

조혈모세포이식을 받은 한국 성인 백혈병환자에서 cyclosporine의 집단약동학 분석

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Population Pharmacokinetics of Cyclosporine after Hematopoietic Stem Cell Transplantation in Leukemic Patients

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Purpose: 본 연구는 한국인 성인 조혈모세포이식환자를 대상으로 경구용 사이클로스포린의 집단약동학 분석을 통하여 사이클로스포린의 약동학적 파라미터에 영향을 미치는 요인 분석을 실시하고자 하였다.

Methods: 2000년 12월부터 2006년 8월까지 서울대학교병원에서 동종조혈모세포이식을 받고 면역억제제로 사이클로스포린을 복용한 성인 백혈병환자를 대상으로 후향적으로 자료를 수집하였다. 사이클로스포린의 약동학에 영향을 미치는 인자로는 연령, 성별, 이식 후 날짜, 신기능, 공여자와의 관계, 질병의 종류, 혈중 빌리루빈 농도, 사이클로스포린의 대사를 유도하는 프레드니솔론의 투여량, 헤마토크리트, 사이클로스포린의 대사를 저해하는 약물의 병용여부 등을 검토하였다. 분석은 NONMEM[®] VI 프로그램을 이용하였으며, 변수를 추가하지 않은 기본 모형을 만든 후에 단계적인 요인의 추가와 제거를 통해 최종모형을 제작하였다.

Results: 최종 상관 모형은 다음과 같다; CL/F (L/h) = $85.6 \times e^{(0.646 \times HCT/28.9 + 0.0464 \times Gender)}$. 사이클로스포린의 겉보기 클리어런스는 환자의 성별이 남자일 때 또는 헤마토크리트가 감소할수록 증가하였다. 그 외 파라미터는 다음과 같이 계산되었다; K_{α} = 0.0787 (h⁻¹); Q = 57.1 (L/kg/h); $V_{d-central\ compartment}$ = 1,100 (L); $V_{d-peripheral\ compartment}$ = 213,000 (L). 개체간 편차는 40% 미만이었으며, 개체내 편차를 포함하는 잔차는 24.02%였다.

Conclusions: 사이클로스포린의 약동학적 특징과 그 클리어런스에 영향을 끼칠 수 있는 임상적 요인을 이해하는 것은 환자 개개인의 용량과 용법의 결정 및 이상반응 발생의 예방에 유용할 수 있다. 한국인 조혈모세포이식환자에서 사이클로스포린의 약동학에 영향을 미치는 최종 파라미터를 구한 본 연구의 결과는 조혈모세포이식을 받은 한국인 성인환자에서 사이클로스포린의 모니터링 및 용량조절에 유용할 것으로 전망된다.

□ Key words - Cyclosporin (CsA), Population pharmacokinetics, NONMEM, Hematopoietic stem cell transplantation (HSCT)

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is used to treat many hematologic malig-

nancies. The major advantages of an allogeneic graft include the absence of contaminating malignant cells in the graft, the potential for an immunological anticancer graft vs. tumor (GVT) effect, and the ability to treat malignant and nonmalignant disorders of the bone marrow, including genetic and immunological diseases. To enhance engraftment and the GVT effect and to prevent

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graft vs. host disease (GVHD), various immunosuppressive regimens are used.

Cyclosporin A (CsA) is the pharmacological agent most commonly used to prevent GVHD after allo-HSCT, and is used primarily in combination with methotrexate.^{1,2)} However, the pharmacokinetics (PK) and pharmacodynamics (PD) of CsA show high inter- and intra-individual variability, making drug exposure difficult to predict. Furthermore, the therapeutic window with acceptable CsA tolerance is limited.^{3,4)} Levels below the window are associated with high risk for GVHD, whereas levels above the window correlate with side effects such as nephrotoxicity, infection, hepatotoxicity, and tumors.⁵⁻¹¹⁾

Despite years of extensive clinical experience with CsA and the development of clinical algorithms for dose adjustments, prompt achievement and maintenance of the CsA therapeutic target is still a challenge. Some studies have reported the adjustment of CsA doses in various organ-transplantation patients, but no study has clearly adjusted the whole-blood CsA concentrations in adult HSCT patients. Therefore, we estimated the population PK parameters of oral CsA after allo-HSCT in adult leukemia patients and identified clinical factors affecting the PK of CsA, with non-linear mixed-effect modeling (NONMEM).

METHODS

Data collection

Data were obtained retrospectively from the records of randomly selected adult patients who had undergone related or unrelated allo-HSCT using a GVHD prophylaxis regimen consisting of CsA, at Seoul National University Hospital between 2000 and 2006 in Korea. The data were collected after reviewing the electronic medical records.

GVHD prophylaxis regimen

The patients who underwent allo-HSCT received CsA at 5 mg/kg every 24 h, given as a continuous intravenous infusion from days -2 to 3. From days 4 to 14 and

from days 15 to 35, CsA was given at 3 and 3.75 mg/kg, respectively, every 24 h, as a continuous intravenous infusion. On day 36, oral CsA (Neoral or Sandimmune, Novartis Pharmaceuticals, East Hanover, NJ; or Cypol-N, Chong Kun Dang Pharmaceutical, Korea) was substituted at 5 mg/kg twice a day as tolerated and was tapered gradually according to the whole-blood CsA concentrations. In patients without GVHD, full-dose CsA therapy was continued until at least day 120. In conjunction with CsA, methotrexate (10-15 mg/m²) was given on days 1, 3, 6, and 11 to the majority of patients.

The patients who underwent allogeneic non-myeloablative stem cell transplantation received intravenous CsA at 3 mg/kg every 24 h, given as a continuous infusion from day -1 to day 30. Subsequently, oral CsA was started at 3 mg/kg twice a day and tapered gradually according to the whole-blood CsA concentrations.

Blood sampling and CsA analysis

Blood samples were collected at 7 a.m. after initiating CsA therapy and then approximately twice a week as part of routine patient care during the hospital stay. Subsequent samples were obtained at each outpatient visit. The desired trough target range was 150–300 ng/mL. The CsA concentrations in whole blood were measured using a gamma counter (Hewlett Packard, Palo Alto, CA). Only those concentrations obtained at steady state were analyzed, where steady state was defined as at least 60 h at the same dose.

Pharmacokinetic analysis

NONMEM, version VI, level 0.9 with double precision analysis was used for the analysis.¹²⁾ The first-order method was used for the estimation, and ADVAN4 TRANS4 was chosen considering a two-compartment open model of CsA absorption and elimination. Steady-state concentrations of CsA in the blood were analyzed to estimate the population PK parameters such as apparent clearance (CL/F), apparent volume of the central compartment (V_2/F), absorption rate (k_a), apparent volume of the peripheral compartment

(V_3/F), and inter-compartmental clearance (Q), as well as their variability. Here, F refers to the oral bioavailability. The inter-individual variability in the PK parameters of CsA was modeled using additive, proportional, and exponential error models. In addition, a proportional error model, additive model, and combined proportional and additive error model were evaluated for residual variability.

In the first step, a base model with the lowest objective function value (OBFV) without covariates was developed. Scatter plots of parameters against each covariate helped to identify the trends and regression pattern. Then, stepwise inclusion and backward elimination were used to build the final regression model. During stepwise forward inclusion, a change in OBFV greater than 3.84 on testing a single covariate was statistically significant ($p = 0.05$). During backward elimination, selected covariates were eliminated individually from the full regression model to confirm their significance. An increase in OBFV of more than 6.62 indicated that removal of the covariate resulted in a significantly inferior model ($p = 0.01$), and it was concluded that the covariate was meaningful. A final model was developed that kept only those covariates that maintained significance during backward elimination.

Ten covariates were entered into the regression model as continuous, dichotomous, or categorical variables. The baseline patient characteristics collected were age,^{13, 14)} gender¹⁵⁻²⁰⁾ (SEXF), type of disease (TOD), type of donor (RU), and creatinine clearance¹⁹⁻²¹⁾ (CRCL) as calculated using the equation of Cockcroft and Gault. Additional data were recorded with each CsA trough concentration: CsA dose; post-transplant days^{19, 20, 22)} (POD); total bilirubin level²³⁻²⁶⁾ (TBIL); hematocrit^{13, 19)} (HCT); alanine transferase (ALT); aspartate transaminase (AST); presence of concurrent cytochrome P450 (CYP450) inhibitors²⁷⁻³⁰⁾ such as isoniazid (INH), itraconazole, fluconazole, diltiazem, amlodipine, and simvastatin, and presence of CYP450 inducers^{31, 32)} such as prednisolone and methylprednisolone. Continuous variables were modeled linearly using centering of the covariate about its standard value. Other covariates such as recipient gender

were originally dichotomous variables and were entered into the regression equation as a multiplier associated with the covariate. Type of donor (related or unrelated), POD (≤ 50 or >50 days), and presence of a concurrent CYP450A inhibitor (yes or no) were also categorized as dichotomous variables. Type of disease and corticosteroid dose as a CYP450 3A inducer (prednisolone dose 0 vs. >0 , ≤ 50 vs. >50 mg) were investigated as categorical covariates.

RESULTS

Patient characteristics

As shown in Table 1, a total of 757 whole-blood CsA concentrations were obtained from 46 adult leukemia patients after allo-HSCT. There were 24 male (53%) and 22 female (47%) patients. The median patient age was 40 (range, 18-67) years. The mean CsA dose was 242.36 ± 24.152 mg/dose (q12 h), and the mean CsA concentration in the blood was 202.43 ± 76.14 ng/mL.

Table 1. Characteristic of Study Patients

Characteristics	Value
No. of patients	46
No. of blood samples	757
No. of samples per patients	16
Age, years (median, range)	40 (18-67)
Gender (n, %)	
Male	24 (53)
Female	22 (47)
Presence of concomitant drugs (n, %)	
CYP450A inhibitor	8 (17)
CYP450A inducer	7 (15)
Transplant type (n, %)	
Related allogeneic transplantation	29 (63)
Unrelated allogeneic transplantation	17 (37)
Postoperative day (mean \pm SD, range)	104.60 \pm 52.47 (13-390)
CsA dose (mean \pm SD, range, mg/dose, q12 h)	242.36 \pm 24.152 (25~500)
CsA blood concentration (mean \pm SD, range, ng/mL)	202.43 \pm 76.14 (42-478)
Type of Disease (n)	
Acute myelocytic leukemia	20
Acute lymphocytic leukemia	8
Chronic myelocytic leukemia	11
Myelo-dysplastic syndrome	7

Table 2. Summary of univariate analyses showing covariate models with significant effects on PK parameters of CsA

	MODEL	OBFV	COFV
BASE	$Ka = TVKa * EXP(ETA(1))$ $CL/F = TVCL * EXP(ETA(2))$ $Q = TVQ * EXP(ETA(3))$	4511.829	-
HCT on CL/F	$TVCL = \Theta(2) * EXP(\Theta(6) * HCT/28.9)$	4469.947	41.882
INH on CL/F	$TVCL = \Theta(2) * EXP(\Theta(6) * INH)$ if inhibitor is present, $INH=1$	4498.312	13.517
SEXF on CL/F	$TVCL = \Theta(2) * EXP(\Theta(6) * SEXF)$ if patients are male, $SEXF=1$	4482.045	29.784
RU on CL/F	$TVCL = \Theta(2) * EXP(\Theta(6) * RU)$ if unrelated, $RU=1$	4472.166	39.663
HCT on Ka	$TVKa = \Theta(1) * (1 + \Theta(6) * HCT/28.9)$	4496.807	15.022
INH on Q	$TVQ = \Theta(4) * (1 + \Theta(6) * INH)$ if inhibitor is present, $INH=1$	4500.422	11.407
CRCL on Ka	$TVKa = \Theta(1) * EXP(\Theta(6) * HCT/28.9)$	4478.612	33.217
TBIL on Q	$TVQ = \Theta(4) * (1 + \Theta(6) * TBIL/1.31)$	4490.771	21.058
POD on Q	$TVQ = \Theta(4) * EXP(\Theta(6) * POD)$ if $POD > 50$, $POD=1$	4502.141	9.688
PD on Ka	$TVKa = \Theta(1) * (1 + \Theta(6) * PD)$ $IF(PD.EQ.2) TVKa = \hat{E}(1) * (1 + \Theta(7) * PD/2)$ If $50 \geq PD \text{ dose} > 0$, $PD=1$; $PD \text{ dose} > 50$, $PD=2$	4504.284	7.545
TBIL on Ka	$TVKa = \Theta(1) * EXP(\Theta(6) * TBIL/1.31)$	4473.163	38.666

Abbreviations: CL/F , apparent clearance; Ka , absorption rate; Q , inter-compartmental clearance; POD, post operative days; SEXF, gender factor; CRCL, creatinine clearance; TBIL, total bilirubin; HCT, hematocrit; RU, related or unrelated; PD, prednisolone dose; INH, presence of CYP450A inhibitor; OBFV, objective function value; COFV, Change of objective function value

Of the 46 patients, 15% received a CYP450A inducer, and 17% received a CYP450A inhibitor. There were 29 (63%) related transplantations and 17 (37%) unrelated transplantations. In all, 151 (19.94%) CsA concentrations were estimated in patients with $TBIL \geq 2$ mg/dL, and 78 (10.4%) CsA concentrations were obtained in patients with a serum creatinine ≥ 2 mg/dL.

NONMEM pharmacokinetic analyses of CsA

According to the two-compartment PK model, the population mean and inter-individual variability (expressed as percent coefficient of variation, CV%) of the estimated parameters from the base model for CL/F , k_a , V_2/F , V_3/F , and Q were 52 L/h (CV = 42.22%), 0.0821 h⁻¹ (CV = 48.24%), 941 L, 210000 L, and 43.8 L/h (CV = 38.375%), respectively. The estimated random residual exponential was CV = 26.34%.

Table 2 shows the effect of the various patient characteristics when added individually as covariates for CL/F , k_a , or Q . In these analyses, eight covariates, TBIL, HCT, INH, SEXF, RU, CRCL, POD, and PD, reduced OBFV by more than 3.84 ($p < 0.05$) compared with the base model. Age and TOD were initially excluded from the regression model, because they did not influence the

CsA PK parameters. During stepwise forward inclusion, the change in OBFV for the HCT effect on CL/F was largest, at 41.882, and thus this factor was deemed the most substantial and was incorporated into the regression model in the first selection. In the second selection, the effect of the dichotomous covariate SEXF on CL/F reduced OBFV by 33.289 and was therefore incorporated into the regression model. Table 3 outlines

Table 3. Stepwise estimation of model covariates by the forward inclusion method

	1st Selection	2nd Selection	3rd Selection
HCT on CL/F	41.882	Involved	Involved
INH on CL/F	13.517	13.396	Increased
SEXF on CL/F	29.784	33.289	Involved
RU on CL/F	39.663	3.271	-
HCT on Ka	15.022	Increased	-
INH on Q	11.407	0.624	-
CRCL on Ka	33.217	3.544	-
TBIL on Q	21.058	2.279	-
POD on Q	9.688	Increased	-
PD on Ka	7.545	Rounding error	-
TBIL on Ka	38.666	Increased	-

Abbreviations: CL/F , apparent clearance; Ka , absorption rate; Q , inter-compartmental clearance; POD, post operative days; SEXF, gender factor; CRCL, creatinine clearance; TBIL, total bilirubin; HCT, hematocrit; RU, related or unrelated; PD, prednisolone dose; INH, presence of CYP450A inhibitor

Table 4. Backward elimination and change of objective function value

Factor	OBFV	COFV	P-value
HCT on CL/F	4469.947	41.882	<0.001
SEXF on CL/F	4482.045	29.784	<0.001

Abbreviations: CL/F , apparent clearance; OBFV, objective function value; COFV, change of objective function value; SEXF, gender factor; HCT, hematocrit

the stepwise forward inclusion of the covariates. In the full regression model, HCT and SEXF affected CL/F .

$$CL/F = \theta_2 \times \text{EXP}(\theta_6 \times \text{HCT}/28.9 + \theta_7 \times \text{SEXF}),$$

where SEXF = 1 for male patients.

To validate the significant effect of the included covariates,

each covariate was eliminated from the full regression model. Each OBFV was more than 6.68, which indicated statistical significance ($p < 0.001$). The process of backward elimination is shown in Table 4. The final model for CsA was as follows:

$$CL/F \text{ (L/h)} = 85.6 \times e^{(-0.646 \times \text{HCT}/28.9 + 0.0464 \times \text{SEXF})}$$

where SEXF = 1 for male patients; k_a (h^{-1}) = 58.433; Q (L/h) = 269.024; V_2/F (L) = 1100; and V_3/F (L) = 213000.

The final estimations of the population PK parameters, the inter-patient standard error mean, and the inter-individual variability are shown in Table 5. The inter-individual variabilities of CL/F , k_a , and Q were 36.02,

Table 5. PK parameters, the inter-patients and residual variability and the precision of the estimation of final model of CsA in HSCT patients

Parameter	Symbol	Population mean	%SEM	Inter-individual Variability (CV%)
Apparent Clearance (CL/F , L/kg/hr)	θ_2	85.6	23.48	36.02
Effect of HCT on CL/F	θ_6	-0.646	-34.98	
Effect of SEXF on CL/F	θ_7	0.0464	61.33	
Absorption rate (K_a , h^{-1})	θ_1	0.0787	26.30	27.92
Apparent Central volume (V_2/F , L)	θ_3	1100	48.45	
Apparent Peripheral volume (V_3/F , L)	θ_5	2.13E+05	79.34	
Intercompartmental clearance (Q , L/kg/h)	θ_4	57.1	67.08	19.265
Inter-individual variance of CL/F	ω_{CL}^2	0.122	28.52	
Inter-individual variance of K_a	ω_{Ka}^2	6.61	74.47	
Inter-individual variance of Q	ω_Q^2	1.55	104.52	
Residual variance	σ^2	0.0561	13.44	
Random residual error Exponential model				24.02

Abbreviations: CL/F , apparent clearance; K_a , absorption rate; Q , inter-compartmental clearance; SEM, standard error mean; CV, coefficient of variation

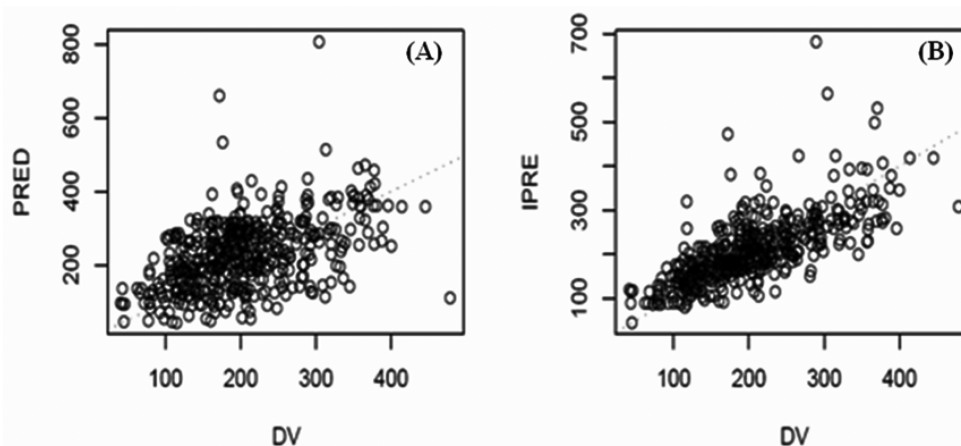


Fig. 1. (A) Scatter-plot of observed plasma CsA concentration vs. population predicted plasma CsA concentration by final covariate model. (B) Scatter-plot of observed plasma CsA concentration vs. individual predicted plasma CsA concentration by final covariate model.

27.92, and 19.265%, respectively. Figure 1 plots the population and individual predictions versus the observed concentration in the final model. There was large variability between the population prediction and the observed concentrations; however, the variability was less for the individual prediction versus the observed concentrations.

DISCUSSION

The PK of CsA are complex. CsA has a narrow therapeutic index and exhibits significant, unpredictable toxicity, including nephrotoxicity, neurotoxicity, and hyperglycemia. Although previous studies have identified several clinical factors that influence its behavior *in vivo*, several of these clinical factors can occur together and may simultaneously influence the PK of CsA in critically ill patients such as HSCT recipients. Unfortunately, few studies have evaluated the clinical factors governing CsA disposition after allo-HSCT in leukemia patients. Therefore, this study estimated the population PK parameters of CsA and the effects of clinical factors on the PK parameters in adult leukemia patients.

In this study, hematocrit and gender significantly influenced the apparent clearance of CsA in leukemia patients after allo-HSCT. The CL/F of CsA increased as HCT decreased, consistent with previous reports. Yee *et al.* reported that HCT significantly influenced CsA PK.¹³⁾ This is probably because 50% of CsA is bound to red blood cells and only unbound drug in the blood is eliminated. However, Yee *et al.* did not evaluate the effect of HCT on CL/F in HSCT patients owing to the paucity of measurements made on the same day as the CsA concentration was determined and owing to the high frequency of red blood cell transfusions in the early post-transplant period.¹⁹⁾ In our study, biochemical parameters were examined routinely and HCT was measured frequently, allowing evaluation of the relationship between CL/F and HCT.

Various studies have examined gender differences in CsA PK, but the results are controversial.¹⁵⁻¹⁸⁾ We

found that the CL/F was increased 4.06 in males, which concurs with a report of Rui *et al.* that the CL of CsA increased 4.31 in males.¹⁵⁾ Although 4.06 indicates a statistically significant gender-associated difference, it does not imply a significant change in renal function. In an animal study,¹⁸⁾ CsA blood and tissue levels were significantly higher in male rats than in females, except in adipose tissue where the concentrations were twice as high in females. These authors also reported that in male rats, the highest CsA concentrations were in the liver, followed in order by the kidneys, spleen, fat, skin, muscle, and finally blood. In comparison, female rats had the highest drug levels in fat, followed by the liver, kidneys, spleen, skin, muscle, and blood. Differences in the distribution and metabolism of CsA may be responsible for gender-associated differences in CsA PK, and clinicians need to consider patient gender. Generally, there was a correlation between HCT and gender. The correlation among these covariates can make an error in model building steps. Therefore, we checked the correlation among the covariates and inter-individual variability between the base model and the final model. We confirmed the decrease in inter-individual variability since there was no-correlation found between HCT and gender, using correlation matrix ($r < 0.5$) in the final model.

Cyclosporin A is metabolized by CYP450 3A, and the PK of CsA are influenced by the induction or inhibition of the CYP450 3A enzyme system.²⁷⁻³⁰⁾ Nevertheless, the presence of CYP450 3A inhibitors or inducers had no effect on CsA PK in our study, perhaps because there were too few individuals in the inducer (15%) and inhibitor (17%) groups. And, in our study, age did not influence CsA CL/F or other PK parameters; perhaps because all of our subjects were adults.

Total bilirubin had no dramatic effect on the CsA PK parameters, although 151 (19.94%) CsA concentration points were obtained in patients with a TBIL ≥ 2 mg/dL. A previous PK study in HSCT found that the patients with moderate (bilirubin, > 2 mg/dL) hepatic dysfunction had a lower mean CsA oral clearance (29.60 ± 7.10 mL/min/kg) than in patients with no or

mild dysfunction (50.2 to 52.4 mL/min/kg).²³⁾ A similar reduction has also been observed in renal transplantation.²⁴⁾ However, in those studies, the CsA concentrations were measured using a nonspecific radioimmunoassay, which cross-reacts with CsA metabolites and overestimates CsA concentrations, particularly in the setting of hepatic dysfunction where metabolites readily accumulate.^{22, 25, 26)} As a result, the *CL* estimates were lower than those obtained using concentrations measured with specific assays. Therefore, it is not surprising that no effect was observed on the CsA *CL* in patients with hyperbilirubinemia.

This study has a few limitations probably due to insufficient retrospective concentration data that does not provide adequate information for analysis of the CsA PK parameters. However, since the values of PK parameters were compared with the data from previous studies, we got acceptable PK parameters considering differences of the characters that might exist between the populations from the previous study and the present study. And in this study, the V2/F and V3/F were estimated higher than the data from previous studies. This can be explained by the parameter; fraction of absorbed CsA (F). CsA had a large inter-individual variability on absorption because it was P-glycoprotein substrate. Therefore many NONMEM users estimated the population PK parameters after fixing the F parameter of CsA to obtain the reasonable value of V and CL. However, the V/F that we estimated and presented in the results section seems like high estimation.

In conclusion, we describe the mixed effect modeling of CsA PK parameters in leukemia patients after allo-HSCT. The following equation, which has been rearranged to simplify the determination of the initial CsA dose, illustrates how the regression model for *CL/F* may be used in a clinical setting.

$$\text{Total daily dose} = C_{\text{target}} \times CL/F \times 24 = C_{\text{target}} \times 85.6 \times e^{(-0.646 \times \text{HCT}/28.9 + 0.0464 \times \text{SEXF}) \times 24}, \text{ for male patients, SEXF} = 1$$

Understanding the CsA PK and the clinical events that lead to alterations in the PK parameters and immunosuppressive exposure in HSCT is critical to improving the clinical outcome. The development of clinical

models that can predict immunosuppressive exposure is an important factor in reducing toxicity, preventing and controlling GVHD, and promoting engraftment. Based on the present study, special attention should be paid to the patient in whom a key covariate value is abnormal. A simulation using our final model may help in treating individual patients and ensuring that the CsA concentration remains within the therapeutic range.

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