ELSEVIER

Interaction Between Tacrolimus and Antiretroviral Agents in Human Immunodeficiency Virus–Positive Liver and Kidney Transplantation Patients

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SOLID ORGAN TRANSPLANTATIONS have been performed successfully in selected human immunodeficiency virus (HIV)–positive patients using highly active anti-retrovirus therapy (HAART).[1] However, some of the medications in the HAART regimen require metabolism via the cytochrome P4503A family. The same enzyme complex is 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.[2–4]

AIM

The aim of the present report is to examine the extent of potential drug interactions between anti-retroviral agents and tacrolimus after liver and kidney transplantation.

MATERIALS

Seven patients infected with HIV underwent liver transplant (LT) (six males and one female); four patients infected with HIV underwent kidney transplantation (KT) (all male). All of the patients underwent transplantation between September 1997 and January 2001. Initial immunosuppression consisted of tacrolimus and steroids for LT patients or tacrolimus, steroids, and Mycophenolate Mofetil for KT recipients. Their current baseline immunosuppression and HAART regimen were examined retrospectively.

RESULTS

Of the seven liver recipients, one (Case 4) died 2 weeks after LT 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 five; indinavir in one) based on known viral sensitivities or history of a previous clinical response. Kidney recipients received NRTI and non-nucleoside reverse transcriptase inhibitors (NNRTI). The mean dose of tacrolimus in liver recipients was 0.6 mg/d, with mean trough concentration of 9.7 ng/mL. Compared to contemporary controls (LT 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 appeared to have more profound effects than indinavir. When patients on nelfinavir alone ($n = 5$) were compared with a control group not on anti-retroviral therapy, the tacrolimus dose was 38 times lower (mean dose of 0.26 mg/d). One post-LT patient (Case 1) was on tacrolimus 2 mg/d in the third postoperative week with trough concentrations of 11.1 ng/mL. When nelfinavir was added, his trough concentration increased to 30 ng/mL by the fourth day on HAART. Tacrolimus was discontinued for 10 days and then reintroduced at 1 mg twice a week, which was subsequently further reduced to 1 mg every sixth day to achieve a trough level of 10 ng/mL. In the 39th posttransplant week, when this patient discontinued nelfinavir without our knowledge, his tacrolimus level decreased drastically necessitating dose increase to 10 mg/d (70 mg/wk—an increase of 60 times in dose) to achieve a trough concentration of 6.5 ng/mL providing confirming evidence of the extent of the drug interaction between tacrolimus and nelfinavir (Table 1).

CONCLUSION

Profound drug interactions between PI and tacrolimus have been observed requiring up to a 50-fold reduction in dosage. This effect appears to be most pronounced with the use of nelfinavir as opposed to indinavir, although further experience is required to confirm this observation. In

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Table 1. Tacrolimus Dose/Level and Antiretroviral Agents

Case No.	Tacrolimus Dose mg	Tacrolimus Level ng/mL	Anti Retroviral Medications and Dosage
LT Patients			
1	*	*	Lamivudine 150 mg bid, Zidovudine 300 mg bid, Nelfinavir 750 mg tid
2	0.5 mg q 5 d	9.5	Lamivudine 150 mg bid, Nelfinavir 750 mg tid, Stavudine 40 mg bid
3	1 mg q 4d	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	1 mg qod	7.1	Lamivudine 150 mg bid, Zidovudine 300 mg bid, Nelfinavir 1250 mg bid
6	1 mg bid	10.2	Lamivudine 150 mg bid, Zalcitabine 0.75 mg/tid, Indinavir 800 mg tid
7	0.5 mg q 3 d	12.1	Lamivudine 150 mg bid, Zidovudine 1 bid, Nelfinavir 750 mg tid
KT Patients			
8	6	10.3	Lamivudine 150 mg bid, Abacavir 300 mg bid, Zidovudine 300 mg bid
9	4	5.8	Lamivudine 150 mg bid, Stavudine 20 mg bid, Nevirapine 100 bid
10	24	12.5	Lamivudine 150 mg bid, Efaviren 600qd, Zidovudine 300 mg bid
11	4	9.7	Lamivudine 150 mg bid, Stavudine 40 mg bid, Nevirapine 200 mgb bid

contrast, HAART using NRTI and NNRTI without the use of PI, as demonstrated 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.

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