Chapter 6

Evaluation of limited sampling strategies for tacrolimus

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Abstract

Background and aim

In literature, a great diversity of limited sampling strategies (LSS) have been recommended for tacrolimus monitoring, although proper validation is limited. The question is if these LSS might be useful for AUC prediction of other patient populations.

Materials and methods

The performance of 24 of these LSS in 37 renal transplant patients with known AUC's has been evaluated and the results were also compared with the predictability of the trough concentrations, C_0 and C_{12}. Criterion was an absolute prediction error (APE%) that differs less than 15% from the complete AUC_{0-12}.

Results

Thirteen of the 18 (72%) LSS based on regression analysis were capable of predicting at least 90% of the 37 individual AUC_{0-12} within an APE of 15%. Predictions based on C_0, C_{12} and Bayesian fitting were lower than 90%: 62% and 67%, respectively.

Conclusion

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

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 optimal 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 tacrolimus concentration curve (AUC_{0-12})[1]. Elevated tacrolimus concentrations may lead to severe side effects such as nephrotoxicity, neurotoxicity and hyperglycaemia[2-4] while sub-therapeutic 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 hour pharmacokinetic profiles, which implicates that the tacrolimus concentration should be measured on at least six different time points. The AUC_{0-12} can then be calculated according to the trapezoidal rule using the tacrolimus concentrations measured at different time points. Since recording a complete 12 hour pharmacokinetic profile for every patient is not feasible in clinical practice, traditionally many transplant centres use tacrolimus trough (C_0) concentrations to estimate the tacrolimus exposure. Although tacrolimus C_0 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 AUC_{0-12} 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 C_0 concentrations and the AUC_{0-12}, while tacrolimus concentrations measured at other time points showed much better correlations with the AUC_{0-12}. Additionally, strategies have been developed that consisted of a limited number of sampling time points within a short time post dose, the so called limited sampling strategies. Several two and three time point sampling strategies showed a high correlation with the AUC_{0-12} in the published studies and were able to predict the AUC_{0-12} more accurately than the C_0 concentration alone[12,15,16,18,20,22]. Based on the number of published studies regarding limited sampling strategies for tacrolimus, there seems to be a growing interest for non C_0 concentration measurements as an indicator of between patient variability and as a guide for dose adjustments. Most of these studies recommend different limited sampling strategies but these strategies have not been validated with a separate population. Ting *et al.*[23] recently reported that validation of the different limited sampling strategies with an independent transplant population is without doubt an absolute prerequisite. The question is if limited sampling strategies, described in literature could be used for the own population. Different limited sampling strategies have been selected for an evaluation in this study based on their predictive performances claimed in previous studies and their number of sample points (two or three) within a short time post dose ($\leq$ 4 hours). Evaluation of these limited sampling strategies was performed by evaluating the predictive value of 24 different limited sampling strategies from literature and also

the trough concentrations C_0 and C_{12}, determined in our own population. Parameters used for the strategy comparison was the associated determination coefficient (R^2) between the $AUC_{predicted}$ (AUC_{pred}) from the limited sampling strategy and the actual 12 hour AUC (AUC_{actual}) calculated by the trapezoidal rule, the percentage of prediction error (PE%) and the percentage of absolute prediction error (APE%) was determined using our own well-characterised late posttransplant patient group of 37 patients.

Materials and methods

Patient populations

In total 37 Caucasian renal transplant recipients of whom in the past, for a clinical trial, a 12 hour time tacrolimus concentration curve was performed, were included in this study. The transplant recipients underwent a renal transplantation at least one year ago. Patients taking medication known to interact with tacrolimus, suffered from gastro-intestinal or liver disease, pre-transplantation diabetes mellitus or other disorders that could have altered the absorption of tacrolimus were excluded for this study as is illustrated in Table 6.1. Prior to the blood sample collection, there was no tacrolimus dose change for at least one week. After overnight fasting the blood samples were collected immediately pre (C_0) and 0.5 ($C_{0.5}$), 1 (C_1), 2 (C_2), 3 (C_3), 4 (C_4), 5 (C_5), 7.5 ($C_{7.5}$) and 12 (C_{12}) hours after the morning tacrolimus administration. Patients were not allowed to take food until one hour after ingesting the tacrolimus dose and were advised to avoid grapefruit juice to prevent alterations in the tacrolimus metabolism. Demographic as well as clinical data were determined at the time of recording the 12 hour time tacrolimus concentration curve. Figure 6.1 shows the mean pharmacokinetic profile of the renal transplant recipients. The study was performed in accordance to 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 (LC) tandem mass spectrometry (MS/MS). The assay is linear from 1 to 300 μg/l. Intra-assay precision and accuracy was 3.4%, 2.2%, 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%, 4.6% and 102%, 94% and 93% (n = 9) respectively. Limit of quantification was 1.0 μg/l. The laboratory participates in an International Tacrolimus Proficiency Testing Scheme.

Table 6.1 Demographic characteristics of the two renal transplant recipients groups.

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/m^2, mean ± SD)		25.6 ± 3.42
Primary kidney disease	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	First	30
	Second	6
	Third or more	1
Tacrolimus mono therapy		29
Tacrolimus dose (mg/kg/day, mean ± SD)		0.054 ± 0.029
C_0 (ng/mL, mean ± SD)		6.59 ± 1.39
$AUC_{0\text{-}12}$ (ng × hr/ml, mean ± SD)		122.5 ± 31.1
C_{max} (ng/ml, mean ± SD)		20.9 ± 6.5
T_{max} (hr, mean ± SD)		1.24 ± 0.43
Use of azothioprine, MMF[a], rapamycine, steroids		3/4/0/0
Time since transplantation (days, mean, (range))		1542 (453–4128)
Haemoglobin (mmol/l, mean ± SD)		8.52 ± 0.83
Haematocrit fraction (mean ± SD)		0.41 ± 0.04
ALAT (U/l, mean ± SD)		24 ± 13
ASAT (U/l, mean ± SD)		17 ± 10
Serum albumin (g/l, mean ± SD,)		37.0 ± 3.84
Serum creatinine (μmol/l, mean ± SD)		128 ± 29
Creatinine Clearance (Cockcroft – Gault; ml/min, mean ± SD)		58.4 ± 26.6

[a] mycophenolate mofetil

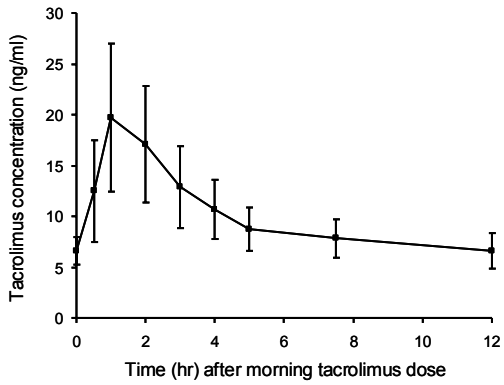

Figure 6.1 Mean (± SD) whole blood concentrations of tacrolimus in 37 renal transplant recipients.

Pharmacokinetical and statistical analysis

The area under the time tacrolimus concentration curve (AUC_{0-12}) was calculated from the time *versus* tacrolimus concentration plot using the linear trapezoidal rule in MWPharm 3.50 (Mediware, Groningen, the Netherlands). The predicted AUC_{0-12} (AUC_{pred}), calculated with 24 limited sampling strategies, 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 the validation in the studies that describe limited sampling strategies[12,14-16,18,20,22]. 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 ($\leq$ 4 hour) and is able to predict at least 90% of AUC_{0-12} within an APE (%) of 15%. Given the high pharmacokinetic variability, an APE (%) of less than 15% was considered clinically acceptable[16,25,26]. Finally, a strategy based on the tacrolimus C_0 and C_{12} concentrations is developed for our own renal transplant patient population and compared with the different limited sampling strategies that already have been published.
Prediction bias was measured by a percentage of the prediction error (PE (%)) using the following formula:

$$PE\ (\%) = 100 \times (AUC_{pred} - AUC_{actual})/AUC_{actual}$$

Prediction precision was measured by the percentage of the absolute prediction error (APE (%)) using the following formula:

$$APE\ (\%) = 100 \times |(AUC_{pred} - AUC_{actual})|/AUC_{actual}$$

The variance in the strength of association between the AUC_{pred} and the AUC_{actual} was reflected by the linear regression coefficient of multiple determination (R^2). All values are expressed as mean $\pm$ 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 6.2 shows an overview of the studies describing the limited sampling strategies evaluated in the present study. The regression equations and the R^2 found by the investigators of the limited sampling strategies evaluated are summarised in Table 6.3.

Table 6.2 Overview of the characteristics of the transplant patients included in the studies that described limited sampling strategies.

Study	Transplanted Organ	Number of patients[a]	Number of AUC_{0-12} curves for validation (I[b]/NI[c])	Analytical method[d]	Time since transplantation[e]	Inclusion criteria[f]
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[g]	2
Ragette *et al.*[22]	Lung	15	0/31	IMx	7.3 months	---

[a] number of transplant patients used in the included study for both developing and validating the limited sampling strategies. [b] number of AUC_{0-12} used for developing the limited sampling strategies described in this study. [c] number of independent (I) and dependent (NI) AUC_{0-12} used in the study to validate the created limited sampling strategies. [d] the analytical method used to determine the whole blood tacrolimus concentration. [e] the mean time after transplantation. [f] the inclusion criteria used for the transplant patients in the different studies. 1. tacrolimus is administrated when patients were in the fasting state. 2. patients have been selected for using no interfering medication with tacrolimus. 3. patients have been selected with a normal liver function test. [g] Twenty-two pharmacokinetic profiles were obtained within two weeks after transplantation, 11 pharmacokinetic profiles were obtained between two and six weeks after transplantation and 51 pharmacokinetic profile were obtained between 6 and 52 weeks after transplantation.

Table 6.3 Overview limited sampling strategies and their reported correlation coefficient (R^2) with the complete tacrolimus AUC_{0-12}.

Equation	Time points	Regression equations	R^2	Ref
1.	C_0	$14.550 + 16.387 \times C_0$	0.54	
2.	C_{12}	$15.892 + 17.852 \times C_{12}$	0.79	
3.[a]	C_0, C_2, C_4	$13.3 + 1.2 \times C_0 + 2.4 \times C_2 + 5.6 \times C_4$	0.93	16
4.[a]	C_2, C_4	$16.2 + 2.4 \times C_2 + 5.9 \times C_4$	0.93	16
5.[a]	C_0, C_2, C_4	$0.98 + 4.17 \times C_0 + 2.29 \times C_2 + 5.3 \times C_4$	0.97	20
6.	C_0, C_4	$3.75 + 5.52 \times C_0 + 6.97 \times C_4$	0.95	20
7.	C_0, C_1, C_2	$-5.496 + 7.189 \times C_0 + 2.357 \times C_1 + 2.131 \times C_2$	0.93	18
8.[a]	C_0, C_1, C_4	$3.85 + 3.688 \times C_0 + 1.355 \times C_1 + 6.649 \times C_4$	0.97	18
9.[a]	C_0, C_2, C_4	$-6.103 + 2.383 \times C_0 + 1.911 \times C_2 + 7.582 \times C_4$	0.97	18
10.[a]	C_1, C_2, C_4	$1.304 + 0.465 \times C_1 + 1.636 \times C_2 + 8.256 \times C_4$	0.96	18
11.	C_0, C_1	$9.345 + 8.408 \times C_0 + 3.23 \times C_1$	0.91	18
12.[a]	C_0, C_4	$8.231 + 2.316 \times C_0 + 9.636 \times C_4$	0.95	18
13.[a]	C_1, C_4	$13.114 + 0.873 \times C_1 + 9.291 \times C_4$	0.95	18
14.[a]	C_2, C_4	$-0.192 + 1.888 \times C_2 + 8.783 \times C_4$	0.96	18
15.[a]	C_0, C_1, C_4*	$4.5 \times C_0 + 2 \times C_1 + 5.5 \times C_4$	0.97	18
16.[a]	C_0, C_2, C_4*	$5 \times C_0 + 2 \times C_2 + 5 \times C_4$	0.96	18
17.	C_0, C_1, C_4	$8.90 + 4.0 \times C_0 + 1.77 \times C_1 + 5.47 \times C_4$	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_2	Bayesian estimation of the actual AUC_{0-12}	0.94	15
22.	C_0, C_3	Bayesian estimation of the actual AUC_{0-12}	0.96	15
23.	C_0, C_4	Bayesian estimation of the actual AUC_{0-12}	0.95	15
24.[a]	C_0, C_2, C_4	$5.87 + 4.50 \times C_0 + 1.05 \times C_2 + 5.87 \times C_4$	0.98	22
25.	C_0, C_4	$1.16 + 4.41 \times C_0 + 7.71 \times C_4$	0.96	22
26.[a]	C_2, C_4	$24.36 + 0.97 \times C_2 + 7.94 \times C_4$	0.94	22

Limited sample strategies derived from the linear trapezoidal rule and the actual AUC_{0-12}. [a] 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%.

Table 6.4 describes the R^2 that represents the association between AUC_{pred} and AUC_{actual} and the calculated PE (%) and APE (%) of the 24 evaluated limited sampling strategies for our 37 pharmacokinetic profiles. Additionally, all but three of the LSS examined gave a better prediction of the complete AUC_{0-12} in comparison with trough concentrations C_0 and C_{12} (mean 62%). Predictivity of all six limited sampling strategies based on Bayesian fitting was < 90% (mean 66.8%).

Table 6.4 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.	C_0, C_4[c]	0.760	-14.9 ± 13.8 (-46.0-33.2)	17.9 ± 9.43 (1.12-46.0)	13 (35%)
22.	C_0, C_3[c]	0.779	-11.5 ± 14.0 (-41.9-33.1)	15.7 ± 8.83 (2.0-41.9)	21 (57%)
1.	C_0	0.536	2.11 ± 14.8 (-27.1-24.4)	12.3 ± 8.22 (0.7-27.1)	22 (59%)
11.	C_0, C_1	0.703	6.58 ± 14.8 (-26.5-43.7)	12.6 ± 10.1 (0.1-43.7)	24 (65%)
2.	C_{12}	0.80	9.56 ± 11.6 (-12.7-29.9)	12.0 ± 8.97 (0.3-29.9)	24 (65%)
19.	C_0, C_2, C_3[c]	0.502	-4.44 ± 17.4 (-45.3-50.6)	13.7 ± 11.4 (0.4-50.6)	25 (68%)
20.	C_0, C_2, C_4[c]	0.537	-5.1 ± 16.3 (-43.1-50.3)	12.9 ± 10.4 (0.2-50.3)	28 (76%)
18.	C_0, C_1, C_3[c]	0.525	9.95 ± 19.4 (-29.7-88.8)	13.1 ± 17.4 (0.4-88.8)	30 (81%)
25.	C_0, C_4	0.911	-7.83 ± 6.36 (-21.3-2.4)	8.08 ± 6.02 (0.1-21.3)	30 (81%)
7.	C_0, C_1, C_2	0.869	2.35 ± 9.96 (-17.2-27.3)	8.03 ± 6.22 (0.0-27.3)	31 (84%)
6.	C_0, C_4	0.896	-5.97 ± 6.71 (-20.1-4.7)	6.63 ± 6.04 (0.6-20.1)	31 (84%)
21.	C_0, C_2[b]	0.802	-3.69 ± 10.2 (-19.6-18.6)	9.10 ± 5.67 (0.4-19.6)	31 (84%)
17.	C_0, C_1, C_4	0.943	5.91 ± 7.06 (-8.8-26.3)	7.02 ± 5.93 (0.2-26.3)	33 (89%)
15.	C_0, C_1, C_4[b]	0.934	5.00 ± 7.28 (-9.8-25.8)	6.81 ± 5.57 (0.2-25.8)	34 (92%)
14.	C_2, C_4	0.964	2.28 ± 6.58 (-17.1-16.1)	5.45 ± 4.24 (0.7-17.1)	35 (95%)
24.	C_0, C_2, C_4	0.941	-4.81 ± 5.26 (-17.3-2.8)	5.32 ± 4.73 (0.1-17.3)	35 (95%)
13.	C_1, C_4	0.973	6.30 ± 4.84 (-5.9-17.8)	6.68 ± 4.28 (0.3-17.8)	36 (97%)
8.	C_0, C_1, C_4	0.967	3.37 ± 5.21 (-5.2-17.7)	4.87 ± 3.80 (0.2-17.7)	36 (97%)
9.	C_0, C_2, C_4	0.962	0.10 ± 6.37 (-16.7-14.7)	4.71 ± 4.22 (0.3-16.7)	36 (97%)
26.	C_2, C_4	0.959	3.38 ± 5.24 (-7.6-15.5)	5.20 ± 3.37 (0.0-15.5)	36 (97%)
10.	C_1, C_2, C_4	0.976	3.07 ± 5.40 (-14.9-13.2)	4.99 ± 3.64 (0.1-14.9)	37 (100%)
16.	C_0, C_2, C_4[b]	0.953	-1.58 ± 5.29 (-14.9-10.1)	4.00 ± 3.75 (0.0-14.9)	37 (100%)
12.	C_0, C_4	0.930	3.55 ± 6.30 (-9.8-14.3)	6.29 ± 3.46 (0.1-14.3)	37 (100%)
4.	C_2, C_4	0.963	-1.66 ± 4.99 (-12.0-14.3)	4.13 ± 3.20 (0.2-14.3)	37 (100%)
5.	C_0, C_2, C_4	0.959	1.33 ± 5.24 (-11.8-14.0)	4.22 ± 3.32 (0.5-14.0)	37 (100%)
3.	C_0, C_2, C_4	0.965	-0.20 ± 4.79 (-10.4-13.7)	3.64 ± 3.06 (0.2-13.7)	37 (100%)

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

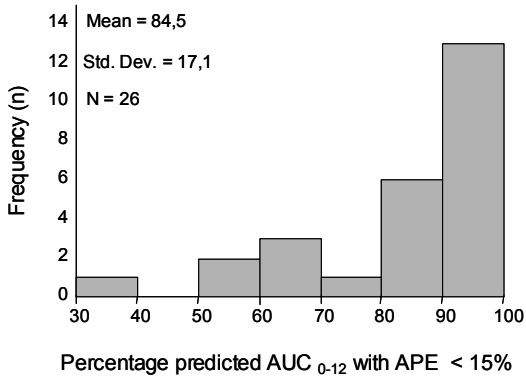

Figure 6.2 An overview of the predictive performances of the limited sampling strategies published using 37 different pharmacokinetic profiles recorded in 37 different renal transplant recipients. The mean prediction error (PE%) < 15% is plotted *versus* the frequency of the limited sampling strategies examined.

Discussion

Our results indicate like several other studies[12,14-16,18,20,22] that trough concentrations C_0 and C_{12} have a lower predictive value for the complete 12 hour AUC than most limited sampling strategies already published. Bayesian estimation of the AUC_{actual} using different two or three time point strategies is not able to predict the AUC_{actual} reliably in the renal transplant recipient group examined. The Bayesian estimation strategies showed for at least 16% of the complete AUC $_{0\text{-}12}$ an APE of more than 15%. Two or three time points in the early phase ($\leq$ 4 hour) post dose seems not to be sufficient for a Bayesian estimation strategy to fit correctly most of the $AUC_{0\text{-}12}$ and thus predict the complete $AUC_{0\text{-}12}$ reliably. The differences in variability and shape between the curves of late posttransplant recipients combined with just two or three sample points may have caused the large differences found between the AUC_{pred} calculated according to the Bayesian estimation strategy and the complete AUC_{actual}. Ting *et al.*[23] recently suggests that limited sampling strategies should only be applied on transplant patient populations that are comparable with the transplant patient population that has been used to develop the limited sampling strategy. However, the renal transplant patient group examined in the present study is not exactly comparable with the transplant patient populations in which the equations for the limited sampling strategies are developed. For example: Aumente Rubio *et al.*[20] and Ragette *et al.*[22] used respectively heart and lung transplant recipients to develop and validate their limited sampling strategies. Despite these limited sampling strategies being developed with the pharmacokinetic

profiles of patients who underwent a different kind of transplantation, equation 5, 24 and 26 are able to predict at least 90% of the AUC_{0-12} within an APE (%) of 15% which suggests that these limited sampling strategies are more robust than is expected by Ting *et al.* [23]. In conclusion, the present study indicates that limited sampling strategies from literature based on regression analysis, could produce satisfactory predictions with own patients, although careful evaluation of its reliability is mandatory.

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