{12}. Moreover, LSS could produce satisfactory predictions for AUC\textsubscript{0–12} recorded in an independent renal transplant patient population, although further evaluation of their reliability is necessary.

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