Clinical Utility of Monitoring Tacrolimus Blood Concentrations in Liver Transplant Patients

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*The relationship between the dose of tacrolimus, trough tacrolimus blood concentration, and selected clinical endpoints (acute rejection, nephrotoxicity, and other toxicities) were examined in a prospective, multicenter clinical trial to validate the use of an enzyme-linked immunosorbent assay (ELISA) for monitoring whole-blood concentrations of tacrolimus in liver transplant patients. A total of 111 subjects from six transplant centers were evaluated over 12 weeks posttransplantation. In addition to trough tacrolimus blood concentrations, hematocrit, ALT, AST, GGTP, alkaline phosphatase, total bilirubin, serum creatinine, BUN, serum potassium, serum magnesium, blood glucose, and serum albumin were also measured. The relationship between trough tacrolimus blood concentrations and clinical endpoints was analyzed using both a logistic regression model and a Cox proportional hazard model. By logistic regression analysis, a statistically significant (*p = *0.0465) relationship between increasing trough tacrolimus blood concentrations and decreasing risk of acute rejection was demonstrated over a 7-day time window. Nephrotoxicity and other toxicities also demonstrated statistically significant relationships with trough tacrolimus blood concentrations. The results of the Cox analysis were consistent with the logistic regression analysis. Using receiver operator characteristic curves, trough tacrolimus concentrations as measured by the ELISA method were able to differentiate the occurrence of nephrotoxicity and toxicity from nonevents. To minimize nephrotoxicity of tacrolimus, it is necessary to maintain trough blood concentrations below 15 ng/ml. This study demonstrates that the ELISA method used to measure tacrolimus blood concentrations in this study provides information of predictive value for managing the risk of nephrotoxicity, other toxicity, and rejection in liver transplant patients.*

Journal of Clinical Pharmacology, 2001;41:542-551

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The contribution of tacrolimus to effective immunosuppression in the field of organ transplantation is well established.[1-4] While tacrolimus is a potent immunosuppressive drug, it has a narrow therapeutic index.[5-7] The large interindividual variation in the pharmacokinetics of tacrolimus necessitates individualization of the dosing regimen of tacrolimus in transplant patients.[8-10] In addition, to achieve long-term graft survival, it is essential that the patients are compliant with the prescribed dosing regimen. Optimization of tacrolimus therapy in organ transplant patients currently uses routine tacrolimus trough-level monitoring as an integral component.[11-12] One of the fundamental premises in the application of therapeutic drug

monitoring is the documentation of a relationship between the blood concentrations of a drug and its efficacy or toxicity. While there have been several causal observations of association of rejection at lower concentrations and toxicity at higher concentrations of tacrolimus,[13-18] there has been only one thorough retrospective analysis of the relationship between tacrolimus blood concentrations and efficacy and toxicity in transplant patients.[19] In addition, the methods available to monitor tacrolimus concentrations differ particularly with respect to analytical sensitivity.[20-23] The primary goal of the current study was to prospectively evaluate the relationship between tacrolimus blood concentrations, as determined by an enzyme-linked immunosorbent assay (ELISA), and the risk of rejection and toxicity in liver transplant patients in a multicenter trial.

PATIENTS AND METHODS

Patient Population

In the present prospective study, we enrolled 111 adult liver transplant subjects between August 1996 and July 1997 at six clinical sites in the United States. These sites were the following: University of Pittsburgh Medical Center, Pittsburgh; University of Pennsylvania Medical Center, Philadelphia; Mt. Sinai Medical Center, New York; Emory University, Atlanta, Georgia; University of Miami Medical School and VA Medical Center, Miami, Florida; and University of Wisconsin Hospitals and Clinics, Madison. The study protocol was approved by the institutional review board at each site. The study population was restricted to subjects receiving tacrolimus as a primary immunosuppressant following liver transplantation. Subjects receiving a liver from an ABO incompatible donor, subjects who had prior organ transplantation other than the liver, or subjects who underwent transplantation of other organs at the time of liver transplantation were excluded from the study. Subjects were on a combination of tacrolimus, steroid, and azathioprine or mycophenolate mofetil. Subjects did not receive any investigational immunosuppressant, with the exception of mycophenolate mofetil. Informed consent for participation in the study was obtained from the subject or the subject's authorized legal representative prior to enrollment in the study.

The sample size estimation for the study was based on previous logistic and Cox regression analyses of clinical trials in which tacrolimus blood levels were correlated positively with toxicity in populations as small as 92 subjects.[19] In addition, the difference in the incidence of toxicity was shown to be 20% to 30% when subjects with high concentrations of tacrolimus were compared with subjects with low concentrations of tacrolimus. Assuming a between-group difference of 25% and a toxicity rate of 35% in the low concentration group, a sample size of 94 subjects would be required to detect such a difference, assuming $\alpha = 0.05$ (one-sided) and $\beta = 0.20$.

Tacrolimus was given intravenously for the first few days after transplantation in two centers. Tacrolimus was given orally to all the subjects in other centers. Adjustments in the dose of tacrolimus were made on the basis of the standard of care at each center and included blood level monitoring of tacrolimus[20] and other clinical indices such as serum bilirubin, alkaline phosphatase, ALT, and AST.

Data Collection

Baseline characteristics that included demographics, medical history, and clinical laboratory values were collected from all the subjects. Subjects were evaluated for 12 weeks posttransplantation. Morning trough tacrolimus concentrations (collected before the morning dose) and clinical laboratory measurements that included ALT, AST, alkaline phosphatase, GGTP, total bilirubin, serum creatinine, BUN, serum potassium, serum magnesium, blood glucose, albumin, and hematocrit were measured three times a week during weeks 1 and 2, twice a week during weeks 3 and 4, once a week during weeks 5 and 6, and once every 2 weeks during weeks 7 through 12.

Tacrolimus trough concentrations were assayed in whole blood by PRO-Trac™ II ELISA.[21,22] Venous blood was collected in 5 or 10 mL evacuated glass tubes containing EDTA or heparin as the anticoagulant. No further additive or preservative was required to maintain the integrity of the samples. Specimens not processed immediately were stored at –18°C to –25°C and analyzed within 7 days. Under this storage condition, tacrolimus has been shown to be stable.[22]

Subjects were monitored for three primary endpoints: acute rejection confirmed by histology, nephrotoxicity defined as a serum creatinine elevation to greater than two times the baseline value, and evidence of toxicity defined as any adverse event that required a reduction in dose of tacrolimus. In addition, two secondary endpoints, death and retransplantation due to graft failure, were also monitored. Parameters calculated included time to endpoint (days from transplant to endpoint), tacrolimus trough level 0 to 7 days prior

to that endpoint, lowest tacrolimus trough within the time window for rejection, and highest tacrolimus trough within the time window for all other endpoints.

Statistical Analysis

The relationship between the dose of tacrolimus and the trough blood concentrations of tacrolimus was analyzed, using samples collected after 2 or more days of tacrolimus administration. The relationship of tacrolimus dose to steady-state tacrolimus trough levels was assessed using a repeated-measure analysis of variance model. The predictive relationship between tacrolimus concentration (measured using the PRO-Trac™ II ELISA) and the subject's risk of experiencing endpoint events was evaluated using logistic regression and Cox proportional hazard regression analyses. Liver function tests were added to the model to assess their ability to predict rejection.

The logistic regression model underlying these analyses is as follows:

$$\text{The logit (probability of event)} = \alpha + \beta X,$$

where α is the intercept parameter, and β is the vector of slope parameters.

For the nephrotoxicity, toxicity, death, and retransplantation endpoints:

$$X = (\textit{maximum} \text{ tacrolimus trough level}).$$

For the rejection endpoint:

$$X = (\textit{minimum} \text{ tacrolimus trough level, liver function test}).$$

The Cox proportional hazard regression model was as follows:

$$h_i(t) = h(t;z_i) = h_0(t)\exp(z_i \beta),$$

where $h_0(t)$ is an arbitrary and unspecified baseline hazard function, z_i is the vector of measured explanatory variables for the ith individual, and β is the vector of unknown regression parameters associated with the explanatory variables.

For the nephrotoxicity, toxicity, death, and retransplantation endpoints:

$$z = (\textit{maximum} \text{ tacrolimus trough level}).$$

For the rejection endpoint:

$$z = (\textit{minimum} \text{ tacrolimus trough level, liver function test}).$$

The clinical sensitivity and specificity were calculated for rejection, toxicity, and nephrotoxicity using receiver operator characteristic (ROC) curves. Analyses were performed using principles from the National Committee for Clinical Laboratory Standards, NCCLS document GP10-T (ISBN 1-56238-213-6). The receiver operator curves were displayed using a logistic regression model to calculate the predictive accuracy of this model. The model includes tacrolimus blood concentrations as continuous data and occurrence of rejection, toxicity, or nephrotoxicity as the dependent variable. Bootstrapping and cross-validation methods were used to correct for the bias that results from using the same data for both fitting and testing the accuracy of the model. PC-SAS release 6.11 was used for all the statistical analyses.

Data collection and management were performed under the supervision of an independent contract research organization. Quality assurance procedures included monitoring of data to ensure that complete, timely, and accurate data were submitted and that protocol requirements were followed.

RESULTS

The pretransplant diagnosis and the demographics of the study subjects are listed in Table I. In total, 111 subjects were enrolled at six sites. Ten percent of the subjects were hepatitis B positive, 35% of the subjects were hepatitis C positive, 18% were diabetic, and 5% were on dialysis. A total of 91 subjects received tacrolimus treatment throughout the 12 weeks of study. Twenty subjects received less than 12 weeks of treatment with tacrolimus, and the reasons for early termination of treatment were death, retransplantation, toxicity resulting in conversion to cyclosporine, or diagnosis of lymphoma.

Tacrolimus was administered intravenously during the immediate postoperative period at two sites. At one site, IV doses of tacrolimus were administered on an as-needed basis to achieve desired blood levels of tacrolimus, followed by orally administered maintenance doses. At the second site, the standard of care called for tacrolimus to be administered intravenously at the time of surgery and for 2 to 3 days postoperatively, when patients often have difficulty tolerating orally administered drugs. After the immediate postoperative period, maintenance therapy was provided as oral doses. The mean oral tacrolimus dosage during week 1 was 0.07 mg/kg/day, was essentially stable at 0.10 to 0.11 mg/kg/day during weeks 2 through 9, declined to 0.09 mg/kg/day during weeks 10 and 11, and was 0.07 mg/kg/day at week 12. Tacrolimus was ad-

Table I Subject Demographics and Relevant Medical History

Characteristic/Parameter	Result
Total subjects	111
Mean (*SD*) age (years)	50.8 ± 10.4
Age range (years)	25-72
Gender, *n* (%)	
Males	62 (56)
Females	49 (44)
Race, *n* (%)	
Caucasian	91 (82.0)
Hispanic	11 (9.9)
Black	6 (5.4)
Other	3 (2.7)
Mean (*SD*) height (cm)	171.5 ± 10.5
Mean (*SD*) weight (kg)	80.2 ± 18.5
Reasons for transplant, *n* (%)	
Postnecrotic cirrhosis	39 (35.1)
Hepatitis C	20 (18.2)
Alcoholic liver disease	20 (18.2)
Cryptogenic cirrhosis	12 (10.8)
Primary sclerosing cholangitis	10 (9.0)
Hepatic cancer	9 (8.1)
Primary biliary cirrhosis	6 (5.4)
Fulminant hepatic failure	5 (4.5)
Hepatitis B	5 (4.5)
Autoimmune hepatitis	4 (3.6)
Laennec's cirrhosis	4 (3.6)
All others (< 2% incidence each)	26 (23.4)

Table II Distribution of Clinical Endpoints

Clinical Endpoint	All Events (*n*)	First Event Only (*n*)
Acute rejection	36	34
Nephrotoxicity	38	34
Toxicity requiring dose reduction	10	10
Retransplantation	8	
Death	3	
Total of all endpoints reached	95	
Number of subjects reaching endpoints	60	

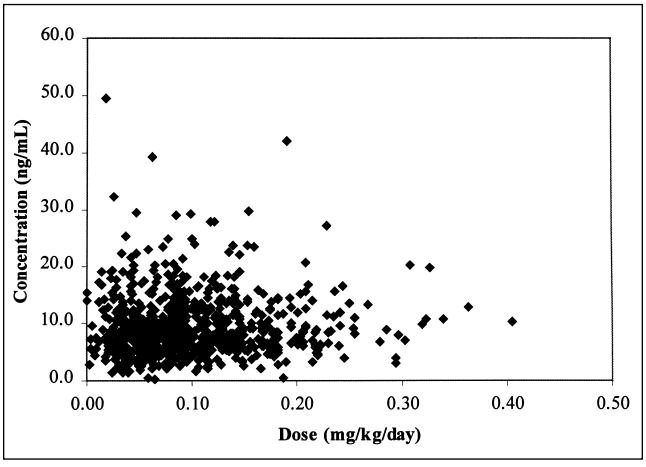

Figure 1. Relationship between tacrolimus dose (mg/kg/day) and steady-state whole-blood trough concentrations of tacrolimus.

ministered twice daily in all the subjects. Mean trough blood concentrations of tacrolimus for the corresponding time periods were 10.4 ng/ml during week 1, trending downward slightly to a low of 7.7 ng/ml during week 11, and was 8.1 ng/ml during week 12. The relationship of dose to tacrolimus blood concentrations for individual subjects is shown in Figure 1. The ability to predict the trough blood concentrations of tacrolimus based on the dose administered for a given individual is poor.

Clinical Endpoints

Of the 111 subjects enrolled in the study, 60 (54%) experienced a total of 95 clinical endpoint events. Thirty-six subjects experienced acute rejection, 38 subjects experienced nephrotoxicity, 10 subjects experienced other toxicity thought to be related to tacrolimus, 3 subjects died, and 8 were retransplanted. The distribution of the clinical endpoints reached is shown in Table II. Any instance of rejection not confirmed by histology was excluded from analysis. Forty-seven percent of the first-rejection episodes occurred within the first 10 days, 16% occurred between 11 and 20 days, 13% occurred between 21 and 30 days, and 24% after 30 days of transplantation. During the 12 weeks of this study, patient survival was 97% (3 of 111 subjects died), and graft survival was 93% (8 of the 111 subjects had retransplantation).

Logistic Regression Analysis

The clinical data were subjected to logistic regression analysis to determine the relationship between blood concentrations of tacrolimus and clinical endpoints. The results are summarized in Table III.

Acute rejection. Based on the analysis of the 0- to 7-day window prior to a biopsy-proven rejection event,

Table III Summary of Logistic Regression Analysis

Endpoints	Number of Observations	Effects	Odds Ratio	*p*
Acute rejection with significant mean LFT	80	Trough only	0.797	0.0465
		Mean ALT	1.012	0.0050
Acute rejection with significant max LFT	80	Trough only	0.750	0.0345
		Max ALT	1.007	0.0055
		Max GGTP	1.008	0.0172
Nephrotoxicity	84	Trough only	1.276	0.0001
Toxicity requiring dose reduction	80	Trough only	1.071	0.0964
Death	82	Trough only	1.186	0.0332
Retransplantation	82	Trough only	1.077	0.1243

LFT, liver function tests.

there is a statistically significant ($p = 0.0465$) relationship between increasing trough tacrolimus blood concentrations and decreasing risk of acute rejection. This analysis controls for the additive predictive effects of mean liver function tests in the same time window by including them as covariates in the regression model. The odds ratio associated with increasing tacrolimus trough concentrations and the risk of acute rejection is 0.80 (mean liver function tests controlled).

Nephrotoxicity. Based on the analysis of the 0- to 7-day window prior to nephrotoxicity, a statistically significant ($p = 0.0001$) correlation between increasing tacrolimus trough concentrations and increasing risk of nephrotoxicity is demonstrated. The odds ratio associated with increasing tacrolimus levels and the risk of nephrotoxicity is 1.28.

Toxicity. A statistically significant correlation ($p = 0.0387$) of increasing tacrolimus trough concentrations and increasing risk of toxicity is found in the 0- to 14-day window, with a supportive but nonstatistically significant correlation ($p = 0.0964$) in the 0- to 7-day window. The risk associated between increasing tacrolimus trough concentrations and toxicity (odds ratio of 1.071) is less pronounced than that for acute rejection and nephrotoxicity.

Relationship of Tacrolimus Levels to Clinical Endpoints

The probability of nephrotoxicity, rejection, and toxicity based on logistic regression analysis is plotted in Figure 2. This figure indicates that the probability of rejection decreases as whole-blood levels of tacrolimus increase, the probability of nephrotoxicity increases as tacrolimus blood levels increase, and the probability of toxicity requiring a reduction in tacrolimus dosage increases modestly as tacrolimus concentrations increase.

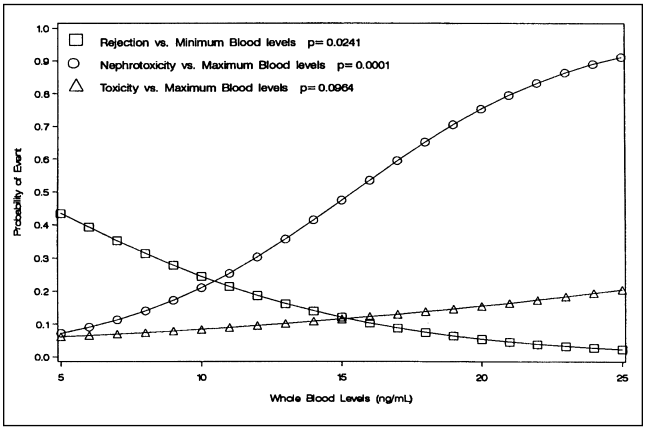

Figure 2. Plot of incidence rate for nephrotoxicity (circles), rejection (squares), and toxicity (triangles) using 0- to 7-day time window for trough concentrations.

Cox Proportional Hazard Regression Analysis

The results with the Cox model as reported in Table IV were consistent with the results from the logistic regression analysis. The directional relationship of tacrolimus trough concentrations to the risk of acute rejection, nephrotoxicity, and toxicity is the same as those of the logistic regression analysis. The magnitudes of the risk ratios were similar to the odds ratios for the logistic regressions, although the risk ratio for

Table IV Summary of Cox Proportional Hazards Analysis

Endpoint	Effects	Coefficient of Variance	Risk Ratio	*p*
Acute rejection with significant mean LFT	Trough only	–0.1421	0.868	0.0495
	Mean bilirubin	0.2760	1.318	0.0001
	Mean AST	0.0024	1.002	0.0116
	Mean GGTP	0.0007	1.001	0.0266
Acute rejection with significant max LFT	Trough only	–0.1187	0.888	0.1106
	Max bilirubin	0.2211	1.247	0.0001
	Max GGTP	0.0006	1.001	0.0089
Nephrotoxicity	Trough only	0.0388	1.040	0.0001
Toxicity requiring dose reduction	Trough only	0.1114	1.118	0.0184
Death	Trough only	0.2022	1.224	0.0240
Retransplantation	Trough only	0.1256	1.134	0.0102

LFT, liver function tests.

rejection and nephrotoxicity was less using the Cox analysis. The strength of the relationship between increasing levels of maximum tacrolimus trough concentrations and the risk of toxicity is greater in the Cox model.

Clinical Sensitivity and Specificity

Clinical accuracy of tacrolimus blood concentrations in predicting the occurrence of primary clinical endpoints is summarized graphically in the ROC curves presented in Figures 3 through 6. Although the tacrolimus blood concentration has a statistically significant contribution in the prediction of acute rejection, ROC curves for rejection indicate that the liver function tests are the major contributors to differentiating the occurrence of acute rejection from a nonevent (Figures 3, 4). The optimal clinical sensitivity/specificity pairs for acute rejection, based on the maximum ALT value in the 7-day window prior to the event, were 88% and 75%, respectively, at 200 IU/L. Described in terms of clinical sensitivity and 1-specificity, the ROC curves for nephrotoxicity and toxicity (Figures 5, 6) indicate that tacrolimus blood levels as measured by Pro-Trac™ II ELISA in the 0- to 7-day window are able to differentiate the occurrence of these adverse events from nonevents.

For nephrotoxicity and toxicity, the trough concentrations that give the highest clinical sensitivity/specificity pairs are summarized in Table V. These clinical study results would indicate that discrimination for toxicity is greatest at trough concentrations of approximately 12 ng/mL and that for nephrotoxicity, discrimination is greatest at a range from 12 to 15 ng/mL. Con-

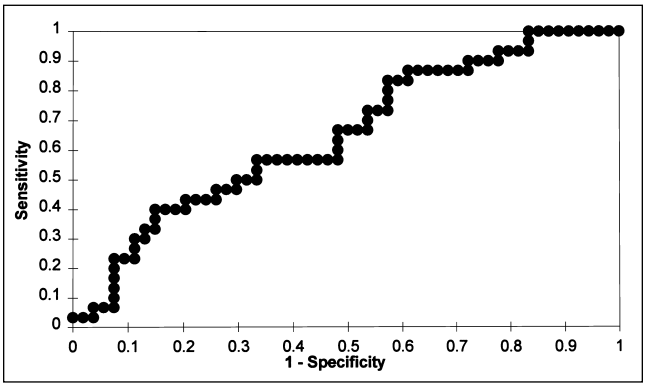

Figure 3. Receiver operating characteristic curve for rejection with trough concentration in the 0- to 7-day window. This curve describes that tacrolimus blood concentrations alone cannot differentiate between acute rejection and a nonevent with good sensitivity.

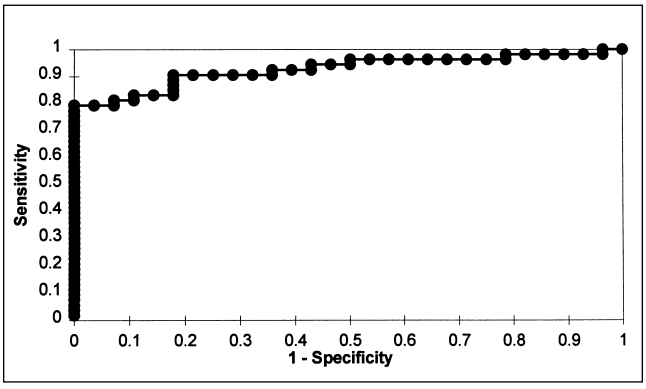

Figure 4. Receiver operating characteristic curve for rejection with trough concentrations and liver function tests (max ALT) in the 0- to 7-day window. This curve describes that liver function tests can predict acute rejection with high sensitivity.

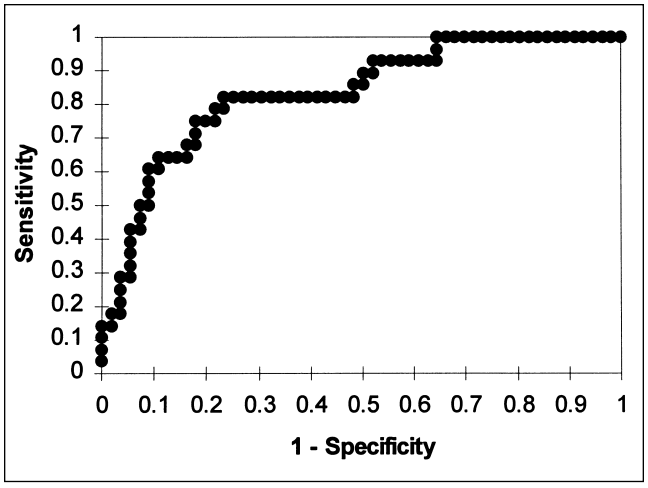

Figure 5. Receiver operating characteristic curve for nephrotoxicity with trough level in the 0- to 7-day window.

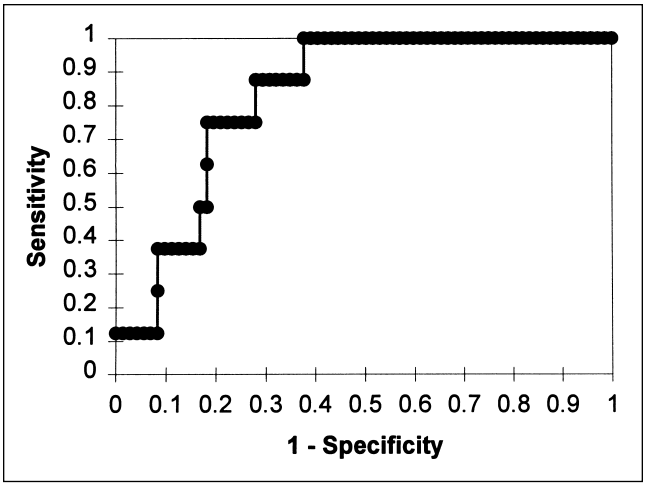

Figure 6. Receiver operating characteristic curve for toxicity with trough level in the 0- to 7-day window. This curve describes that trough levels can differentiate adverse effect from a nonevent.

centrations of 15 ng/mL, which demonstrate higher positive predictive values and greater specificity, are supported by current standards of practice.

There was no correlation between the trough blood concentrations of tacrolimus and the time to first-rejection episode or the time to nephrotoxicity or time to other toxicity events.

DISCUSSION

Therapeutic monitoring of tacrolimus is routinely performed in transplant patients. Therapeutic monitoring of tacrolimus has been recommended due to the narrow therapeutic index, large inter- and intraindividual variation in the pharmacokinetics, and the need for long-term compliance to ensure graft survival in transplant patients.[8-11] The importance of the need for therapeutic monitoring of tacrolimus is also supported by the present study, confirming the poor correlation between the daily dose (mg/kg/day) and the steady-state whole-blood concentrations achieved.

During the early clinical trials, tacrolimus concentrations were measured in plasma due to nonavailability of an assay to measure the concentrations in whole blood. An analysis of tacrolimus concentrations in these early studies indicated that nephrotoxicity, when other nephrotoxic factors were excluded, was associated with high plasma trough concentrations.[6] Elevated

Table V Clinical Sensitivity and Specificity of Tacrolimus Trough Concentrations for Nephrotoxicity and Toxicity Requiring Dose Reduction (in percentages)

	Predictive Values			
Trough Concentration	**Sensitivity**	**Specificity**	**Positive**	**Negative**
Nephrotoxicity				
15.0 ng/mL	64	89	75	83
14.0 ng/mL	64	84	67	83
13.3 ng/mL	71	82	67	85
12.1 ng/mL	79	79	65	88
11.6 ng/mL	82	77	64	90
Toxicity				
11.8 ng/mL	75	82	32	97
9.9 ng/mL	88	72	26	98

plasma tacrolimus concentrations and a higher rate of renal dysfunction, often requiring dialysis, were observed in liver transplant patients with poor graft function.[24-25] This association was subsequently confirmed in a single-center study.[15] A plasma concentration–guided regimen was developed that reduced the incidence of tacrolimus side effects while maintaining adequate immunosuppression.[26] In contrast, a retrospective analysis of 13,000 samples from 248 liver transplant patients suggested a poor correlation between plasma concentration and toxicity.[27]

Subsequently, whole blood has become the preferred matrix for tacrolimus concentration measurement.[11] In a study of kidney transplant patients, whole-blood concentrations of tacrolimus correlated better with kidney function than plasma concentrations.[14] A similar association between blood concentration and toxicity was reported in a retrospective analysis of multiple clinical trials in renal transplant patients.[19]

There have been conflicting reports regarding the association of trough plasma or whole-blood tacrolimus concentrations and acute rejection in liver transplant patients. Whole-blood concentrations have been reported to correlate well,[17,27] while whole-blood or plasma concentrations showed poor correlation[15,19] or no significant difference between patients with and without rejection episodes.[28-30] In pediatric liver transplant patients, rejection was shown to be most frequent at blood concentrations less than 10 ng/mL.[16] However, a more recent study did not show an association between blood concentration and rejection in pediatric liver transplant patients.

Similarly conflicting associations between tacrolimus concentrations and acute rejection have been reported for renal transplant patients.[13-14] In a retrospective analysis of trough whole-blood concentrations within a 7-day window before the onset of rejection, blood concentrations were well correlated with the onset of rejection.[19] As blood concentrations increased, the incidence of acute rejection was reduced while the incidence of adverse events was increased.

A microparticulate enzyme immunoassay (MEIA) procedure for the IMx® analyzer[20] and an ELISA procedure[21,22] are the two commercially available immunoassays for the measurement of tacrolimus in whole blood. In this study, we validated the clinical utility of the ELISA methodology. This method correlates well with the HPLC/MS/MS reference methodology by linear regression, Bland/Altman analysis, and Student's *t*-test.[21,22] Correlation of the ELISA to the MEIA methodology shows a statistically significant difference between the two assays.[22] The inability to correlate concentration to the incidence of rejection in liver transplant patients using the MEIA procedure[19] contrasted to the observations in this study (Figure 2).

This study used logistic regression analysis and a Cox proportional hazards regression model to evaluate the relationship between blood concentration and clinical endpoints within a 7-day window. This approach, applied to a 12-week posttransplant time period when most endpoints occur and complete data collection can be made with reasonable confidence, has been shown to be successful in past analyses.[19] These analyses do not predict an individual subject's response to a specific tacrolimus concentration but instead provide the clinician with an assessment of the relative risks of acute rejection and nephrotoxicity associated with the given tacrolimus blood concentration. This risk assessment, as shown here and by others,[19] is suggested to be dependent on the monitoring methodology.

The ROC curve analysis attempts to provide the clinician with data that can be used in direct patient management. These curves suggest that ALT values may provide the best clinical sensitivity and specificity for the prevention of acute rejection within a 7-day window. Optimal sensitivity/specificity pairs occur at ALT concentrations of approximately 200 IU/L. Tacrolimus concentrations alone were not sufficient to discriminate rejection from nonevents. This is perhaps related to some of the variability in the immunosuppressive regimen used in the study patients. While all the patients received tacrolimus as the primary immunosuppressive agent, 88% of the patients also received methylprednisolone, 53% of the patients were also on prednisone, and 44% of the patients were on mycophenolate mofetil. Less than 5% of the patients received azathiporine or OKT3. It was not possible to carry out statistical analysis of the subgroups due to limitations in the number of subjects in each group.

In contrast, tacrolimus concentrations alone could discriminate between nephrotoxicity and nonevents with optimal sensitivity/specificity achieved at approximately 12 ng/mL. This information provides a confirmation of the evolving clinical standard of practice of reducing the upper limit of the recommended trough tacrolimus blood concentrations from 20 ng/mL as recommended by the Lake Louise Consensus report.[11] Even though not all potential nontacrolimus causes of nephrotoxicity were assessed in this study, none of the subjects exhibiting nephrotoxicity were receiving aminoglycosides or amphoterecin B during the 7-day window prior to the nephrotoxic event.

In conclusion, monitoring tacrolimus blood concentrations by the PRO-Trac™ II ELISA method provides

the clinician with information of predictive value for managing the risk of nephrotoxicity and acute rejection in liver transplant patients. Routine monitoring of tacrolimus blood concentrations must be used in conjunction with appropriate clinical evaluation of the patient to optimize immunosuppressive therapy.

The authors thank the following investigators for their support of the work reported here: V. Esquanazi, S. Babishkin, I. Fernandez, S. Mehta, B. Forrester, S. Zuckerman, E. Culligan, R. Cupiola, D. Wiebe, R. Miller, L. Ramanathan, L. Maxwell, R. Wheaton, and L. Fields.

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