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BEST SINGLE TIME POINT CORRELATIONS WITH AUC FOR CYCLOSPORINE AND TACROLIMUS IN HIV-INFECTED KIDNEY AND LIVER TRANSPLANT RECIPIENTS

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Abstract

Background—Interactions between antiretrovirals (ARVs) and transplant immunosuppressant agents (IS) among HIV-infected transplant recipients may lead to lack of efficacy or toxicity. In transplant recipients not infected with HIV, cyclosporine (CsA) and tacrolimus (TAC) trough levels (C0) or those drawn two hours after dosing (C2) correlate with drug exposure (AUC/dose) and outcomes. Due to ARV-IS interactions in HIV-infected individuals, and the high rate of rejection in these subjects, we investigated the correlations between IS concentrations and exposure to determine the best method to monitor immunosuppressant levels.

Methods—We prospectively studied 50 HIV-infected transplant recipients undergoing kidney or liver transplantation evaluating the pharmacokinetics of the IS over time after transplantation

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Conflicts of Interest

The authors report no conflict of interests.

All of the authors declare they have no conflicts of interest.

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(weeks 2 to 4, 12, 28, 52, and 104). IS levels were measured with LC/MS/MS and AUC calculated using WinNonLin 9.0. Correlation analyses were run on SAS 9.2

Results—CsA concentration at C4 correlated better with AUC than C0 or C2, and TAC concentration correlated better at C0 or C2.

Conclusions—We suggest that C0 is acceptable for TAC monitoring, but poor predictability will occur at C0 with CsA. The low correlation of C0 with CsA AUC could be responsible for the higher rejection rates on CsA that has been reported in these subjects.

Keywords

immunosuppressants; antiretrovirals; pharmacokinetics; drug interactions; HIV

Introduction

With the advent of highly active anti-retroviral therapy (HAART), improved opportunistic infection control, and human immunodeficiency virus (HIV) infected patient care, HIV is now a chronic condition in the developed world. With increasing survival, the incidence of end-stage renal and liver disease is increasing (1,2), and with it, the demand for transplant as definitive treatment. Multiple centers around the world are now doing kidney and liver transplants in these patients (3). But, due to the requirements to treat these subjects with both HAART and immunosuppressive drugs, many of which interact with each other, appropriate drug dosing is a challenge (4). Recent analysis of data from the NIH multicenter trial in HIV solid-organ transplant patients shows associations with use of IS to both increased rejection episodes and declining renal function (5, 6). To date, only very small studies of the effects of ARVs on IS have been reported, and most of those patients did not have repeat studies over time. (7, 8, 9, 10)

In non-HIV kidney and liver transplantation, trough (C0) or C2 levels are used to monitor levels of cyclosporine (CsA) and tacrolimus (TAC), two of the most commonly used immunosuppressant drugs, because the level of IS at these time points correlate with AUC and outcomes (11). In HIV transplant, whether these levels correlate with outcomes or toxicity is still unclear (6,12).

We have previously shown in HIV-infected transplant recipients in the second week after transplant that CsA C4 correlated better with area under the curve (AUC) than C0 or C2 when CsA was given with protease inhibitors (13). We now extend that analysis over a greater period of time in larger numbers of subjects and include the use of TAC as well as CsA. Achieving optimal IS dosing should potentially help prevent organ rejection and toxicity in HIV-infected transplant recipients.

Results

Patients

Fifty HIV infected transplant recipients (25 liver recipients, 25 kidney recipients, 47 men and three women) were studied. The average age was 49 (range 15-71) years at the time of

transplantation. Twenty-eight subjects were Caucasian, 17 were African-American and five were Asian or other.

Cyclosporine

AUCs—Dose and weight adjusted AUCs for CsA for subjects on protease inhibitors (PIs), with or without non-nucleoside reverse transcriptase inhibitors (NNRTIs), were significantly higher than for subjects taking NNRTIs (p=0.04). See Table 1, Figure 1A and 1C, vs. 1B. Adjusted AUC in nonHIV infected subjects on CsA is given for comparison.

Maximum Concentrations (Cmax at Tmax)—For patients on PIs (with or without NNRTIs), Tmax was three hours after oral administration of CsA, whereas it was initially closer to two hours in patients on the NNRTIs efavirenz (EFV) and nevirapine (NVP) (Figure 1, Table 2). Values for Cmax were dose and weight adjusted. The concentration-time curves of patients on PIs and CsA shifted to the right slightly over time (Figure 1A); there was no change with NNRTIs ((Figure 1B) and there were no differences between those on NVP and EFV (data not shown).

Cyclosporine Concentration-Time (Cx) Correlations with AUC—As can be seen in Table 3, Cx correlated significantly with AUC at many time points. At week 2, when subjects were on PIs with or without NNRTIs, C4 correlated best with AUC. When subjects were on NNRTIs alone, C3 or C4 correlated best with AUC. At later weeks for the subjects on CsA, C2 to C4 remained the best correlations for both the NNRTIs and the PIs.

Tacrolimus

AUC—Dose and weight adjusted AUCs for TAC fo subjects on PIs, with or without NNRTIs, were significantly higher than for subjects taking NNRTIs (p=0.002)(Table 1, Figures 2A and 2C vs 2B). There was an ~30% increase over time for dose and weight adjusted TAC AUC when TAC was given with protease inhibitors with or without NNRTIs, No change in AUC is seen when NNRTIs are dosed with TAC. Adjusted AUC in nonHIV infected subjects on TAC is given for comparison.

Maximum Concentrations (Cmax at Tmax)—For patients on PIs, Tmax was about six hours after oral administration of TAC, whereas in patients on NNRTIs (with or without PIs), Tmax was within 2-3 hours after TAC dosing (Table 4). Cmax was dose and weight adjusted. Over time, Tmax for the NNRTIs alone decreased while for the combination PI +NNRTIs Tmax doubled (Figure 2).

TAC Concentration-Time Curves (Cx) Correlations with AUC—As can be seen in Table 5, Cx correlated significantly with AUC at many time points. For the first few months, for subjects on PIs, with or without NNRTIs, the best correlation time point with AUC was C4. After 6 months, the best correlation time point became C0. For subjects on NNRTIs, C0 or C1 usually correlated better.

However for TAC, C0 or C1 had the best correlations for both the PIs and NNRTIs.

Discussion

This study is the largest PK study of IS that we know of, over the longest period of time, in HIV-infected transplant subjects. We have previously shown that those HIV-infected kidney and liver transplant recipients studied two weeks post transplant on CsA and protease inhibitors require lower doses of CsA and have higher AUCs than those subjects on NNRTIs (13). In that paper, we also demonstrated that C_4 in both groups correlates better with AUC than trough levels or C2. The results of the present analysis expand on those findings by describing changes in AUC and the concentration-time curves over time for up to 104 weeks post transplant, and for both CsA and tacrolimus.

We confirmed our early finding that at week 2, for subjects taking CsA with either PIs or NNRTIs, CsA concentration at C4 correlated better with AUC than did C0 or C2. After week 2, timepoints from C2 to C4 correlated best for CsA. In comparison, in transplant recipients who are not infected with HIV and therefore not taking ARVs, CsA concentrations at C2 correlate best with the AUC (14,15).

CsA raises serum creatinine levels and over time can lead to damage to the kidney. Kumar et al (16) in their kidney transplant patients treated with CsA, kept CsA troughs between 150-200 ng/mL. Although they had lower rejection rates than in the NIH multicenter trial, their eGFR decreased from 55 to 40 mL/min over two years, while in the NIH study, there was no change in renal function over time in the renal transplant group (6). Doing C2 or C4 levels is clinically more difficult than C0 levels, and so most centers (including UCSF) use C0. Whether using C4 would lead to less CsA toxicity or fewer rejection episodes has not been studied in this transplant population.

We also found that tacrolimus concentration after week 2, C0 correlated best. Some investigators have suggested that because of the flat AUC curves seen with TAC, trough levels should be kept higher than what was done in this trial (17). Higher TAC trough levels did correlate with decreased rejection rates in the NIH multicenter trial (6). Higher TAC levels were also associated with new onset DM in HCV-positive liver transplant (OR 2.21, p=0.12), but not in renal transplant patients (6).

There are several limitations to this study. First, there were relatively few patients in the TAC group. In addition, this was a clinical trial, and drug regimens were not uniform. The patients were usually taking two or more other antiretroviral drugs that were not measured because the assay for these intracellular phosphorylated medications was not very reproducible. To mitigate these confounders, our subjects were studied when they had no intercurrent illnesses and concomitant use of interacting medications during the pharmacokinetic studies was avoided. Prior studies have shown that taking two drugs that are P-glycoprotein and CYP3A4 inhibitors a few hours apart can decrease the degree of interaction between the drugs (18).

Newer ARVs, such as raltegravir and likely maraviroc, do not affect IS levels at the doses used (19), and so may be an alternative that can avoid these current ARV-IS interactions. Individualization of ARV treatments, or perhaps initially post transplantation maintaining CsA or TAC troughs at higher levels than used in the NIH trial and then adjusting the levels

down after the first year, are other possibilities. Finally, in this group of transplant subjects, the clinical importance of using non C0 levels to guide clinical care remains to be tested.

METHODS

Study Design and Subjects

This was an observational study of kidney and/or liver transplantation in HIV-infected patients. To be eligible for transplantation, HIV-infected kidney transplant candidates had to have an undetectable plasma HIV RNA level and CD4+ T-cell count greater than 200/mm^3, while liver transplant candidates had to have an undetectable plasma HIV RNA level (or the prediction of HIV suppression post-transplant) and a CD4+ T-cell count greater than 100/mm^3 (or greater than 200/mm^3 if there was a history of an opportunistic complication). Subjects were usually taking three or more ARV medications prior to and following transplantation. This study was approved by the UCSF Institutional Review Board, and all study subjects gave signed informed consent. The NIH multicenter trial is registered at clinicaltrials.gov, NCT00074386. A subset of this data has been previously reported (4, 13).

Study Procedures

Study drug regimens—Because our protocol does not mandate a specific antiretroviral regimen, some patients were taking protease inhibitors, some were taking NNRTIs, and some were taking both. Subjects were usually also on nucleoside antiretrovirals. In accordance with UCSF's transplant protocol, CsA or TAC was started in patients on post-transplantation day 0 or when their serum creatinine concentration was below 3 mg/dL. Subsequent dose changes for CsA or TAC were made according to trough levels that were measured at a CLIA-certified clinical laboratory. In general, drug dosing was adjusted to maintain CsA trough concentrations between 75-150 ng/mL and TAC troughs between 4-9 ng/mL.

Standard post-transplantation management included a tapering dose of steroids, mycophenolate mofetil, and antiviral (daily acyclovir or valganciclovir), anti-pneumocystis (daily trimethoprim-sulfamethoxazole or dapsone), and antifungal (weekly fluconazole) prophylaxis.

Pharmacokinetic studies—Pharmacokinetic (PK) studies were done before transplantation and for at least 2 years after transplantation (at weeks 2 to 4, 12, 28, 52, and 104). Antiretroviral or immunosuppressant drug regimens were modified in response to drug side effects, increases in HIV-1 RNA levels (viral load), low drug troughs, or rejection episodes. A change in drug regimen required starting the cycle of PK studies again. Thus, there are more PK studies over time than there are subjects. Details of the PK studies have been previously described (4, 13).

Analysis of blood samples

Blood samples were frozen at −70°C until analyzed. Whole blood samples were analyzed for CsA and TAC by a validated HPLC/MS assay in combination with automated online

sample preparation (LC/LC-MS) (Hewlett-Packard; Palo Alto, CA). Method validation has been described in detail by Christians et al. (20).

Pharmacokinetic analysis

After oral administration of CsA and TAC, individual serum concentration-time data were used to determine maximal serum concentration (C_{max}), time to maximal concentration (t_{max}), and area under the concentration-time curve up to the last quantifiable concentration (AUC_{0-t}). AUCs were calculated using the linear-log trapezoidal method for AUC estimation (WinNonlin software, Professional Edition, version 5.0; Pharsight, Mountain View, CA).

Statistical analysis

CsA and TAC levels (in nanograms per milliliter) were adjusted for each subject's actual dose (in milligrams) and body weight (in kilograms). The rank-sum test was used to compare AUC levels between various ARV regimens. Correlation analyses were run between AUC and Cx for CsA and TAC separately, where x was an individual time point. A two-sided p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS version 9.2, Cary, NC.

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Abbreviations

ARV	Antiretrovirals
AUC	Area under the curve
CsA	Cyclosporine
EFV	Efavirenz
HIV	Human Immunodeficiency Virus
IS	Immunosuppressants
NVP	Nevirapine
NNRTI	Non nucleoside reverse transcriptase inhibitors
PK	Pharmacokinetic

PI	Protease inhibitors
TAC	Tacrolimus

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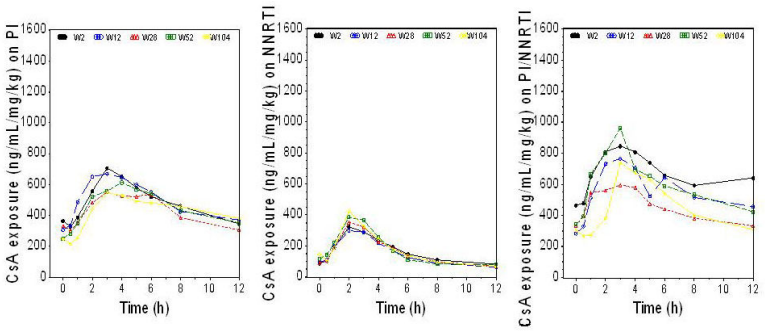

Figure 1.

Concentration-time curves for CsA; Cx is dose and weight adjusted. 1A. CsA exposure on PIs; 1B. CsA exposure on NNRTIs; 1C. CsA exposure on both NNRTIs and PIs.

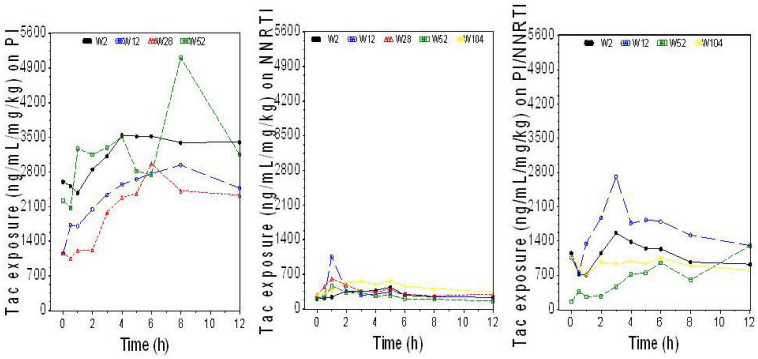

Figure 2.

Concentration-time curves for TAC; Cx is dose and weight adjusted. 2A. TAC exposure on PIs; 2B. TAC exposure on NNRTIs; 2C. TAC exposure on both NNRTIs and PIs.

CsA	All weeks	
	Median [IQR] Dose (mg/kg)	Median [IQR] AUC (ng*hr/mL/mg/kg)
+PI	0.35 [0.32-0.56]	5603 [3325-7574]
+NNRTI	2.20 [1.45-2.99]	1570 [933-2169]
+PI/NNRTI	0.39 [0.31-1.22]	6649 [3756-10226]
nonHIV tx*	4	7000-9000

TAC	All weeks	
	Median [IQR] Dose (mg/kg)	Median [IQR] AUC (ng*hr/mL/mg/kg)
+PI	0.007 [0.006-0.009]	26889 [17208-42250]
+NNRTI	0.042 [0.02-0.057]	3142 [2121-5157]
+PI/NNRTI	0.013 [0.012-0.013]	12587 [8524-18780]
nonHIV tx*	0.10	200-500

* ref (21)

Table 2

Median CsA C_x(ng/mL/mg/kg) Levels Post-Transplant

Week	Time Point	PI (n=19)	NNRTI (n=19)	PI-NNRTI (n=5)
W2	C_0	316	42	635
	C_1	359	127	726
	C_2	419	233	759
	C_3	523	204	865
	C_4	677	183	934
		(n=9)	**(n=15)**	**(n=6)**
W12	C_0	295	46	291
	C_1	416	104	461
	C_2	635	235	765
	C_3	745	246	649
	C_4	569	161	762
		(n=7)	**(n=11)**	**(n=5)**
W28	C_0	324	89	220
	C_1	397	94	64
	C_2	508	339	750
	C_3	697	274	615
	C_4	596	191	510
		(n=7)	**(n=9)**	**(n=3)**
W52	C_0	266	106	215
	C_1	315	190	530
	C_2	476	324	694
	C_3	513	351	621
	C_4	502	279	479
			(n=5)	
W104	C_0		97	
	C_1		187	
	C_2		418	
	C_3		312	
	C_4		218	

Table 3

Correlations Between CsA C_x and AUC

Week	Time Point	R^2 (PI) (n=19)	R^2 (NNRTI) (n=19)	R^2 (PI-NNRTI) (n=5)	R^2 combined (n=43)
W2	C_0	0.79	0.91	0.82	0.87
	C_1	0.74	0.70	0.49*	0.74
	C_2	0.89	0.85	0.54*	0.84
	C_3	0.59	0.96	0.88	0.70
	C_4	0.94	0.97	0.98	0.96
		(n=9)	**(n=15)**	**(n=6)**	**(n=30)**
W12	C_0	0.57	0.94	0.38*	0.75
	C_1	0.48	0.53	0.56*	0.41
	C_2	0.75	0.70	0.02*	0.59
	C_3	0.76	0.85	0.34*	0.78
	C_4	0.91	0.92	0.74	0.92
		(n=7)	**(n=11)**	**(n=5)**	**(n=23)**
W28	C_0	0.60	0.38	0.95	0.85
	C_1	0.31*	0.00*	0.49*	0.43
	C_2	0.45*	0.35*	0.37*	0.41
	C_3	0.67	0.43	0.75*	0.69
	C_4	0.87	0.49	0.92	0.91
		(n=7)	**(n=9)**	**(n=3)**	**(n=19)**
W52	C_0	0.73	0.47	0.94*	0.78
	C_1	0.29*	0.52	0.99*	0.28
	C_2	0.23*	0.85	0.79*	0.41
	C_3	0.76	0.92	0.88*	0.71
	C_4	0.95	0.97	0.97*	0.94
			(n=5)		**(n=8)**
W104	C_0	†	0.58*	†	0.55
	C_1	†	0.21*	†	0.20*
	C_2	†	0.99	†	0.15*
	C_3	†	0.89	†	0.78
	C_4	†	0.98	†	0.94

* P value non-significant at 0.05 level.

Table 4

Median Tac C_x(ng/mL/mg/kg) Levels Post-Transplant

Week	Time Point	PI (n=4)	NNRTI (n=4)
W2	C_0	963	199
	C_1	1045	225
	C_2	1687	338
	C_3	2325	280
	C_4	2332	272
		(n=4)	**(n=4)**
W12	C_0	638	213
	C_1	1590	420
	C_2	2049	368
	C_3	2341	290
	C_4	2550	296
			(n=3)
W28	C_0		193
	C_1		497
	C_2		368
	C_3		275
	C_4		223
			(n=4)
W52	C_0		148
	C_1		301
	C_2		322
	C_3		242
	C_4		208

Table 5

Correlations between TAC C_x and AUC

Week	Time Point	R^2 (PI) (n=4)	R^2 (NNRTI) (n=4)	R^2 combined (n=8)
W2	C_0	0.97	0.87*	0.95
	C_1	0.98	0.91	0.97
	C_2	0.99	0.84*	0.99
	C_3	0.99	0.98	0.99
	C_4	0.99	0.99	0.99
		(n=4)	**(n=4)**	**(n=8)**
W12	C_0	0.22*	0.84*	0.45
	C_1	0.80*	0.91	0.28*
	C_2	0.99	0.40*	0.91
	C_3	0.92	0.45*	0.75
	C_4	0.92	0.63*	0.90
			(n=3)	**(n=5)**
W28	C_0	†	1.00	0.85
	C_1	†	1.00	0.62*
	C_2	†	1.00	0.83
	C_3	†	1.00	1.00
	C_4	†	0.99*	0.97
			(n=4)	**(n=6)**
W52	C_0	†	1.00	0.97
	C_1	†	0.29*	0.91
	C_2	†	0.73*	0.97
	C_3	†	0.80	0.98
	C_4	†	0.88	1.00

At week 2, C_X and AUC levels correlated well, with most coefficients of determination (R^2) being above 0.70. The best correlation time point with AUC, for both CsA and Tac and for all the presented ARV classes, was C_4.

*P value non-significant at 0.05 level.

†Sample size too small for correlations