The Interaction Between Antiretroviral Agents and Tacrolimus in Liver and Kidney Transplant Patients

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Solid organ transplantations have been performed successfully in selected HIV-positive patients with highly active antiretrovirus therapy (HAART). However, some of the medications in the HAART regimen require metabolism via the cytochrome P4503A, the same enzyme complex responsible for clearance of the calcineurin inhibitors cyclosporine and tacrolimus. Several case reports have described significant interactions between the agents used in HAART and immunosuppressive drugs. The goal of this report is to examine the extent of potential drug interactions between antiretroviral agents and tacrolimus after liver and kidney transplantation. Seven liver transplant (LTx) patients (M = 6, F = 1) and four kidney transplant (KTx) patients (M = 4) infected with HIV underwent surgery between September 1997 and January 2001. Initial immunosuppression consisted of tacrolimus and steroids for LTx patients or tacrolimus, steroids, and mycophenolate mofetil for KTx recipients. Their current baseline immunosuppression and HAART regimen were examined retrospectively. Of the seven liver recipients, one (case 4) died 2 weeks after LTx and never received HAART therapy posttransplantation. The remaining six patients were placed on a regimen consisting of two nucleoside reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI) (nelfinavir in 5, indinavir in 1) based on known viral sensitivities or history of a previous clinical response. Kidney recipients received NRTI and nonnucleoside reverse transcriptase inhibitors (NNRTI). The mean dose of tacrolimus in liver recipients was 0.6 mg/d, with mean trough concentration of 9.7 mg/mL. Compared with historic controls (liver transplant patients not on HAART), the average tacrolimus dose was 16-fold lower in patients on HAART. In contrast to liver recipients, HIV-positive kidney recipients not on PI therapy required a mean tacrolimus dose of 9.5 mg/d to maintain a mean trough concentration of 9.6 ng/mL. Of the two protease inhibitors used, nelfinavir seems to have a more profound effect than indinavir. When patients on nelfinavir alone (n = 5) were compared with a control group not on antiretroviral therapy, the need for a tacrolimus dose was 38 times lower (mean dose, 0.26 mg/d). Profound drug interactions between PI and tacrolimus have been observed requiring up to 50-fold reductions in dosage. This effect seems to be most pronounced with the use of nelfinavir as opposed to indinavir, although further experience is required to confirm this observation. In contrast, HAART using NRTI and NNRTI without the use of PI, as shown in kidney recipients, produces less significant effects on tacrolimus metabolism. Great caution and frequent drug level monitoring are necessary when HAART is introduced or withdrawn in HIV-positive recipients of organ transplants. (*Liver Transpl 2002;8:841-845.*)

The increasing success of liver and kidney transplantation has led to a broadening of their indications. In selected HIV-positive patients, liver and kidney transplantation have been successfully performed.[1-3] This requires continued use of highly active antiretrovirus therapy (HAART) after transplantation along with careful immunosuppressive management. As with other liver and kidney recipients, HIV-positive patients typically receive calcineurin inhibitors (cyclosporine or tacrolimus), which are primarily eliminated by cytochrome P450 3A (CYP3A)–mediated metabolism.[4,5] They also receive a HAART regimen that usually consists of a combination of nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zalcitabine, and so on), protease inhibitors (indinavir, nelfinavir, saquinavir, ritonavir), and/or nonnucleoside reverse transcriptase inhibitors (delavirdine, efavirene, nevirapine, zidovudine). Several of the antiretroviral agents have significant drug-drug interactions.[6-11] There have been a few case reports documenting the interaction between immunosuppressive drugs and antiretroviral agents.[3,6,12] Here we report a drastic reduction in the dose of tacrolimus that was necessary in HIV-positive transplant patients who were on concomitant antiretroviral therapy that included protease inhibitors. In contrast, the HIV-positive transplant patients who were on antiretroviral therapy that did not include protease inhibitors received conventional doses of tacrolimus.

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Materials and Methods

Between September 1997 and January 2001, seven HIV-positive patients underwent orthotopic liver transplantation (OLTx) for end-stage liver failure and four patients underwent kidney transplantation. All received tacrolimus-based immunosuppression. The liver transplant patients received 1 g methylprednisone on reperfusion of the liver and a 600-mg methylprednisone taper over the next 6 days. Kidney transplant patients also received mycophenolate mofetil. Trough tacrolimus blood concentrations were measured in all the patients by a microparticulate enzyme immunoassay using the IMx analyzer (Abbott Laboratories, Abbott Park, IL). In liver transplant patients, trough tacrolimus concentrations were maintained between 12 to 15 ng/mL during the first month, 10 to 12 ng/mL during the second and third months, 8 to 10 ng/mL during the third to sixth months, and 6 to 8 ng/mL after 6 months posttransplantation. Kidney transplant patients were maintained at approximately 30% higher concentrations of tacrolimus as compared with the liver transplant patients. HAART was instituted postoperatively (with return of normal liver function in the case of liver recipients) based on preoperative viral sensitivity or history of clinical response.

Results

The demographics of the patients are shown in Table 1.

Liver Transplant Patients

One liver transplant patient (case 4) died within 2 weeks after transplantation and did not receive any antiretroviral therapy. All other liver transplant patients received a combination of two nucleoside reverse transcriptase inhibitors and one protease inhibitor. Nelfinavir, 1.5 to 2.5 g/d, was used in divided doses except in case 5, in which the initial dose of nelfinavir was 250 mg twice daily and was increased to 1250 mg twice daily over 4 months because this patient had an acute fulminant hepatic failure from nevirapine, and in case 6, in which indinavir 800 mg three times daily was used. None of the kidney transplant patients happened to have been on any protease inhibitors before transplantation and continued on their nucleoside and nonnucleoside reverse transcriptase inhibitors after transplantation.

Table 1. Demographics

Case No.	Age (yr)	Gender	Diagnosis	Follow-up (mo)
Liver transplant patients				
1	44	M	Hemophilia, HCV	19.52*
2	41	M	Hemophilia, HCV	48.52
3	41.8	M	HCV	33.50
4	43.1	M	Hemophilia, HCV	0.5*
5	40.8	F	Drug-induced (nevirapine) FHF	16.40
6	33	M	Hemophilia, HCV	11.57
7	53	M	Hemophilia, HCV	8.51
Kidney transplant patients				
8	47	M	Hypertension/diabetes	41.06
9	48	M	Polycystic kidney	37.94
10	33	M	Focal proliferative glomerulonephritis	7.30
11	59	M	Polycystic kidney	7.26

Abbreviations: HCV, hepatitis C virus; FHF, fulminant hepatic failure.
*Died, see text.

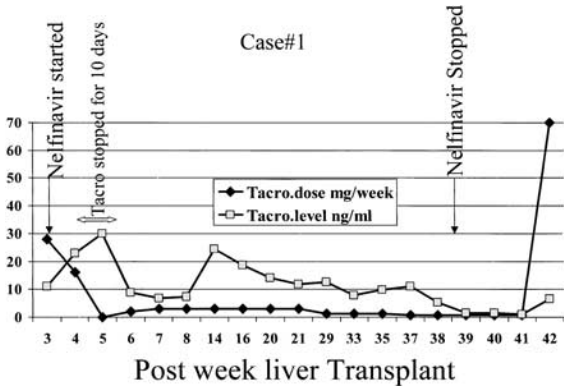

Figure 1. Changes in tacrolimus weekly dose and tacrolimus trough concentration when nelfinavir was added or discontinued in case 1, a post–liver transplant patient. ⟺ shows discontinuation of tacrolimus for 10 days when nelfinavir was added.

The extent of the interaction between tacrolimus and protease inhibitors was evident in case 1. In the third postoperative week, the patient was on a tacrolimus dose of 2 mg/d with a trough concentration of 11.1 ng/mL. When nelfinavir was resumed at a dose of 750 mg three times daily, the trough concentration of tacrolimus increased to 30 ng/mL on the fourth day. Tacrolimus was discontinued for 10 days and then reintroduced at 1 mg twice per week; this was subsequently readjusted to 1 mg every sixth day to achieve a trough target level of about 10 ng/mL (Fig. 1). At week 39, the patient discontinued the protease inhibitor without our knowledge; this led to undetectable tacrolimus blood concentrations and moderate-to-severe acute rejection of the liver allograft. His tacrolimus dose was increased to 5 mg twice daily (60 times increased from baseline) to achieve a concentration of 6.5 ng/mL. Rapamycin was added to his immunosuppressive regimen. Unfortunately, this patient eventually developed chronic

Table 2. Liver and Renal Function With Tacrolimus Dose/Level and Antiretroviral Agents

Case No.	Follow-up (mo)	BUN (mg/dL)	Creatinine (mg/dL)	T. Bili (mg/dL)	ALT (μ/L)	AST (μ/L)	GGT (μ/L)	AP (μ/L)	Tacrolimus dose (mg)	Tacrolimus level (ng/mL)	Antiretroviral Medications and Dosage
Liver transplant patients											
1	19.53	41	3.4	20.3	169	836	1168	0	*	*	Lamivudine 150 mg bid, zidovudine 300 mg bid, nelfinavir 750 mg tid
2	48.52	23	1	1	82	99	89	211	0.5 mg every 5 d	9.5	Lamivudine 150 mg bid, nelfinavir 750 mg tid, stavudine 40 mg bid
3	33.50	10	0.8	0.9	17	27	71	88	1 mg every 4 d	9.5	Lamivudine 150 mg bid, nelfinavir 500 mg tid, stavudine 40 mg bid
4	0.50	Died 13th postoperative day from sepsis/renal failure, HAART not started									
5	16.40	12	1	0.3	18	28	86	26	1 mg qod	7.1	Lamivudine 150 mg bid, zidovudine 300 mg bid, nelfinavir 1250 mg bid
6	11.57	48	1.4	0.9	68	46	108	82	1 mg bid	10.2	Lamivudine 150 mg bid, zalcitabine 0.75 mg tid, indinavir 800 mg tid
7	8.51	20	0.8	0.3	45	42	162	71	0.5 mg every 3 d	12.1	Lamivudine 150 mg bid, zidovudine 1 mg bid, nelfinavir 750 mg tid
Kidney transplant patients											
8	41.06	36	1.7	0.6	30	31	386	195	6	10.3	Lamivudine 150 mg bid, abacavir 300 mg bid, zidovudine 300 mg bid
9	37.94	18	1.5	0.4	49	29	50	65	4	5.8	Lamivudine 150 mg bid, stavudine 20 mg bid, nevirapine 100 mg bid
10	7.30	12	1.4	0.4	16	15	70	253	24	12.5	Lamivudine 150 mg bid, efavarenz 600 mg qd, zidovudine 300 mg bid
11	7.26	59	2.5	0.3	22	20	94	114	4	9.7	Lamivudine 150 mg bid, stavudine 40 mg bid, nevirapine 200 mg bid

Abbreviations: BUN, blood urea nitrogen; T. Bili, Total bilirubin; ALT, alanine aminotransferase; AST, asparted aminotransferase; GGT, gamma glutamyltransferase; AP, alkaline phosphatase; bid, twice daily; tid, three times daily; qd, every day; qod, every other day.
*See the text and Figure 1.

rejection progressing to liver failure 19 months after his liver transplantation and died.

The current dosage of the antiretroviral agents and the trough concentrations of tacrolimus in the surviving patients are shown in Table 2. The mean dose of tacrolimus in liver recipients was 0.6 mg/d with mean trough concentration of 9.7 ng/mL. In a large HIV-negative liver transplant patient population not on antiretroviral therapy, the mean dose of tacrolimus necessary to maintain a trough blood concentration of 10 ng/mL was 10 mg/d. A 16-fold lower dose of tacrolimus was necessary in patients who were on protease inhibitors to achieve comparable blood concentrations of tacrolimus. Of the two protease inhibitors used in our institution, nelfinavir seems to have a more profound effect on the trough tacrolimus blood concentrations. When case 6, receiving indinavir and on 2 mg/d of tacrolimus, was excluded from the analysis, the mean tacrolimus dose required in patients on nelfinavir was only 0.26 mg/d, 38 times less than the historical controls.

Kidney Transplant Patients

All four kidney transplant patients are alive with satisfactory renal function. The mean and median tacrolimus dose in these patients was 9.5 and 10 mg/d with a trough blood concentration of 9.6 ng/mL. Two of the patients who were on nevirapine required a lower tacrolimus dose (4 mg/d) compared with the other two (6 and 24 mg/d).

Discussion

Several drugs are known to induce or inhibit the metabolism of tacrolimus.[13,14] Drugs such as phenytoin, phenobarbital, and rifampin are known to decrease the blood concentration of tacrolimus. Drugs such as ketoconazole, itraconazole, fluconazole, and verapamil are known to increase tacrolimus blood concentrations. In the cases presented here, we observed the need for drastic reduction in the dose of tacrolimus to maintain therapeutic concentrations of tacrolimus in liver transplant patients who received protease inhibitors. Such a profound interaction has rarely been observed between tacrolimus and other drugs. These observations can be explained by the profound inhibition of CYP3A enzyme system by protease inhibitors.[6-10] On the other hand, in kidney transplant patients who were taking reverse transcriptase inhibitors only, the mean dose of tacrolimus required to achieve therapeutic levels was similar to that of the HIV-negative recipients.

It is important to realize that some of the protease inhibitors act both as an inducer and an inhibitor of CYP3A4. When coadministered, the inhibitory effect of protease inhibitors predominates. However, after a sudden withdrawal of the protease inhibitor, there will be no more inhibition, but the CYP3A4 system may remain induced for a few days, resulting in a sudden decrease of tacrolimus concentration, as observed in case 1. When nelfinavir was discontinued without our knowledge, the patient developed irreversible acute rejection with undetectable tacrolimus levels. Despite the 60-fold increase in the tacrolimus dose and adding rapamycin, the allograft eventually was lost.

It is extremely important to appreciate protease inhibitors–tacrolimus interactions both when starting and when discontinuing the protease inhibitor. Based on our experience, we recommend at least a four-fold reduction in the dose of tacrolimus when nelfinavir is used, and following up on the trough concentration twice per week for further dosage adjustment. It is also important to increase the dose of tacrolimus if protease inhibitors are withheld. Frequent monitoring of tacrolimus trough blood concentrations is mandatory in patients on agents that are known to induce or inhibit the metabolism of tacrolimus.

Summary

A profound interaction between protease inhibitors, particularly nelfinavir and tacrolimus, has been shown in HIV-positive liver transplant patients. They require a 10- to 50-fold tacrolimus dosage reduction to maintain therapeutic concentrations. Such an extent of drug interaction was not observed in KTx patients who did not receive protease inhibitors. Between the two protease inhibitors used, nelfinavir and indinavir, nelfinavir seems to have more profound drug interactions than indinavir. Nucleosides and nonnucleosides may have even fewer drug interactions compared with a protease inhibitor. However, great caution is required when protease inhibitors are added or discontinued in patients on tacrolimus after transplantation to prevent toxicity or rejection, respectively. A further kinetic study detailing the precise extent of drug interactions between immunosuppressive agents and HAART therapy is essential for better understanding of the drug interaction.

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