

Management of Drug-Drug Interactions between Tacrolimus and Highly Active Antiretroviral Therapy

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BACKGROUND

•Highly active antiretroviral therapy (HAART) has improved the life expectancy of HIV-infected patients, allowing Orthotopic Liver Transplantation (OLT) to become a reasonable treatment option for selected patients with terminal liver disease.

•Non-nucleoside reverse transcriptase inhibitors and protease inhibitors show substantial drug-to-drug interactions via interaction with cytochrome P450 enzymes and P-glycoprotein, both in the liver and gut. Likewise tacrolimus have great potential for drug-to-drug interactions via the same metabolic pathways.

OBJECTIVE

•This study was designed to manage drug-to-drug interactions with immunosuppressive drugs such as tacrolimus and HAART.

METHODS

⇒ Patients

➢ Ten HIV-infected patients transplanted for end-stage chronic hepatitis C

➢ Criteria for transplantation included :

- Absence of opportunistic infection
- CD4-cell count greater than 150 cells/ μ L and undetectable HIV plasma viral load (pVL < 50 copies/mL) under HAART

⇒ Study design

➢ HAART was stopped the same day as liver transplantation and was reintroduced ten days after.

➢ All patients received tacrolimus, prednisolone as immunosuppressive agents and fluconazole 50 mg/day, trimetoprim / sulfamethoxazole and ganciclovir as primary prophylaxis.

➢ Targets for tacrolimus blood concentrations were 8 to 20 ng/mL from day 0 up to week 6 and 5 to 15 ng/mL after week 6.

➢ Tacrolimus pharmacokinetic parameters were calculated by non-compartmental method (WinNonLin® V3.3 Pharsight), in 8 of these patients on 2 occasions :

- **period A** : when liver function normalized (about 10 days post transplantation)
- **period B** : 10 days after HAART reintroduction at standard doses (IP-nelfinavir n=2, lopinavir/r n=3 or NNRTI-efavirenz n=2 + 2 nucleoside analogues) or 3 NRTI (n=1).

➢ Doses of tacrolimus were individually adjusted according to tacrolimus trough blood concentrations.

Table 1 : Patient characteristics and doses of tacrolimus

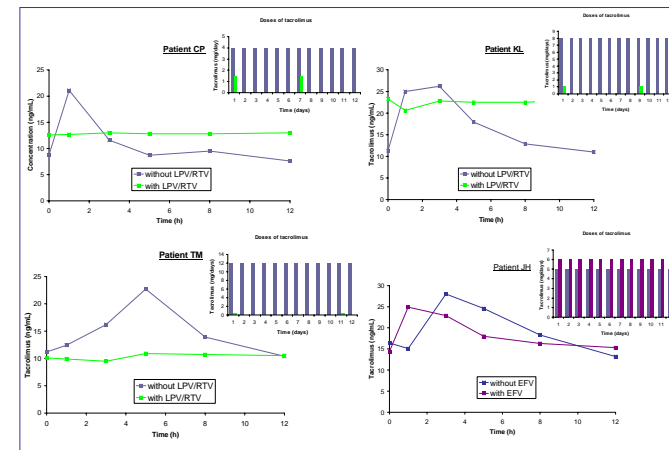
Patient	Sexe	Age (years)	Body weight (kg)	Period A		Period B		Antiretroviral agent at period B
				Dose	every	Dose	every	
M-M	M	46	69	0,5 mg	48h	0,5mg	24h	Nelfinavir + lamivudine + tenofovir
B-N	F	40	61	1 mg	12h	0,5 mg	24h	Nelfinavir + abacavir + tenofovir
C-P	M	50	68	2mg	12h	1,5 mg	144h	Lopinavir/ritonavir + didanosine + lamivudine
T-M	M	40	69	6mg	12h	0,5 mg	240 h	Lopinavir/ritonavir + lamivudine + tenofovir
K-L	M	44	70	4 mg	12h	1 mg	192h	Lopinavir/ritonavir + abacavir + tenofovir
J-H	F	46	58	2,5 mg	12h	3 mg	12 h	Efavirenz + zidovudine + lamivudine
T-J	M	41	72	2 mg	12h	1,5 mg	12h	Efavirenz + lamivudine + abacavir
C-A	M	63	60	0,5	12h	2 mg	12h	Lamivudine + stavudine + tenofovir

Figure 1 : Individual tacrolimus pharmacokinetic parameters



RESULTS

Figure 2 : Individual tacrolimus concentrations



DISCUSSION - CONCLUSION

⇒ Nucleoside analogues or efavirenz lead to little change in tacrolimus PK. In contrast, nelfinavir and lopinavir/ritonavir caused a large inhibition of tacrolimus first pass effect resulting in a prolongation of tacrolimus elimination half-life and a diminution in its clearance, which necessitate an important decrease in tacrolimus dosing.

⇒ No impairment of antiretroviral PK administered at standard doses with tacrolimus was observed.

⇒ These results showed that management of drug-to-drug interaction is feasible by attentive monitoring of tacrolimus blood concentration.

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