A Nomogram for Predicting Optimal Dosage of Cyclosporine in Renal Transplant Patients: Taking Physiological Factors into Consideration for Regimen during Immunosuppressive Therapy

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We constructed a nomogram for determining the optimal regimen of cyclosporine (CyA), based on physiological changes that occur during immunosuppressive therapy. The nomogram consists of a fixed model and a variable model. In the fixed model, the oral dose of CyA (D, mg/kg) is given by the multiple linear function of logarithmic CyA trough level (TL, ng/ml), the surrogate apparent total body clearance of CyA (CL/fuo, 1/h/kg, being equal to D/TL/12), and the erythrocyte-to-plasma distribution ratio of CyA (CyA-EP), as defined by: 

\[ D = 4.938 \times \log(\text{TL}) + 1.5037 \times \text{CL}/fuo - 0.0326 \times \text{CyA-EP} - 10.7165. \]

In the variable model, the CL/fuo is given by the CyA-EP and the patient's intrinsic parameters (P₁, P₂), using a nonlinear equation: 

\[ \text{CL}/fuo = P₁ \times \exp(P₂ \times \text{CyA-EP})/\text{CyA-EP}. \]

An optimal CyA dose to maintain a desired trough level was calculated, and the validity of the nomogram was found satisfactory for clinical use. This offers a very concise and practical method for the therapeutic monitoring of CyA.

Because the pharmacokinetics of CyA depends on physiological changes due to several disease states, and because the CyA-EP reflects the pharmacokinetics of CyA and the patient's disease state, the proposed nomogram is believed to provide an optimal dosage adjustment, taking physiological factors into consideration.

Key words cyclosporine; erythrocyte-to-plasma distribution; renal transplantation; optimal dosage adjustment; nomogram

Cyclosporine (CyA), a potent immunosuppressive agent of fungal origin, has been widely used to inhibit graft rejection in renal, hepatic, cardiac, lung, pancreatic, and bone marrow transplantation.1–3) This drug has been largely responsible for recent successful results in transplantation; however, it has been difficult to distinguish between its clinical efficacy and side effects, since the pharmacokinetics of CyA is affected by changes in various physiological factors relating to the patient's disease state after transplantation.4) In a series of previous reports,5–7) we found that the erythrocyte-to-plasma distribution ratio of CyA (CyA-EP) was a useful indicator for CyA monitoring, since this ratio reflected the disease state and the pharmacokinetics of the agent. To date, however, no optimal CyA dosage regimen suitable for clinical use in the disease states found in transplant patients has yet been established.

In this study, using monitoring data we accumulated in renal transplant patients, we constructed a nomogram for an optimal CyA regimen by introducing the concept of the CyA-EP, a ratio which reflects CyA pharmacokinetics due to physiological changes occurring during various disease states following renal transplantation.

MATERIALS AND METHODS

Patients and Sample Treatment The monitoring data used in creating the fixed model were obtained from 20 patients (13 males, 7 females; aged 9 to 56 years; 12 cadaver donors, 8 living-related donors) during the routine clinical monitoring of CyA. The data used for retrospective evaluation of validity of the model equations were obtained from five other renal transplant patients (A–E). For prospective evaluation, the nomogram was applied to one more patient (F). Informed consent was obtained from all patients. Before renal transplant, physicians outlined to their patients the procedure for the surgery, immunosuppressive therapy with CyA, the lesser and major adverse effects of CyA, and the procedures involved in several clinical tests used to evaluate clinical efficacy, including blood collection for this study. The written agreement of each patient was obtained and this became part of his or her medical record. Immunosuppression after renal transplant was achieved with triple therapy consisting of CyA (Sandimmun®), oral solution or soft gelatin capsules, the two formulations are regarded as bioequivalent4), prednisolone, and azathioprine. Patients received oral CyA (2.2 to 7.5 mg/kg/d), given in two divided doses at 12-h intervals throughout the study period. Blood samples for routine monitoring (trough) were collected in heparinized tubes from the cubital vein in the morning (6:00 a.m.) before the next dose, once or twice a week.

Biochemical Tests Hepatic function was assessed by determining glutamate-pyruvate transaminase activity (GPT, IU/l), and renal function was assessed in terms of serum creatinine (SCr, mg/dl). As factors that regulate the erythrocyte-to-plasma distribution of CyA (CyA-EP), we selected the hematocrit (HCT, %), and triglyceride (TG, mm) and cholesterol (CHO, mm) levels in plasma. TG is a major component of chylomicrons and very low-density lipoprotein, while CHO is a major component of high- and low-density lipoproteins. Thus, TG+CHO is correlated with the total amount of plasma lipoproteins. The results of these biochemical tests were obtained, with the physicians' agreement, employing the SHINE computer on-line system at Shiga University of Medical Science.

Calculation of CyA-EP The CyA-EP was calculated from the following relationship:

\[
\text{CyA-EP} = 6.0831 - 0.2944 \times (\text{TG} + \text{CHO}) - 0.0037 \times \text{TL} - 0.0553 \\
\times \text{HCT} + 0.0463 \times \text{BW} + 0.447 \times \text{SCr} - 0.0366 \times \text{AGE}.
\]

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where TL, BW, and AGE represent the trough CyA concentration (ng/ml) in whole blood, the patient’s body weight (kg), and the patient’s age (years), respectively.\(^6\)

This predictive model is a helpful monitoring device to detect tissue toxicity or changes in CyA pharmacokinetics in several disease states after transplantation. Equation 1 includes important variables (HCT which reflects the volume of erythrocyte fraction, TG + CHO which reflects the amount of lipoproteins) regulating the blood distribution of CyA, and alterations in those variables are due to a disease state such as renal or hepatic dysfunction, anemia, hyperthyroidism, dyshemopoiesis, or hypoadrenalism. Thus, CyA-EP is an intensive parameter reflecting the CyA pharmacokinetics at various disease states after renal transplantation. With using this equation, therefore, we can determine the CyA-EP using routine monitoring data without direct measurement of the CyA-EP, and we used in subsequent analysis.

**Relationship between Surrogate and Nonparametric Apparent Total Body Clearance** The surrogate apparent total body clearance of CyA (\(CL/f_{su}\), l/h/kg) was calculated by the equation:

\[
CL/f_{su} = D/TL/12 \quad (2)
\]

where \(D\) and \(TL\) represent one oral dose (mg/kg) and the CyA trough concentration (µg/ml), respectively, and the dose interval is fixed at 12h. To theoretically expand the use of \(CL/f_{su}\) we first examined the relationship between the \(CL/f_{su}\) and nonparametric apparent total body clearance (\(CL/f_{non}\), l/h/kg). Whole blood CyA concentration versus time curves \((n = 32)\) after oral administration obtained in our laboratory during the therapeutic monitoring of renal transplant patients for the past ten years were used to determine the relationship between the \(CL/f_{su}\) and the \(CL/f_{non}\). Details of sample collection time were described previously.\(^9\)

**Fixed Model** To derive a multiple regression equation for CyA dosage, linear relationships between the TL, the CyA-EP, the \(CL/f_{su}\), and the \(D\) were examined, and the most significant multiple regression equation was selected as judged by its coefficient of determination \((R^2)\). Multiple regression analysis was carried out by the stepwise method, and a regression was considered significant if the \(p\)-value for a correlation coefficient was less than or equal to the 0.05 level of significance determined by the F-distribution test. Multicollinearity between each of the variables was checked with the variance information factor (VIF), as defined by the equation: \(VIF = 1/(1 - r^2)\), where \(r\) represents the correlation coefficient in a bivariate analysis. If the VIF between an independent variable and a dependent variable is >10, the independent variable brings marked error to an estimate of the dependent variable. These regression analyses were performed with a statistical software package, Seto/B (Kyouritsu Publishing Co., Ltd., Japan).

**Variable Model** To reflect the intra- and interindividual variability in CyA pharmacokinetics on the fixed model, we further defined the \(CL/f_{su}\) in the fixed model as a variable model. Since the CyA-EP is a useful index by which to reflect alterations in CyA pharmacokinetics and in the patient’s disease state,\(^5 - 7\) we regarded the \(CL/f_{su}\) as a variable effect function of the CyA-EP as follows:

\[
CL/f_{su} = P_1 \times \exp(P_2 \times CyA-EP)/CyA-EP \quad (3)
\]

where \(P_1\) and \(P_2\) represent individual parameters for each patient.\(^9\)

**Retrospective Evaluation** The mixed model for predicting CyA dosage, consisting of the fixed and variable models, was validated retrospectively by applying it to an additional group of renal transplant patients \((n = 5)\). A nonlinear least squares method (MULTI\(^10\)) was used to estimate individual parameters \((P_1, P_2)\) in Eq. 3. As described by Sheiner and Beal,\(^11\) the accuracy and bias of the model were evaluated by calculating the mean prediction error (ME) and root mean squared error (RMSE).

**Clinical Use** The mixed model was further converted into a prospective version, and we simultaneously drew up a nomogram for a renal transplant patient (F) and evaluated its prospective use. Individual parameters in the variable model were estimated in the same way as in the retrospective study.

**Drug Assay** CyA concentration in whole blood was measured by a monoclonal fluorescence polarization immunoassay (m-FPIA) method, run on the TDx assay system (Abbott Laboratory). The m-FPIA was carried out automatically on the TDx assay system, according to the procedures outlined in the Abbott assay manual.\(^12\) The procedure for sample preparation has been described elsewhere.\(^13\)

**RESULTS**

**Characteristics of Data Used for Analysis** A total of 201 samples from 20 renal transplant patients were used for the data analysis. The basic statistics of these data are summarized in Table 1. Data sampling period was from days 5 to 3751 after renal transplantation. Samples in the no-episode group (GPT < 40 IU/l, SCr < 1.5 mg/dl) numbered 70 (34.8% of total, obtained on days 31 to 2928 after transplantation); those in the renal dysfunction phase (GPT < 40 IU/l, SCr > 1.5) numbered 113 (56.2% of the total, obtained on days 5 to 3751); in the hepatic dysfunction phase (GPT > 40, SCr < 1.5) there were 10 samples (5% of total, obtained on days 38 to 59); and during the hepatic and renal dysfunction phase (GPT > 40, SCr > 1.5) there were 8 (4.0% of the total, obtained on days 32 to 66). For all data, the \(CL/f_{su}\) and the CyA-EP ranged from 0.30 to 4.46 l/h/kg and 0.906 to 10.002, respectively. Figure 1 shows the relationship between the \(CL/f_{su}\) and \(CL/f_{non}\) defined by dividing the oral CyA dose by area under the concentration versus time curves (AUC). There was a strong correlation between these parameters \((r = 0.615, p < 0.001, n = 32)\), suggesting that the \(CL/f_{su}\) calculated by Eq. 2 from the routine monitoring data provides an adequate estimate of the \(CL/f_{non}\). We thus used the \(CL/f_{su}\) in subsequent analyses.

**Fixed Model for CyA Dosage** The logarithmic expression of the CyA trough level correlates more closely with CyA dosage than the actual level,\(^14\) therefore, prediction of the logarithm of the CyA trough level in
whole blood (TL, mg/mL), determined by multiple regression analysis, was defined as follows:

\[
\text{log}(TL) = 2.1701 - 0.3045 \times \text{CL/}f_{\text{tu}} + 0.2025 \times D + 0.0066 \times \text{CyA-EP}
\]

(4)

where \(D\) represents one oral dose of CyA (mg/kg). Linear regression between the predicted and actual TL in a logarithmic form resulted in a strong correlation (\(R^2 = 0.910, p < 0.00001\)), suggesting that almost 91% of variance in the log(TL) was explained by the \(D\), the \(\text{CL/}f_{\text{tu}}\), and the CyA-EP (Fig. 2). We obtained the largest value of \(R^2\) with the combined use of these variables. In addition, no strong correlations due to model-dependent multicollinearity (VIF > 10) were found between the variables used in Eq. (4) (Table 2). Thus Eq. 4 was judged adequate and it led to the development of a fixed model for CyA dosage. The predictive equation for the dosage, \(D\), depending on Eq. 4 is given by rearranging for \(D\) as follows:

\[
D = 4.938 \times \text{log}(TL) + 1.5037 \times \text{CL/}f_{\text{tu}} - 0.0326 \times \text{CyA-EP} - 10.7165
\]

(5)

In this fixed model, the oral dose is given by the logarithmic TL, the CyA-EP by Eq. 1, and the \(\text{CL/}f_{\text{tu}}\) by Eq. 2.

**Retrospective Evaluation of the Mixed Model** In the resultant mixed model, CyA dosage (\(D\), mg/kg) was then given by Eqs. 1, 3, and 5. Individual parameters for Eq. 3, employing MULTI analysis in the five other renal transplant patients (A—E) are shown in Table 3, and the relationships between the CyA-EP and the \(\text{CL/}f_{\text{tu}}\) in these patients are shown in Fig. 3. Data to estimate \(P_1\) and \(P_2\) for individuals was obtained within 2 weeks after renal transplantation, and 3 to 5 sampling points were used for the MULTI analysis. Great interindividual variation was
found in the shape of the relationship between the CyA-EP and the $CL/f_{\text{su}}$ (Fig. 3). These observations suggest that individualization of CyA pharmacokinetics can be achieved by estimating the $CL/f_{\text{su}}$ from the CyA-EP, which value reflects the effects of physiological changes on CyA pharmacokinetics. The results obtained from the retrospective evaluation of the mixed model are shown in Table 4. When the model-derived dosage obtained from all five patients was compared with the actual dose, the ME and the RMSE were $-0.057$ and $0.365$, respectively. In addition, there were no marked differences between the 95% confidence interval of the observed CyA dosage and that of the predicted CyA dosage determined by the mixed model. These findings suggest that the predictive performance of the mixed model would be satisfactory for clinical use.

**Picturing Nomogram Based on the Mixed Model** For the prospective use of the mixed model, we further interpret the model as a developed one. When the desired CyA trough level in whole blood ($DTL$, ng/ml), corresponding to the therapeutic phase, is selected, the optimal dosage of CyA ($OD$) to obtain the $DTL$ is then given by the equation:

$$OD = 4.938 \times \log(DTL) + 1.5037 \times CL/f_{\text{su}} - 0.0326 \times \text{AEP} - 10.7165$$  

(6)

where the $CL/f_{\text{su}}$ is given by

$$CL/f_{\text{su}} = P_1 \times \exp(P_2 \times \text{AEP})/\text{AEP}$$  

(7)

![Fig. 3. Relationship between $CL/f_{\text{su}}$ and CyA-EP in Renal Transplant Patients (A—E) Indicated by Eq. 3](image)

The CyA-EP by Eq. 1 and the $CL/f_{\text{su}}$ by Eq. 2 were fitted to Eq. 3. Solid lines represent the relationship between the $CL/f_{\text{su}}$ and the CyA-EP when the individual parameters ($P_1$, $P_2$) listed in Table 3 were used.

**DISCUSSION**

The pharmacokinetics of CyA is very complex, since it depends on the physiological changes that occur with various disease states after transplant. In a series of previous reports\(^5\) we introduced the concept of the CyA-EP to elucidate the pharmacokinetics; the CyA-EP was shown to depend on the physiological changes in blood constituents induced by a disease state, such as nephrotoxicity, hepatotoxicity, anemia, or hyper- and hypolipidemia,\(^15\) and it was a useful indicator for predicting tissue toxicity and disease state-dependent changes in CyA pharmacokinetics.\(^5\) Since the CyA-EP is regulated by alterations in blood constituents in both the erythrocyte and the plasma fractions,\(^15\) changes in the CyA-EP are believed to reflect alterations in unbound CyA that is pharmacologically active.\(^16\) Despite the requirement for an optimal CyA regimen that takes physiological changes in CyA pharmacokinetics into consideration,\(^17\) no method suitable for use in the disease states found in transplant patients has yet been established. In our research, to establish an optimal CyA regimen during immunosuppressive therapy, we have been investigating ways in which the concept of CyA-EP can be adopted for routine CyA monitoring.

Based on fundamental research, apparent total body clearance should be obtained by an adequate pharmacokinetic equation involving the $AUC$. Calculation of the $AUC$, however, requires frequent blood collection after oral administration, and this sampling protocol is not suitable for routine monitoring, since it is invasive for the patient. The surrogate estimate, $CL/f_{\text{su}}$, given by Eq. 2, is therefore a good estimate in clinical use to obtain the apparent total body clearance of CyA (Fig. 1). In the multiple regression analysis to create the mixed model, we used the $CL/f_{\text{su}}$ given by Eq. 2, and the resultant multiple regression provided

**Table 4. Retrospective Evaluation of Mixed Model to Predict CyA Dosage**

<table>
<thead>
<tr>
<th>Patient</th>
<th>$n^{a)}$</th>
<th>Observed CyA dose (mg/kg)$^{b)}$</th>
<th>Predicted CyA dose (mg/kg)$^{b)}$</th>
<th>ME</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12</td>
<td>2.917 (0.863)</td>
<td>2.429 to 3.405</td>
<td>2.892 (0.802)</td>
<td>2.438 to 3.346</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>2.973 (0.528)</td>
<td>2.581 to 3.364</td>
<td>2.799 (0.863)</td>
<td>2.159 to 3.438</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>2.948 (0.074)</td>
<td>2.889 to 3.007</td>
<td>2.772 (0.385)</td>
<td>2.463 to 3.080</td>
</tr>
<tr>
<td>D</td>
<td>10</td>
<td>2.958 (0.161)</td>
<td>2.858 to 3.052</td>
<td>2.873 (0.612)</td>
<td>2.494 to 3.252</td>
</tr>
<tr>
<td>E</td>
<td>6</td>
<td>3.357 (0.233)</td>
<td>3.170 to 3.543</td>
<td>3.496 (0.474)</td>
<td>3.117 to 3.876</td>
</tr>
<tr>
<td>All</td>
<td>41</td>
<td>2.917 (0.863)</td>
<td>2.429 to 3.405</td>
<td>2.948 (0.695)</td>
<td>2.735 to 3.161</td>
</tr>
</tbody>
</table>

$^{a)}$ Number of samples used to evaluate accuracy of the mixed model. $^{b)}$ Values observed during hospitalization. $^{c)}$ 95% confidence interval. $^{d)}$ Predicted data using the mixed model.
an excellent predictive performance (Fig. 2, Table 2).

To our knowledge, there have been no other reports on the relationship between CyA pharmacokinetics and the CyA-EP. We earlier proposed that the total body clearance of CyA and its bioavailability decreased with rise in the CyA-EP, and the relationships of these two factors with the CyA-EP showed hyperbolic decay and exponential decay, respectively. Therefore, we demonstrated that the relationship between $CL_{\text{fen}}$ and CyA-EP exhibits a biphasic pattern due to relative changes in the total body clearance of CyA and its bioavailability. An increase in the $CL_{\text{fen}}$ means that a patient is in a disease state of renal dysfunction, or that there is enhanced total body clearance. In these cases, the CyA-EP is increased or decreased, respectively. As shown by Eq. 1, the CyA-EP is obtained from routine monitoring results. Therefore, using Eqs. 1 and 3 the apparent total body clearance can be obtained from the results of CyA trough level monitoring, without the necessity for a special blood-collecting protocol such as frequent blood collection over time.

Our data shown in Fig. 3 strongly suggest wide intra- and interindividual variation in the pharmacokinetics of CyA. Sakami et al. reported time-dependent changes in the total body clearance of CyA after intravenous administration in patients who had received bone marrow transplantation, and several other reports have indicated that the apparent total body clearance of CyA was reduced in the early phase of therapy after renal transplantation. The model formula in Eq. 3 clearly showed the change in apparent total body clearance after renal transplantation, and supported these reports. We then used this model formula as a variable model for creating a mixed model to predict CyA dosage. For the variable model, solutions for $P_1$ and $P_2$ by a nonlinear least squares method (Table 3) allowed for wide inter- and intraindividual variation in the apparent total body clearance (Fig. 3). The ME and RMSE values calculated only by the fixed model (Eq. 5) for all data of the five other patients were $-0.447$ and $0.636$, respectively, larger than those determined by the mixed model (Table 4). Thus, the individualization of CyA dosage with the mixed model was superior to that obtained with the fixed model alone.

Various nomograms for drug regimens are used in therapeutic drug monitoring, since they are concise and convenient in clinical practice. Our analytical data suggest the prospective use of the mixed model for adjusting CyA dosage in the form of a nomogram (Fig. 4). At all DTL, changes in the AEP up to 3 have profound effects on the shape of the curves, and the OD decreases with rise in the AEP. On the other hand, increasing the AEP above 3 produces a gradual increase in the OD. There are two steps for the practical use of this nomogram. First, the curve that corresponds to a DTL on the lower axis, and the horizontal line from the AEP calculated by Eq. 1 involving the DTL on the left axis, are selected, and the point of intersection of these lines is then identified. Second, a vertical line from that point to the upper axis indicates an optimal single oral dose. The optimal daily oral dose of CyA is then calculated by doubling. The nomogram pictured in Fig. 4 is for patient F, and clinical application of this nomogram is summarized in Fig. 5. After renal transplantation, renal and hepatic function markers were smoothly reduced (Fig. 5b, c) with decrease in the CyA-EP calculated by Eq. 1. The CyA-EP at day 15, however, increased, and tissue toxicity was suspected. At this point (1), the nomogram was initially applied. Parameters for Eq. 3 were estimated using four points obtained within day 15. The estimated parameters, $P_1$ and $P_2$, for patient F were 0.913 and 0.385, respectively (Fig. 5a), and the
nomogram shown in Fig. 4 was drawn, from which the optimal daily dosage to maintain the trough levels at 250 ng/ml is seen as 300 mg/d (AEP = 3.26, BW = 55.5 kg). From day 17, the daily oral dose was reduced from 350 mg/d to 300 mg/d (Fig. 5d). As might have been expected, from day 19, a slight increase in SC, was found (Fig. 5c). As a reduction in CyA absorption from intestinal tract was anticipated thereafter, the oral daily dose of CyA was increased from 300 mg/d to 325 mg/d on day 21. Persistent increases in SC, and the CyA-EP were found up to day 28, however, renal function thereafter recovered with a rise in the CyA trough level (Fig. 5c, d). The CyA trough level on day 35 reached 349 ng/ml, and the nomogram was applied for the second time (§2). Also, at this time, the optimal daily dose to maintain the CyA trough level at 250 ng/ml was 300 mg/d (AEP = 3.38, BW = 54.0), and the level reached 251 ng/ml on day 46. There were no episodes of acute renal rejection or infections during hospitalization, and the patient was discharged on day 48. This clinical study suggests that the nomogram provides a rational regimen that allows for the physiological changes which occur in renal transplantation.

It is well known that CyA trough levels in the early phase of therapy after renal transplantation (within 30 d) should be maintained at relatively higher levels than those thereafter.\(^4\) During this period, the CyA-EP has a value of more than 5, and it is gradually reduced with the recovery of transplanted renal function.\(^9\) In addition, the absorption of CyA from the intestinal tract during this phase is retarded, and the absorption gradually recovers during the progress of therapy.\(^13\) Therefore, in the early phase of therapy, a relatively higher oral dose is required to achieve an optimal CyA trough level until the transplanted renal function is stable, and the oral CyA dose must be reduced with the progress in renal function and with decreases in the CyA-EP. There are several conditions under which the CyA-EP is reduced. For instance, increases in plasma lipid levels and hematocrit decrease the CyA-EP and increase total body clearance.\(^9,19\) In such cases, unbound CyA that is pharmacologically active is also decreased, and the CyA trough level is reduced. Under these circumstances, the oral dose must therefore be increased to maintain an optimal CyA trough level. Our nomogram in Fig. 4 provides an excellent representation of the above relationships between the therapeutic phase, the CyA trough level and CyA pharmacokinetics, various disease states, and the CyA oral dose.

It is important to note, however, that there are some limitations in use of the nomogram we have constructed to predict CyA dosage. 1) The nomogram based on the mixed model in Fig. 4 is essentially for patient F, and it should not be applied to other patients, since the intrinsic parameters for patient F are incorporated in the model. If the model is to be applied to another patient, the parameters \(P_1, P_2\) for him must be obtained. 2) The nomogram is applicable to renal transplant patients who receive triple therapy consisting of CyA, prednisolone, and azathiopurin. Renal transplant patients usually receive varying doses of prednisolone, a drug that is a known inducer of cytochrome P-450III\(A\).\(^4,14,20\) It therefore seems unlikely that the model can be used for patients who receive CyA alone. 3) The CyA monitoring data we used for the analysis were trough measurements; measurements after dosing should not be used. 4) Different methods of monitoring CyA in whole blood (i.e., radioimmunoassay with a polyclonal antibody, FPIA with a polyclonal antibody) can provide different results. When the nomogram is used, CyA measurements determined by m-FPIA should be employed. Finally, for the biochemical test data employed to estimate the CyA-EP, data
corresponding to the CyA measurements determined by m-FPIA should be used.

In conclusion, the results of our theoretical study suggest that, at a given desired CyA trough level during immunosuppressive therapy after renal transplantation, the mixed model can be used to predict an optimal CyA dosage for an individual from the routine monitoring results without the employment of specific techniques. In addition, it is easy to draw up a nomogram limited to one person, and this will provide an objective criterion for deciding the optimal CyA dosage in various disease states after renal transplantation. In our hospital, we have just begun (from January, 1995) to use this nomogram in routine CyA monitoring in renal transplant patients. Further studies in regard to prospective evaluation and other factors in mass populations will appear in subsequent reports.

REFERENCES AND NOTES