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**Monitoring immunosuppression after liver transplantation :  
development of individualized Bayesian limited sampling monitoring**  
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## **CHAPTER 5**

# **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**

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## ABSTRACT

*Background:* Trough (C0) monitoring is not optimal for therapeutic drug monitoring of tacrolimus. To better estimate systemic exposure of tacrolimus and achieve clinical benefit, an improved therapeutic drug monitoring strategy should be developed.

*Methods:* The authors examined which single and combination of time points best estimated the empiric "gold standard"  $AUC_{0-12h}$  and developed and validated a new, flexible, and accurate limited sampling model for monitoring tacrolimus in patients having undergone liver transplantation. Twenty-three stable patients with full  $AUC_{0-12h}$  were divided into two groups based on area under the concentration-time curve/dose. With multiple regression analysis, limited sampling formulae were derived and population-pharmacokinetic-based limited sampling models were developed and validated. A regression analysis was performed between either area under the concentration-time curves calculated with formulae or models with the reference trapezoidal  $AUC_{0-12h}$ .

*Results:* Both formulae and models based on single samples C4-C6 ( $r^2 = 0.94$  [MPE/MAPE 0/7]-0.90 [2/8] and 0.97 [0/7]-0.97 [1/5]) showed excellent performance. The calculated area under the concentration-time curve target range for tacrolimus was 90 to 130 h\* $\mu$ g/L. Multiple point sampling performed better, especially when using models ( $r^2 > 0.94$ ). C0 was a less precise predictor of  $AUC_{0-12h}$  compared with both formulae and models ( $r^2$ 's 0.68 [5/17] and 0.87 [2/14]).

*Conclusion:* Trough concentration monitoring is not an accurate method for assessing systemic exposure to tacrolimus in stable patients having undergone liver transplantation. This new limited sampling model, based on single time points C4-C6, shows excellent performance in estimating the  $AUC_{0-12h}$ .

## **INTRODUCTION**

The calcineurin inhibitor tacrolimus is widely used for immunosuppression after orthotopic liver transplantation (OLT). Tacrolimus has a small therapeutic window, underexposure can result in rejection whereas overexposure can lead to adverse effects, especially nephrotoxicity. Accurate monitoring of this drug is therefore mandatory to improve clinical outcome<sup>1,2</sup>. For cyclosporine, another calcineurin inhibitor, different methods have been developed to estimate systemic exposure using the area under the concentration-time curve (AUC), which can result in better clinical outcome in terms of reduction of toxicity and improved renal function<sup>3-13</sup>.

Monitoring tacrolimus (FK-506, Prograf Astellas Pharma, Stainer, UK) therapy is still based on trough concentration (C<sub>0</sub>) monitoring in most centers. However, recent data have shown that C<sub>0</sub> does not accurately reflect systemic exposure over the first 12 hours after dosing<sup>14</sup>. Patients with similar C<sub>0</sub> tacrolimus concentrations can have very different AUCs. Other studies in liver and kidney transplantation have suggested different time points at which better predictions of systemic exposure of tacrolimus can be made than using trough concentrations<sup>14-17</sup>.

When better prediction of total systemic exposure of tacrolimus in the first 12 hours after dosing is possible, we may see improved clinical outcome in terms of fewer rejection episodes and lowering of toxicity.

The aim of the present study was to examine which single time point or combination of time points best reflect systemic exposure of tacrolimus by calculating the area under the curve and then to develop and validate a new, flexible, and accurate limited sampling model, which is easy to apply in clinical practice as we have shown previously for cyclosporine<sup>18,19</sup>.

## **PATIENTS AND METHODS**

Twenty-three stable patients having undergone liver transplantation from Leiden University Medical Center, who were at least 6 months post-OLT (11 men, mean age 45 years, range 31-73 years; 12 women, mean age 44 years, range 21-70 years) were included. Twenty-two patients received tacrolimus (Astellas Pharma Inc., Deerfield, IL) twice daily and one patient only once daily 0.5 mg in the morning. Mean morning tacrolimus dose was  $3.0 \pm 0.35$  mg (range, 0.50-8.00 mg). In our liver transplant clinic, trough concentration monitoring is used with a target range of 5 to 10 µg/L for patients more than 3 months after OLT<sup>20</sup>.

All patients provided informed consent and the study was approved by the Medical Ethical Committee of the Medical Center. Stable patients having undergone liver

transplantation were selected and visited our clinic for 1 day. The patients had no infections or other complications and were not receiving any interacting comedication. Specifically, bilirubin and albumin levels were not outside clinical reference ranges. Five minutes before taking the morning dose of tacrolimus (approximately 10:00 AM), blood samples were taken for liver and kidney function and tacrolimus (C0) concentration. The patients were instructed to take their evening dose of tacrolimus the night before the morning of the study visit at 10:00 pm. Further blood samples for tacrolimus concentration were collected at 1, 2, 3, 4, 6, and 8 hours after administration of the morning dose of tacrolimus. Because these were stable patients, the C12h concentration was taken to be the same as the C0h, assuming steady-state conditions<sup>17</sup>. It was checked by interview that there were no dose changes in the previous week. Blood was drawn using an indwelling catheter and collected in a Vacutainer (Becton Dickinson Diagnostics, Franklin Lakes, NJ) containing EDTA. Whole blood tacrolimus concentrations were determined by Microparticle Enzyme Immuno Assay (IMx; Abbott Diagnostics, Abbott Park, IL). To lower the influence of meals, the patients were instructed to take only a light breakfast-tea and a biscuit-on the morning the AUC was measured, and until the 2 hours sample (C2), no additional food or drinks were taken<sup>21</sup>.

AUC<sub>0-12h</sub> of all 23 curves were calculated with the trapezoidal rule using the software package MW\Pharm version 3.60 (Mediware, Groningen, The Netherlands)<sup>22,23</sup>. The patients were assigned to a group on the basis of a climbing AUC/dose ratio in a 1:1 fashion. Starting with a low ratio, the first patient entered one group and the second patient entered the other group until all patients were divided among the two groups. Therewith, two groups with a comparable clearance distribution were formed: group 1 (n = 11) and group 2 (n = 12). Data from group 1 were used to calculate limited sampling formulae (LSF) and for the development of a population pharmacokinetic (POP-PK) model. Data from group 2 were used to validate this POP-PK model. The POP-PK model integrated all available information obtained from PK sampling and generated a population model. This model was used to obtain individualized pharmacokinetic parameters (individualized PK model based on Bayesian fitting) on the basis of new PK information (samples at single or multiple time points) from new patients, allowing individualized dose advice to be given. This Bayesian approach is a flexible alternative to methods using limited sampling formulae that have fixed sampling times<sup>24</sup>.

Several single blood sampling time points (C0, C1, C2, C3, C4, C6, and C8) and combinations of these samples were examined, 23 in total. We compared the performance of limited sampling models (LSM) with the more rigid limited sampling formulae. Finally, we performed a validation step and calculated a new target range as a basis for future implementation in clinical practice.

### Limited Sampling Formulae

Using multiple regression analysis (SPSS software; SPSS Inc., Chicago, IL) for group 1, relatively simple limited sampling formulae (linear functions) were calculated based on one sample or a combination of measured blood concentrations: 0 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 0 + 1 h, 0 + 2 h, 0 + 3 h, 0 + 1 + 2 h, 0 + 1 + 3 h, 0 + 2 + 3 h, 0 + 1 + 2 + 3 h, 1 + 3 h, 1 + 4 h, 2 + 3 h, 2 + 4 h, 2 + 3 + 4 h, 3 + 4 h, 3 + 4 + 6 h, 3 + 6 h, and 4 + 6 h. Their ability to estimate the AUC was tested on group 2.

### Limited Sampling Models

Using the "Kinpop module" of MW\Pharm, a population two-compartment model with first-order absorption pharmacokinetics and without a lag time was calculated from the tacrolimus dosing, body weight, and blood concentration values of group 1. This program uses an iterative two-stage Bayesian procedure and calculates means, medians, and standard deviations of the pharmacokinetic parameters<sup>25</sup>. During this procedure, pharmacokinetic parameters were set to be distributed log-normally, and bioavailability was fixed for tacrolimus at 0.23 as a result of the absence of intravenous data and on the basis of literature values<sup>26</sup>.

The calculated mean POP-PK parameters based on group 1 were individualized for the 12 patients of group 2 based on tacrolimus dosing and weight and one or a combination of measured blood concentration as mentioned for LSF.

AUCs ( $\mu\text{g/L}\cdot\text{h}$ ) for group 2 were calculated using the following formula:

$AUC = (F_{po} * dose * 1000) / clearance$  in which  $F_{po}$  is bioavailability, which is fixed at 0.23 for tacrolimus, the dose (mg) is the morning dose of tacrolimus, and clearance (L/h) is the clearance of tacrolimus calculated for any of the 12 patients of group 2 for each time point or combinations of time points as for LSF (Figure 1).

Finally, a regression analysis was performed for both the LSF and the LSM with the reference trapezoidal  $AUC_{0-12h}$ .

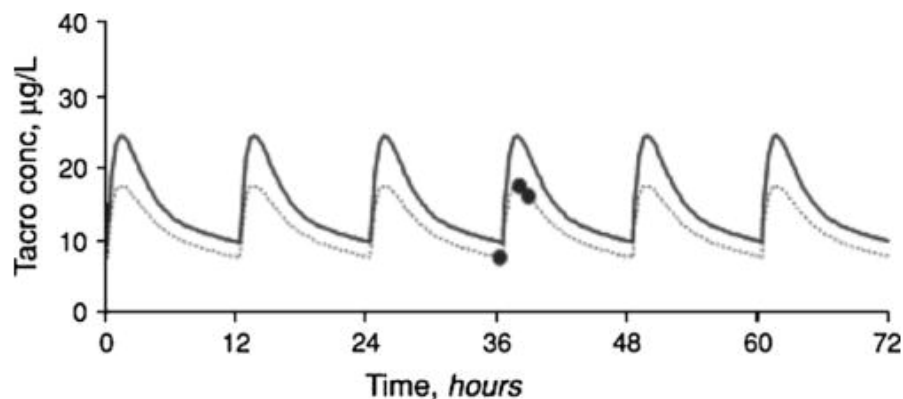


FIGURE 1. Tacrolimus blood concentration-time curve according to the population-based model (continuous line), the measured tacrolimus blood concentrations at  $t = 0$  h, 2 h, 3 h in a patient ( $\bullet$ ), and the tacrolimus blood concentration-time curve according to the model after fitting the population parameters to the measured concentrations (dotted line) after which the  $AUC_{0-12h}$  is calculated by the model.

## Statistics

Statistical analysis of patient data was performed using SPSS 13.0 for Windows. Results are expressed as mean  $\pm$  standard deviation and as median and range.

AUCs calculated by the different methods were compared with the trapezoidal calculated  $AUC_{0-12h}$  by linear regression analysis (MW\Pharm) and Pearson correlation coefficient. P values below 0.05 were considered statistically significant.

Predictive performance of the different methods was also investigated by calculating the prediction precision and bias, which is deduced from the paper by Sheiner and Beal<sup>27</sup>.

Prediction bias was calculated as the mean prediction error (MPE), that is the mean of differences between the  $AUC_{0-12h}$  according to the different methods and the gold standard  $AUC_{0-12h}$ . Prediction precision was calculated as the mean absolute prediction error (MAPE), that is the mean of the absolute differences between  $AUC_{0-12h}$  according to the different methods and the gold standard  $AUC_{0-12h}$ . Smaller values for MPE and MAPE indicate less bias and greater precision (practical clinical range based on smallest possible dose adjustment:  $\pm 10\%$ ).

## RESULTS

Using multiple regression analysis, LSFs were calculated from 11 curves (group 1) based on one or a combination of measured blood concentrations. A few examples are shown in Table 1. The results of the performance in estimating the gold standard  $AUC_{0-12h}$  (derived by the trapezoidal rule) of these LSFs are shown in the lower part of Table 2.

| Time points<br>blood sampling | Formula  |
|-------------------------------|--|
| LSF 0 h                       | $AUC_{0-12h} = 40.858 + 12.53 * C_0$                             |
| LSF 4 h                       | $AUC_{0-12h} = -0.083 + 11.555 * C_4$                            |
| LSF 6 h                       | $AUC_{0-12h} = 18.694 + 11.967 * C_6$                            |
| LSF 8 h                       | $AUC_{0-12h} = 17.399 + 13.386 * C_8$                            |
| LSF 0, 1, 3 h                 | $AUC_{0-12h} = 5.023 + 4.27 * C_0 + 1.24 * C_1 + 5.04 * C_3$     |
| LSF 0, 2, 3 h                 | $AUC_{0-12h} = 11.884 + 5.842 * C_0 + 1.252 * C_2 + 3.841 * C_3$ |
| LSF 1, 4 h                    | $AUC_{0-12h} = -4.9 + 0.843 * C_1 + 10.556 * C_4$                |

TABLE 1. Examples of Limited Sampling Formulae (LSF) Derived Using Multiple Regression Analysis.

| Time Points Blood Sampling  | r <sup>2</sup> | MPE (%) | MAPE (%) |
|---|----------------|---------|----------|
| Without model or formula  |                |         |          |
| 0   | 0.69           |         |          |
| Individualized POP-PK model (LSM)                                 |                |         |          |
| 0   | 0.87           | 2       | 14       |
| 4   | 0.97           | 0       | 7        |
| 6   | 0.97           | 1       | 5        |
| 8   | 0.88           | 0       | 8        |
| 0, 2  | 0.96           | 3       | 6        |
| 0, 1, 3   | 0.99           | 3       | 5        |
| 0, 2, 3   | 0.98           | 2       | 5        |
| 1, 3  | 0.98           | 2       | 10       |
| 1, 4  | 0.96           | 4       | 7        |
| 3, 4  | 0.95           | -1      | 9        |
| 4, 6  | 0.98           | 1       | 4        |
| Limited sampling formulas (LSFs)                                  |                |         |          |
| 0   | 0.68           | 5       | 17       |
| 4   | 0.94           | 0       | 7        |
| 6   | 0.90           | 2       | 8        |
| 8   | 0.93           | 2       | 8        |
| 0, 2  | 0.89           | 1       | 8        |
| 0, 1, 3   | 0.98           | 0       | 4        |
| 0, 2, 3   | 0.95           | 1       | 6        |
| 1, 3  | 0.94           | 1       | 7        |
| 1, 4  | 0.96           | 0       | 5        |
| 3, 4  | 0.94           | 0       | 6        |
| 4, 6  | 0.94           | 0       | 7        |
| MPE, mean prediction error; MAPE, mean absolute prediction error. |                |         |          |

TABLE 2. Performance of Estimation of AUC<sub>0-12h</sub> of Limited Sampling Models (LSMs) and Limited Sampling Formulae (LSFs).

The best single point markers for tacrolimus monitoring in terms of predicting systemic exposure (gold standard AUC<sub>0-12h</sub>) to tacrolimus using LSF were C4 (r<sup>2</sup> = 0.94 [MPE/MAPE 0/7]), C6 (r<sup>2</sup> = 0.90 [2/8]), and C8 (r<sup>2</sup> = 0.93 [2/8]), all P < 0.05.

Precise multiple-point combinations using LSF were, for example, C1 + C4 (r<sup>2</sup> = 0.96 [0/5]), C0 + C2 + C3 (r<sup>2</sup> = 0.95 [1-6]), and C0 + C1 + C3 (r<sup>2</sup> = 0.98 [0/4]), all P < 0.05.

The calculated mean POP-PK parameters based on group 1 are shown in Table 3. The upper part of Table 2 shows the performance of the individualized POP-PK model (LSM) in estimating the gold standard AUC<sub>0-12h</sub>, the MPE and MAPE for single- and multiple-point sampling, validated on 12 patients (group 2).



| Parameter                                  | Mean ( $\pm$ Standard Deviation) |
|--|----------------------------------|
| CL <sub>m</sub> (L/h/1.85 m <sup>2</sup> ) | 3.9834 $\pm$ 2.0629              |
| V <sub>1</sub> (L/kgLBMc)                  | 0.2469 $\pm$ 0.0898              |
| K <sub>12</sub> (/h)                       | 0.5661 $\pm$ 0.2311              |
| K <sub>21</sub> (/h)                       | 0.1464 $\pm$ 0.0620              |
| K <sub>a</sub> (/h)                        | 1.2595 $\pm$ 1.1188              |
| F <sub>po</sub>                            | 0.23 (fixed)                     |

CL<sub>m</sub>, apparent clearance; V<sub>1</sub>, volume (central); K<sub>12</sub>, distribution rate constant (central to peripheral compartment); K<sub>21</sub>, distribution rate constant (peripheral to central compartment); K<sub>a</sub>, absorption rate constant; F<sub>po</sub>, oral bioavailability.

TABLE 3. Population Pharmacokinetic Parameters Calculated Using an Iterative Two-Stage Bayesian Procedure.

The best single point samples in terms of estimating systemic tacrolimus exposure using LSM appeared to be C4 and C6, which show excellent performance with the gold standard AUC<sub>0-12h</sub> (both  $r^2 = 0.97$ ,  $P < 0.05$ ) with excellent precision and bias (MPE/MAPE 0/7 and 1/5) (Figure 2).

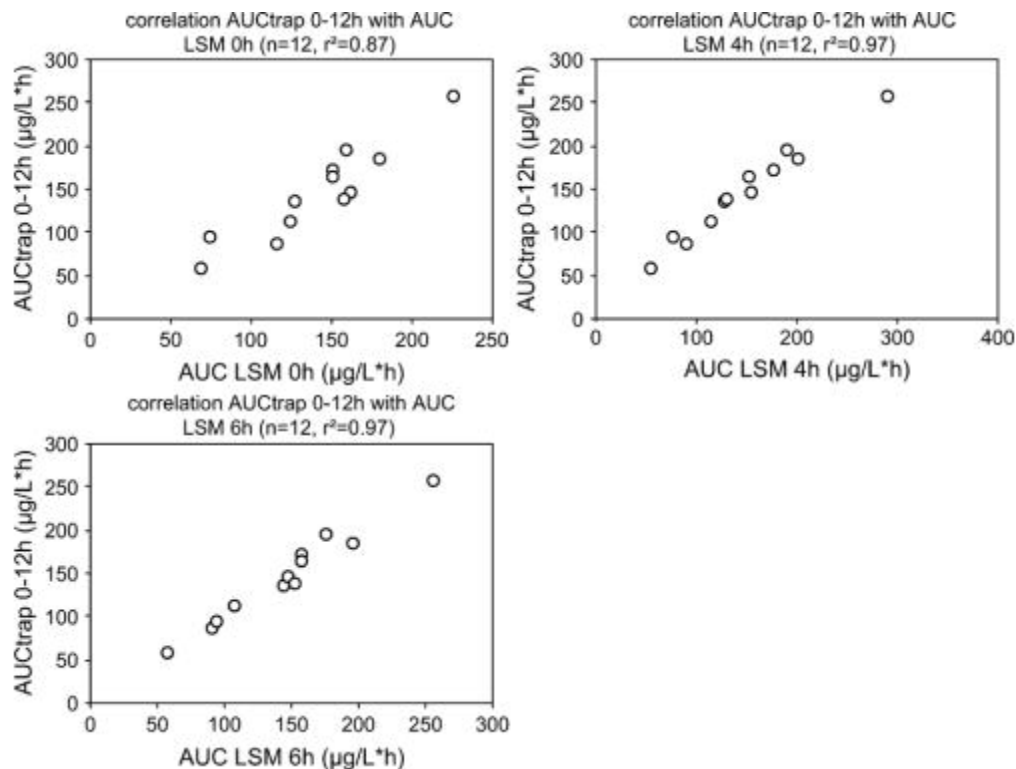


FIGURE 2. Performance of area under the concentration-time curves limited sampling model (LSM) 0 h, LSM 4 h, and LSM 6 h with "gold standard" AUC<sub>0-12h</sub>.

Except for LSM 0 + 1 h, all examined multiple-point LSMs showed excellent performance in estimating the gold standard  $AUC_{0-12h}$  (Table 2;  $r^2 = 0.94$  or higher, not all data shown).

The widely used C0 showed poorer performance with the gold standard  $AUC_{0-12h}$  both for LSF and LSM ( $r^2 = 0.68$  and  $0.87$ ). More importantly, prediction precision for both methods was relatively high (MAPE 17% and 14%). Without using a model or formula, the  $r^2$  of C0 with  $AUC_{0-12h}$  was  $0.69$ .

Based on the C0 target range of 5 to 10  $\mu\text{g/L}$  for patients more than 3 months after OLT, we calculated an AUC target range with the use of the pharmacokinetic software package MW\Pharm. This range is 95 to 190  $\text{h}\cdot\mu\text{g/L}$  (target =  $[95 + 190]/2 = 142.5 \text{ h}\cdot\mu\text{g/L}$ ).

The range can also be derived from Figure 3. This figure visualizes the relationship between the tacrolimus trough concentrations and AUC for this population of patients undergoing OLT. A wide range of AUC values is observed corresponding to the C0 monitoring range of 5 to 10  $\mu\text{g/L}$ .

From this figure, possible other (lower) AUC target ranges can be deduced from trough concentration ranges (inserted range; see figure), eg, 4 to 8  $\mu\text{g/L}$  (see "Discussion").

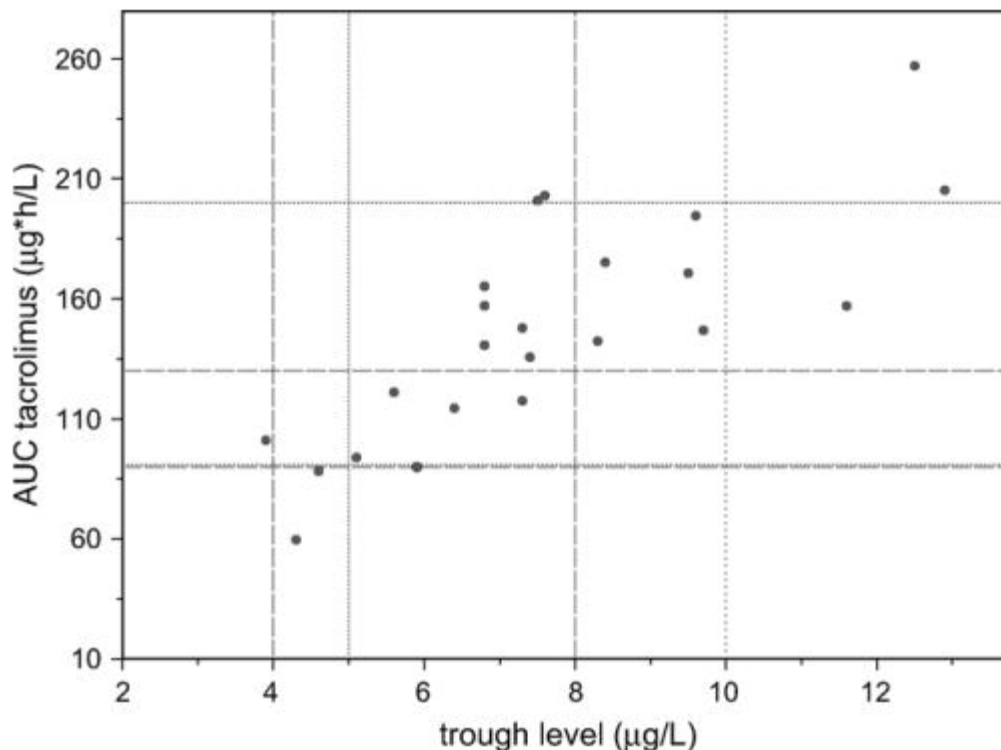


FIGURE 3. Relationship between trough concentration (C0) and area under the concentration-time curve (AUC) of all 23 patients while on C0 monitoring. The thin dotted lines (.....) show the range based on trough concentration monitoring of 5 to 10  $\mu\text{g/L}$  (AUC target 142.5  $\text{h}\cdot\mu\text{g/L}$ ). The other lines ( - - - - ) show the proposed AUC range based on trough concentration monitoring of 4 to 8  $\mu\text{g/L}$ , which is 80% lower than 5 to 10  $\mu\text{g/L}$  (AUC target 110  $\text{h}\cdot\mu\text{g/L}$ ; range, 90-130  $\text{h}\cdot\mu\text{g/L}$ ).

## DISCUSSION

In this study, we demonstrated that C0 monitoring for tacrolimus after liver transplantation is not precise and does not accurately reflect systemic exposure. We developed and validated individualized POP-PK models based on C4 or C6, which appear to accurately reflect systemic exposure of tacrolimus with excellent precision and bias. Recent studies on tacrolimus monitoring have suggested that trough concentrations, as currently used in most centers for therapeutic drug monitoring of tacrolimus, are not the best estimators of systemic exposure of this drug. These studies have involved different types of organ transplantation and vary in time after transplantation<sup>28-30</sup>. In our study, C0 monitoring did not have a good performance in estimating  $AUC_{0-12h}$  without using LSF and LSM ( $r^2 = 0.69$ ), or with using LSF ( $r^2 = 0.68$  [MPE/MAPE 5/17]). Performance of C0 with  $AUC_{0-12h}$  using LSM seems to be acceptable ( $r^2 = 0.87$ ), but concentrating on MPE and MAPE, we conclude that the prediction precision (MAPE) is not in an acceptable range of  $\pm 10\%$  (MAPE 14%). Figure 3, which illustrates all 23 patients while on C0 monitoring, already showed a wide range of AUC values corresponding to the (currently accepted) C0 range of 5 to 10  $\mu\text{g/L}$ . This confirms that trough concentrations do not adequately reflect systemic exposure of tacrolimus. Our finding that sampling between 4 and 6 hours postdosing seems optimal is in line with two other studies that suggested C4 and C5 sampling, respectively<sup>15,16</sup>. Our model has the advantage that it is very flexible. Others also found C0 insufficient in different patient populations<sup>16,17</sup>. Likewise, in cyclosporine monitoring, C0 and even C2 monitoring did not appear to be optimal, and several methods for optimizing therapeutic drug monitoring were developed by our group and others<sup>3,6,7,13,19</sup>. A limitation of our models and formulae is that these were developed and validated in two small independent groups of stable patients more than 6 months after liver transplantation. Given the considerable changes in tacrolimus kinetics shortly after transplantation, we cannot recommend using these models in less stable patients or early posttransplantation. For the period early after OLT, new models would need to be developed and validated.

The results concerning correlation with  $AUC_{0-12h}$  for both LSF and LSM were satisfying with slightly better results for the model. The advantage of this model over LSF is that the model is flexible and no fixed time points are needed in contrast to the rigid formulae. As long as the exact time of blood sampling is noted, it is possible to use this time (and blood concentration) in the model as a result of the fact that this approach is based on Bayesian estimation. The AUC is calculated after estimating the individual clearance and dose advice is given.

Comparing single and multiple point monitoring, the latter group showed, in most cases, a slightly better performance in estimating  $AUC_{0-12h}$ .

However, despite this slightly better performance, LSM C4 and LSM C6 already had  $r^2$ 's of 0.97 (MPE/MAPE 0/7 and 1/5). Therefore, these single point LSMs seem sufficient. For practical reasons, both the C4 and the C6 model seem feasible. Patients can take their medication at home, visit the hospital for checkups, and blood can be drawn 4 to 6 hours after the morning dose, not interrupting the medication schedule. There is no need to take the blood sample exactly on time as long as the dosing and blood sampling time are recorded. These factors, in combination with the adequate performance of the model in the outpatient setting, which is normally a source of variability, provides a tool for adequate monitoring of tacrolimus.

The calculated AUC target range based on C0 monitoring (90-195 h\* $\mu$ g/L) is rather wide, which also suggests that C0 monitoring is not the optimal way for therapeutic drug monitoring of tacrolimus. In kidney transplantation in our clinic, for stable patients, a target AUC of 125 h\* $\mu$ g/L is adhered to (range, 100-150 h\* $\mu$ g/L), corresponding to a trough concentration of 7.5  $\mu$ g/L<sup>17</sup>.

Currently, in the field of OLT, a trend with regard to reduction in calcineurin inhibition is noticeable. In a review article from Staatz et al, lower targets are described for liver transplantation compared with kidney transplantation<sup>31</sup>. With respect to this trend, and after observing Figure 3, we decided to adopt a new target, slightly lower than used for kidney transplantation, in the stable period more than 6 weeks posttransplantation<sup>17</sup> and also lower than the range corresponding with C0 = 5 to 10  $\mu$ g/L, which we were using in our clinic.

Thus, for the last 6 months, we have lowered the C0 range from 5 to 10  $\mu$ g/L to the arbitrary range of 4 to 8  $\mu$ g/L, which is 80% of the original range, without rejection (data not shown). We now calculate a new AUC target and AUC target range, which is 80% of the original AUC target (142.5  $\mu$ g/L) and which is based on the lowest possible dose adjustment of 0.5 mg, which would be, respectively, 110 h\* $\mu$ g/L for the target and 90 to 130 h\* $\mu$ g/L for the range. The new target AUC of 110 h\* $\mu$ g/L is based on the C0 concentration of  $(4 + 8)/2 = 6$   $\mu$ g/L. The new range (90-130 h\* $\mu$ g/L) is wider than the lowest possible dose adjustment of 0.5 mg, which makes it practical in daily use. The new target is visualized in Figure 3 and the clinical consequences will be studied prospectively.

The current trend toward lower target ranges underlines the need for precise monitoring, because tacrolimus underexposure should be avoided with respect to the prevention of rejection episodes. High tacrolimus exposure should be avoided as well, especially in the stable phase post-OLT, with regard to clinical toxicity such as nephrotoxicity, which could have a clear negative impact on patient and graft survival<sup>1,2</sup>.

With more accurate prediction of systemic exposure of tacrolimus in the first 12 hours after dosing with the individualized LSMs C4 or C6, we have developed we expect

improvement in clinical outcome such as decrease in rejection rate, less (nephro)toxicity, and fewer infections. We are planning further validation with a prospective, randomized, controlled trial comparing C0 and LSM 4 h (or 6 h) monitoring, which includes clinical outcome parameters such as renal function, blood pressure, rejection, and laboratory parameters.

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