

Cyclosporine Pharmacokinetics and Dosing Modifications in Human Immunodeficiency Virus-Infected Liver and Kidney Transplant Recipients

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Background. With advances in antiretroviral therapy, many human immunodeficiency virus (HIV)-infected individuals are living longer and developing end-stage renal or hepatic disease requiring transplantation. Maintaining the viability of the transplant and suppressing HIV replication requires concomitant use of immunosuppressants (e.g., cyclosporine) and antiretrovirals (e.g., protease inhibitors or nonnucleoside reverse transcriptase inhibitors), which leads to drug interactions. To assist in appropriate clinical management of HIV-infected transplant recipients, the authors describe the pharmacokinetic interactions between cyclosporine and the antiretroviral medications, and required modifications of cyclosporine dosing.

Methods. Eighteen HIV-infected subjects with end-stage kidney or liver disease underwent transplantation. Subjects had pharmacokinetic studies before transplantation and for up to 2 years posttransplantation (at weeks 2–4, 12, 28, 52, and 104). Protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and cyclosporine concentrations were measured by liquid chromatography-mass spectrometry in plasma and whole blood, respectively.

Results. Subjects using protease inhibitors and cyclosporine had a threefold increase in cyclosporine area under the curve ($4,190 \pm 2,180$ – $11,900 \pm 1,600$ ng*hr/mL, $P < 0.01$), necessitating an 85% reduction in cyclosporine dose over a 2-year period (1.3 ± 1.5 – 0.2 ± 0.0 mg/kg/dose), leading to a progressive increase in oral cyclosporine bioavailability ($R^2 = 0.92$, $P < 0.02$). Subjects on nonnucleoside reverse-transcriptase inhibitors showed minimal interactions with cyclosporine, and subjects on both HIV treatments had intermediate responses.

Conclusions. HIV-infected transplant recipients on protease inhibitors require markedly lower doses of cyclosporine, with continued lowering of the cyclosporine dose over time and ongoing cyclosporine trough monitoring because of progressively increasing cyclosporine bioavailability. Medication changes must be carefully managed to avoid insufficient immunosuppression or toxicity resulting from drug interactions.

Keywords: Human immunodeficiency virus, Cyclosporine dose, Transplantation.

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Traditionally, patients with human immunodeficiency virus (HIV) have been excluded from consideration for transplantation because of concerns about the safety of

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further immunosuppression from transplant medications and reluctance to allocate scarce resources to those with a poor prognosis. With the tremendous advances in antiretroviral therapy (ARV) in the last few years, patients are now living much longer and dying as a result of concomitant liver disease or suffering complications of long-term dialysis therapy rather than dying as a result of complications of HIV. Increasingly, such patients are being offered solid organ transplantation.

Cyclosporine (CsA) and the HIV protease inhibitors (PI) used as antiretroviral therapy are substrates and inhibitors of the cytochrome P450 metabolizing enzyme CYP3A4 and tend to increase systemic blood levels, whereas nonnucleoside reverse-transcriptase inhibitors (NNRTI) are often CYP3A inducers (1) that increase drug metabolism and decrease blood levels. In addition, both CsA and PI are substrates and inhibitors of P-glycoprotein (2), a transporter found on the apical membranes of intestinal and hepatic epithelial cells, whose function is to decrease absorption and increase excretion of its substrates (3). In intestinal and hepatic cells, P-glycoprotein and CYP3A4 act as a “gauntlet,” where the interplay between the two proteins causes sub-

strates to exhibit increased metabolism and transport back into the intestinal lumen or the bloodstream (3, 4). Therefore, concomitant administration of inhibitors of both P-glycoprotein and CYP3A4 systems, such as CsA with PI, would be expected to increase both CsA and PI uptake and systemic blood levels.

However, the extent of their potential drug interactions is not well characterized. Because both types of medications have narrow therapeutic windows, understanding the degree of interaction would help clinicians correctly dose CsA and antiretroviral medications. We report on CsA interactions with antiretroviral medications in the first 18 subjects studied for up to 2 years posttransplantation.

PATIENTS AND METHODS

Study Design and Subjects

HIV-infected subjects with end-stage renal or liver disease, who met the standard University of California, San Francisco (UCSF) criteria for liver or renal transplantation, were eligible for the study. CsA pharmacokinetics were evaluated after transplantation. Antiretroviral pharmacokinetics (PI and NNRTI) were studied first before transplantation and then after transplantation in combination with oral CsA (Noral or Gengraf). Subjects were usually also taking two or three other antiretroviral medications including nucleoside reverse-transcriptase inhibitors; however, these were not measured in this study.

In this article, we report on the first 18 HIV-positive subjects recruited for this study: 17 men and 1 woman (mean age at the time of transplantation, 44±9 years; range, 15–53 years) (Table 1). Eleven were white, four were African-American,

two were Asian, and one was Hispanic. All subjects were nonsmokers and had no intercurrent illnesses when studied. One subject initially had a liver transplant and then required a combined liver-kidney transplant when the first graft failed, and one subject received a combined liver-kidney transplant; all other transplants were single organ grafts. This study was approved by the UCSF Institutional Review Board, and all study subjects gave signed informed consent.

Study Procedures

Study drug regimens

All subjects initiated CsA posttransplantation on day 0 (liver recipients) or when the serum creatinine was below 3 mg/dL (kidney recipients), according to UCSF's transplant protocol. Initial CsA dosing was dependent on which antiretroviral medications patients were taking (Table 2). Subsequent changes in CsA doses were made in response to CsA trough levels obtained just before the morning dose of CsA and measured at the UCSF clinical laboratory. The study protocol did not mandate a specific ARV regimen; thus, some subjects were on PI, some were on NNRTI, and some were using drugs from both classes. Standard posttransplantation management included tapering steroids and mycophenolate mofetil, and antiviral (daily acyclovir or valganciclovir), anti-*Pneumocystis* (daily dapsone or trimethoprim-sulfamethoxazole), and antifungal (weekly fluconazole) prophylaxis.

Pharmacokinetic studies

Subjects had pharmacokinetic studies before transplantation and for up to 2 years posttransplantation (at weeks 2–4, 12, 28, 52, and 104). ARV or immunosuppressant drug regimens were modified in response to drug side effects, increase in HIV-1 RNA levels (viral load), low drug levels, or rejection episodes. A change in drug regimen required reinitiating the cycle of studies (e.g., weeks 2, 12 [vide infra]). Tacrolimus, sirolimus, or both could be used as alternative antirejection therapy; these data were excluded from this analysis because of limited data.

Subjects were admitted to the UCSF General Clinical Research Center for the pharmacokinetic studies. Each study started at 8 AM after an overnight fast. An indwelling catheter was inserted into a forearm vein. After drawing baseline safety laboratory and trough blood samples, at 8 AM, subjects took their antiretroviral therapy and, if posttransplant, their CsA dose. Blood was sampled from the indwelling catheter at different time intervals, depending on which drugs subjects were taking: for medications dosed on an every-12-hr schedule, blood was sampled at 0, 30, 60, 120, 150, 180, 210, 240, 300, 360, 480, and 720 min; and for indinavir dosed every 8 hr, blood was sampled at times 0, 30, 45, 60, 90, 120, 150, 180, 240, 360, and 480 min. For efavirenz, which is taken once daily at bedtime (11 PM or 15 hr), additional blood was sampled at 15, 19, and 24 hr. No food was allowed for the first 3 hours after the study was started, and all subjects ate a 30% fat meal at the same times relative to taking their medication. No grapefruit or grapefruit juice was allowed. Medications known to be CYP3A and P-glycoprotein inhibitors (e.g., fluconazole, amlodipine) were not administered until after the pharmacokinetic study had been completed.

TABLE 1. Patient and transplant characteristics^a

Characteristic	Values
Organs transplanted	Livers, 5; kidneys, 12; combined liver-kidney Tx, 2 ^b
Sex	Male, 17; female, 1
Age (yr)	Mean, 44; range, 15–54
Race	C, 11; AA, 4; AP, 2; H, 1
Indication for Tx	
Liver	HCV, 2; HBV, 2; ALF, 1
Kidney	HIVAN, 6; HTN, 3; DM, 2; IgA, 1; IN, 1
Donor	LR, 9; HR, 4; CAD, 6
Survival	
Patient	17/18
Graft failure	1/21 ^b
Days post-Tx	Median, 1,028; range, 511–1,514 ^a
Rejection episodes	
Liver	1
Kidney	10

^a As of May 30, 2004.

^b Total of 21 organs; one subject had a liver graft that failed and was retransplanted with a combined liver-kidney graft.

Tx, Transplant; ALF, acute liver failure; HIVAN, HIV nephropathy; HTN, hypertension; DM, diabetes; IgA, IgA nephropathy; IN, interstitial nephritis; LR, living-related; HR, high risk; CAD, cadaver; C, Caucasian; AP, Asian; H, Hispanic; AA, African-American.

TABLE 2. CsA Dosing

Drug	Initial dose of CsA	Maintenance dose of CsA	Mean CsA trough (ng/mL) (Range)
PI			
Nelfinavir	50–75 mg bid	25 mg bid	112 (59–174)
Indinavir	75–100 mg bid	75 mg bid	125 (74–175)
NNRTI			
Nevirapine	200–250 mg bid	100–175 mg bid	122 (45–195)
Efavirenz	350–450 mg bid	250–400 mg bid	117 (84–182)
PI and NNRTI			
Nevirapine-nelfinavir	25 mg bid	25 mg bid or qd	169 (152–176)

bid, Two times per day; qd, every day.

Analysis of Blood Samples

Blood samples were spun down and frozen at -70°C until analyzed. Serum was analyzed for nelfinavir, indinavir, saquinavir, nevirapine, efavirenz, and delavirdine, and whole blood was analyzed for CsA.

Cyclosporine

Whole blood samples were analyzed for CsA by a validated high-performance liquid chromatography (LC)/mass spectroscopy (MS) assay in combination with automated on-line sample preparation (LC/LC-MS) (Hewlett-Packard, Palo Alto, CA). Method validation has been described in detail by Christians et al. (5).

PI and NNRTI

Plasma samples were analyzed for the PI nelfinavir, saquinavir, and indinavir and the NNRTI nevirapine, efavirenz, and delavirdine using a validated high-performance LC/MS assay (6) in combination with automated online sample preparation (LC/LC-MS) (Hewlett-Packard). The assay was validated following the Food and Drug Administration Good Laboratory Practice guidelines (7). In all cases, recovery was greater than 85% and samples were shown to be stable in the autosampler at 20°C for at least 24 hr.

Pharmacokinetic Analysis

The pharmacokinetic parameters maximum concentration (C_{max}), the time to reach C_{max} (T_{max}), area under the curve over a dosing interval (AUC_{0-7}), clearance divided by bioavailability (CL/F), volume of distribution at steady-state divided by bioavailability (V_{ss}/F), and terminal half-life ($t_{1/2}$) were determined after oral administration and based on non-compartmental methods using WinNonlin Professional software (version 2.1; Pharsight, Inc., Mountain View, CA). The values for C_{max} and T_{max} were obtained directly from the concentration-time profile of the data. Individual concentration-time profiles were plotted, and the elimination rate constant was determined by the logarithmic regression of the time points in the terminal elimination phase.

Statistical Analysis

Cyclosporine levels (in nanograms per milliliter) were adjusted for each subject's actual dose (in milligrams) and body weight (in kilograms) unless otherwise specified. All

data are reported as the mean \pm SD. Comparisons between groups were performed using analysis of variance or t tests, with $\alpha=0.05$. Correlation analyses were run between AUC_{0-7} and C_x for CsA, where x was an individual time point or some combination of time points, and for CL/F versus V_{ss}/F . All statistical analyses were performed using SigmaStat (Jandel Scientific, San Rafael, CA).

RESULTS

Patient Outcomes

Seventeen subjects are alive at a median of 1,028 days posttransplant (range, 511–1,514 days as of May 30, 2004). One subject died 445 days after a combined liver-kidney transplant as a result of liver failure caused by recurrent hepatitis C virus infection. All grafts are functioning in surviving subjects. However, there were 11 episodes of rejection in 9 kidney transplant patients; 6 occurred during the first week after transplantation and before CsA was begun; the other 5 required a change in immunosuppressant drug regimen. Three subjects had ARV regimens changed because of inadequate ARV exposure.

Cyclosporine in Combination with PI and NNRTI

Five subjects received PI, seven received NNRTI, and seven received both PI and NNRTI during the pre- and initial posttransplant period. CsA data are depicted in Figures 1 and 2. For subjects on PI, when adjusted for dose and body weight (Fig. 1), AUC (and C_{max}) increased progressively during the 104 weeks of the study from $4,190 \pm 2,180 \text{ ng}^* \text{ hr}/\text{mL}$ at week 2 to $11,900 \pm 1,600 \text{ ng}^* \text{ hr}/\text{mL}$ at week 104 ($P < 0.01$), whereas the CsA average dose decreased during the 104 weeks of study (1.3 ± 1.5 vs. $0.2 \pm 0.0 \text{ mg}/\text{kg}$, $P > 0.05$). Thus, the CsA concentration-over-dose profiles increased over time (Fig. 1).

Adjusted for dose and body weight, the increase in AUC was associated with an increase in C_{max} , from $665 \pm 250 \text{ ng}/\text{mL}$ to $1,470 \pm 90 \text{ ng}/\text{mL}$ (Fig. 1). CL/F decreased over the 104 weeks of study from $22 \pm 14 \text{ mL}/\text{hr}/\text{kg}$ to $5 \pm 1 \text{ mL}/\text{hr}/\text{kg}$, correlating with a decrease in the CsA V_{ss}/F (Fig. 3) ($R^2=0.92$, $P < 0.02$).

In contrast, when CsA was administered concomitantly with NNRTI, the CsA concentration profiles remained relatively uniform over the 104 weeks (Fig. 2), with minimal changes in AUC, C_{max} , $t_{1/2}$, and CL/F and a small decrease in

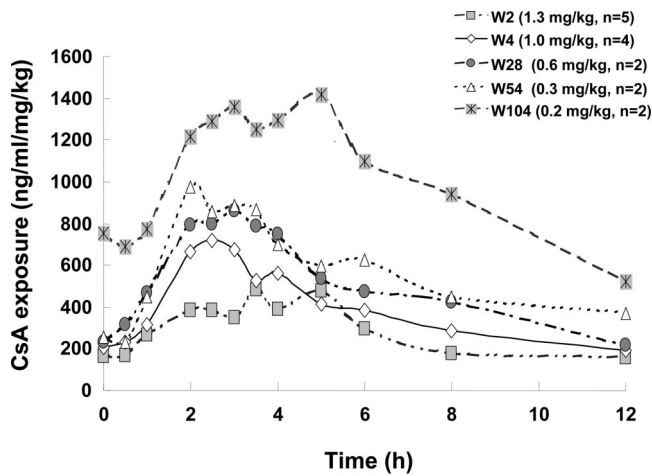


FIGURE 1. Changes in CsA concentration-time curves over a 2-year period for subjects on concomitant PI.

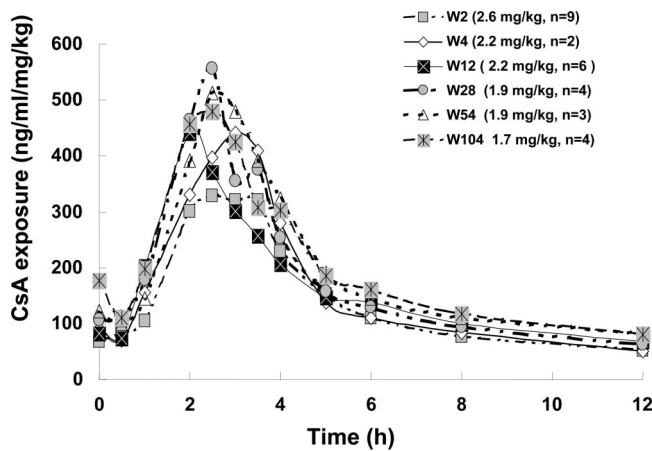


FIGURE 2. Changes in CsA concentration-time curves over a 2-year period for subjects on concomitant NNRTI.

dose (2.6 ± 0.8 to 1.7 ± 0.3 mg/kg; all $P > 0.2$) over the 104 weeks of the study (Fig. 2).

In subjects using concomitant PI and NNRTI, the CsA AUC and dose data were in between those for CsA plus PI or CsA plus NNRTI alone. AUC declined slowly over time ($4,020 \pm 490$ ng*hr/mL to $2,640 \pm 2,650$ ng*hr/mL) as dose decreased (1.1 ± 0.7 mg/kg to 0.8 ± 0.7 mg/kg; all $P > 0.4$).

Effects of CsA on Antiretroviral Pharmacokinetics

PI and NNRTI pharmacokinetic studies were performed pretransplant and at weeks 2 to 4, 12, 28, 52, and 104. Protease inhibitor AUC generally increased over pretransplant baseline over the first few weeks when CsA was added to the drug regimen but returned to baseline by week 28 (data not shown). There were minimal changes in NNRTI pharmacokinetics during the 104 weeks of the study. Because of changes in the protocol's pharmacokinetic sampling dates, there were no data available for subjects on PI and CsA at week 12.

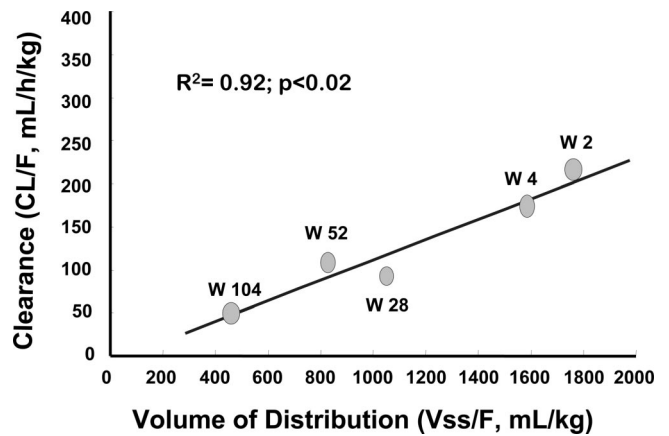


FIGURE 3. Increase in oral CsA bioavailability with time for subjects on PI. The correlations were calculated using the means for the five different doses. Data are depicted to highlight the changes in both the Vss/F and CL/F by week (W) posttransplantation.

Limited Sampling Analysis

The principal limited sampling models and comparisons of correlations between CsA-protease inhibitor, CsA-NNRTI, and CsA AUC_{0-12} in renal transplant patients and C_x (C at time points 0, 2, 3, and 4 hr) are shown in Table 3. For comparison, data extracted from published reports from the Canadian Neoral Renal Transplant Group (8) and the International Neoral Renal Transplant Group (9) are shown.

C_0 was a poor predictor of drug exposure AUC_{0-12} , with R^2 values less than 0.6 in all groups. C_2 correlated best for the PI ($R^2=0.73$), less well in the non-HIV renal transplant studies, and poorly with the NNRTI. The best correlation time point with AUC_{0-12} for both the NNRTI and PI was C_4 . Adding additional pharmacokinetic data time points (e.g., $C_0 + C_2$) into the correlation calculations improved the correlation coefficients only for the PI.

DISCUSSION

For transplant recipients on concomitant protease inhibitor therapy, CsA AUC increased over time, requiring a progressive decrease in CsA dose to maintain CsA trough levels between 75 and 150 ng/mL. Similar increases in the levels of the immunosuppressants tacrolimus and sirolimus have been reported after liver transplantation in subjects on concomitant protease inhibitors (10-12), requiring even

TABLE 3. Correlations between C_x and AUC

Week	Time point	R^2 PI	R^2 NNRTI	R^2 CAN ^a	R^2 INT ^b
W2	C_0	0.36	0.37	0.55	0.31
	C_2	0.73	0.19	0.68	0.71
	C_3	0.87	0.66	0.84	0.71
	C_4	0.92	0.85	0.73	0.63

^a CAN, Canadian Neoral Renal Transplant Group (8).

^b INT, International Neoral Renal Transplant Group (9).

more dramatic decreases in dosing (as low as 1 mg weekly (10)).

This progressive increase in AUC appears to be attributable to a progressive increase in intestinal CsA bioavailability over the 24 months of the study, because an excellent correlation of the decrease in CL/F and Vss/F was observed (Fig. 3). CL/F and Vss/F are independent parameters and would not be expected to change in parallel except for changes in protein binding. Because of the bioavailability change with time in subjects taking PI, dose- and weight-adjusted CsA AUC increased nearly threefold and CsA dose decreased by 85%.

In comparison, patients on NNRTI required much higher doses of CsA, similar to those used for HIV-uninfected transplant patients (8, 9). There was minimal impact of the NNRTI tested on CsA pharmacokinetics, which were similar to CsA pharmacokinetic data in HIV-uninfected renal transplant patients for the first 12 weeks posttransplant (13, 14). There was no significant change over the 104 weeks for any of the pharmacokinetic parameters studied in the NNRTI group.

The low correlation between C_2 and AUC (Table 3) for the NNRTI group may be related to the tendency for CsA levels to decline for the first hour after dosing (Fig. 2). In both the protease inhibitor and NNRTI groups, C_4 correlated more highly with AUC than any other single time point (Figs. 1 and 3 and Table 3). In comparison, in non-HIV transplant subjects, C_2 has been shown to correlate better with AUC (13).

There were several limitations to this study. Although some subjects in this study are now more than 2 years posttransplant, the number of patients at each time point is small, and the drug regimens are not uniform. However, despite the small sample size and the interindividual differences between similar drug regimens, there was a clear difference in pharmacokinetic behavior of CsA in subjects taking PI and those taking NNRTI.

In subjects with multiple medical problems and on multiple drug regimens, drug absorption and drug interactions also have to be considered. However, these subjects were relatively healthy, carefully screened and selected HIV-positive subjects, none of whom had a CD4 count below 100 before transplant. In addition, some of the subjects were on other medications (e.g., calcium channel blockers, HMG-CoA reductase inhibitors) that potentially could have interfered or interacted with P-glycoprotein or cytochrome P4503A4. However, the specific drugs used (i.e., amlodipine in 10 patients and atorvastatin in 6 patients) have relatively weak interactions (15, 16), and these medications were not given concomitantly during the pharmacokinetic studies (usually after the study was completed). Once-weekly fluconazole, a stronger P-glycoprotein–CYP3A inhibitor, was administered only for the first 6 months, and always on a nonstudy day. Prior studies have shown that taking two drugs that are P-glycoprotein and CYP3A4 inhibitors at least a few hours apart can decrease the degree of interaction between the drugs (17, 18).

CONCLUSION

Elevated levels of PI could potentially also contribute to marked increases in CsA AUC. Especially for the PI, high CsA levels could increase PI levels, contributing to further increases in CsA AUC. However, as mentioned, PI levels tended to return to baseline after the first 12 weeks and thus would not explain the ongoing increase in CsA bioavailability. These

are the results for the first 18 patients enrolled in this trial. The study is ongoing, and further analyses with larger numbers of patients are planned.

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