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Differential Dose Adjustments of Immunosuppressants after Resuming Boosted versus Unboosted HIV-Protease Inhibitors Postliver Transplant

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Pharmacokinetic (PK) interactions between protease inhibitors (PI_s) and immunosuppressive agents (IS) are critical elements in the management of HIV-infected patients who undergo liver transplantation (LT_x). The primary objective of this study was to evaluate the decreases in IS dosages necessary to maintain an appropriate therapeutic window (TW) after initiating PI-based antiretroviral therapy regimens post-LT_x. Single-center, PK cross-sectional study of consecutive HIV-infected adult patients who underwent LT_x was done. Blood trough concentrations (C_t) of IS were obtained using a commercial MEIA test; plasma C_t of PI_s were measured using HPLC. Twelve consecutive HIV-infected adult patients (11 males, 1 female) were enrolled. More rapid increases in IS plasma C_t were observed 48 h after initiating ritonavir (RTV)-boosted PI therapy post-LT_x than when using unboosted PI_s. Seven patients developed acute renal failure. The median fold decrease in IS dosages required to regain IS concentrations that were in the TW was 7.5 (range 6–14) after resuming boosted PI_s and 2.9 (range 2–4) after unboosted PI_s. The overall median time necessary to reach IS TW after dose adjustment was 3.5 days (range 0–15). Unboosted PI_s exhibited lesser PK interactions with IS than did RTV-boosted PI_s and were thus more amenable to use in the post-LT_x setting.

Key words: HIV, transplantation, pharmacokinetics, liver transplantation, immunosuppressants

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Introduction

Liver transplantation (LT_x) is a definitive therapeutic option for HIV-infected patients with end-stage liver disease (ESLD), with available data demonstrating patient and graft survival rates similar to those seen in HIV-uninfected individuals (1–7). Pharmacokinetic (PK) interactions between antiretrovirals (ARV_s) and immunosuppressive agents (IS) comprise important clinical management challenges in the early posttransplant period for HIV-infected persons. Differential effects and interactions occur among drugs that are substrates of hepatic cytochrome P450 (CYP3A4) enzymes which are also expressed at high levels in mature villus tip enterocytes. ARV_s can act as inhibitors or inducers of this enzyme. When they work as enzyme inhibitors, e.g. protease inhibitors (PI_s), ritonavir (RTV)-boosted PI_s in particular, they increase concentrations of IS and can lead to drug-induced toxicities (8–10). When ARV_s act as enzyme inducers, e.g. nonnucleoside reverse transcriptase inhibitors ($NNRTI_s$), this results in reduced IS drug levels that can in turn precipitate graft rejection, necessitating administration of increased doses of IS (11). In addition, many of these drugs are also substrates and inhibitors of intestinal P-glycoprotein (P-gp), a multidrug efflux pump present at high levels in the villus tip of enterocytes in the gastrointestinal tract, which is known to decrease the bioavailability of many CYP3A4 substrates. Because of their topographic location in small intestinal enterocytes and the significant overlap in their substrate specificities, the potential interplay between CYP3A4 and P-gp in limiting oral drug delivery should be taken into account (12).

Therefore, the concomitant administration of inhibitors with substrates of both metabolic enzymes and drug efflux transporters, such as IS with ARV_s (PI_s in particular), would be expected to increase the uptake of both drugs (13). While the need to monitor both ARV_s and IS systemic blood levels during the immediate post-LT_x time period in order to maintain drug concentrations in their therapeutic window (TW) and avoid toxicity is well accepted, it is common clinical practice to stop ARV_s at the time of LT_x and then resume it once graft function has stabilized. Currently,

no standard guidelines exist regarding IS dose adjustments necessary once boosted or unboosted PI_s are initiated post-LT_x in HIV-infected patients, and only a few observations underline the importance of the pharmacokinetic interactions between IS and the ARV_s and the required modifications of IS dosing in this setting (14,15). Frassetto et al. have recently described IS dosing modifications in 35 subjects with HIV infection studied at 2 and 12 weeks after liver and kidney transplantation or after a change in their drug regimens, concluding that modifications in ARV_s should be carefully managed to avoid insufficient immunosuppression or toxicity due to drug–drug interactions (13).

In this report, we evaluated dosage decreases of IS required to maintain these medications in their TW after initiating PI_s regimens in patients with HIV infection undergoing LT_x.

Patients and Methods

This is a single-center, open-label, cross-sectional pilot PK study of consecutive HIV-infected patients who underwent LT_x from June 2003 to April 2007. To be immuno-virologically eligible for LT_x, subjects had to have a stable $CD4^+$ cell count $\geq$ 100 cells/mm^3 and an undetectable plasma HIV viral load without history of any opportunistic infection or malignancy. They had to be taking a pre-LT_x ARV regimen including PI_s (boosted or unboosted) and, after transplantation, the same preoperative ARV_s had to be reintroducted. In the post-LT_x period, ARV_s were resumed, at the study team's discretion, once the patient was able to consistently take oral agents and liver function (transaminases, bilirubin, alkaline phosphatase [ALKP], gamma-glutamyl transpeptidase [GGT], international normalized ratio [INR]) and renal function (glomerular filtration rate with modification of diet in renal disease [MDRD]) were stable. This protocol was authorized by the local Ethics Review Board and all subjects provided written informed consent prior to enrollment in the study.

The study population was divided into two groups depending on the PI_s included in the ARV scheme: patients undergoing PI_s boosted with RTV (group A) and patients undergoing unboosted PI_s (group B). Subjects were evaluated prior to transplant and every day for the first month post-LT_x. At baseline, demographic, clinical, hematological and immuno-virological information was collected. Antirejection immunosuppression comprised high dose glucocorticoids and either cyclosporine (CsA), tacrolimus (FK) or rapamycine (RPM), in accordance with the standard protocol of our transplant unit. During the first trimester post-LT_x, IS drug plasma trough concentration (C_t) therapeutic ranges were defined as: 200–300 ng/mL for CsA and 5–15 ng/mL for FK and RPM (16).

The primary outcome of interest was the IS drug dosage decrease in groups A and B when comparing IS doses pre- versus post-ARV_s resumption (after LT_x) necessary to achieve therapeutic levels. This was represented as the ratio of the pre-ARV_s resumption IS dose and the IS dose after ARV_s were resumed and the TW had been achieved. The secondary objective was the median time necessary to gain IS TW in both groups after dose adjustment at 48 h after ARV_s resumption.

IS drug PK assays were performed centrally at the Toxicology Laboratory of the Modena Policlinic, University of Modena and Reggio Emilia (Italy) using whole blood Microplate Enzymatic Immunoassay (MEIA) quantification (17).

Pharmacokinetic assays of PI_s were performed centrally at the Pharmacology Clinic of the Antiretroviral Laboratory, Infectious Diseases Department, University of Turin (Italy). Plasma samples were separated, inactivated in a bath at 58°C for 35 min, and then frozen at −20°C until PK analyses were performed. Plasma C_t levels were measured by a modified high-performance liquid chromatography (HPLC) method with UV detection (18).

Pharmacokinetic assays compared C_t levels with minimal effective concentration (MEC) values. The following suggested MEC_s were used for PI_s: amprenavir (APV) > 250 ng/mL, lopinavir (LPV) > 1000 ng/mL and atazanavir (ATV) > 200 ng/mL (a MEC for unboosted ATV has not yet been established) (19).

Safety outcomes were assessed 48 h after ARV_s resumption and included death, grade III–IV drug toxicities, changes in serum total and unconjugated bilirubin, alanine aminotransferase, GGT, ALKP, INR, albumin and glomerular filtration rates, measured by the MDRD equation. Acute renal failure (ARF) was defined as an MDRD < 60 mL/min and/or a >10 mL/min reduction from baseline levels.

Statistical method

Descriptive statistics were performed using the STATA software, version 9.2 (Statacorp LP, TX; http://www.stata.com). The Mann–Whitney test was used for continuous variables, while Fisher's exact test was performed for categorical variables. A p-value < 0.05 was considered significant.

Results

Twelve consecutive HIV-infected adult patients (11 males, 1 female), with a median age of 44.5 years (range = 37–52), were enrolled. Group A included 4 patients receiving boosted PI_s (LPV/RTV, APV/RTV) and group B the remaining receiving unboosted PI_s (fosamprenavir [fosAPV], ATV).

The etiology of cirrhosis was attributed to HCV infection (alone or in association with hepatitis B virus [HBV], hepatitis delta virus [HDV] or alcohol) in 10 patients, HBV–HDV co-infection in 1 subject and HBV infection alone in 1 patient. The median model for ESLD (MELD) score at inclusion was 32 (range = 18–46). Eight patients had multifocal hepatocellular carcinoma (HCC).

The median cumulative exposure to nucleoside reverse transcriptase inhibitors, $NNRTI_s$ and PI_s were 93 months (range = 12–190), 37 months (range = 0–84) and 29 months (range = 0–93), respectively, with a median HIV history duration of 21 years (range = 16–25). The route of transmission for HIV was intravenous drug use in 11 patients and heterosexual intercourse in 1. All subjects had a baseline undetectable (< 40 copies/mL) plasma HIV viral load. Eight patients (66.7%) had a $CD4^+$ cell count at LT_x > 200 cells/mm^3. In particular, median $CD4^+$ cell count was 378.5 cell/mm^3 (range = 145–496) in group A and 268 cell/mm^3 (range = 119–578) in group B. No significant difference was observed between the two groups (p-value = 0.61)

Table 1: Baseline characteristics of study subjects

Group	Case no.	Age	Sex	HIV (yrs)	HIV CDC	NRTI$_s$ cum exp (months)	NNRTI$_s$ cum exp (months)	PI$_s$ cum exp (months)	CD4$^+$ at LT$_x$ (cells/mm^3)	HIV viral load at LT$_x$ (copies/mL)	ARV therapy at LT$_x$
A	1	46	M	25	A2	84	3	48	496	<40	3TC+TDF+LPV/RTV
	2	44	M	20	B3	80	36	34	145	<40	3TC+TDF+APV+RTV+T20
	4	49	M	22	B2	108	67	0	323	<40	3TC+ABC+LPV/RTV
	10	46	M	20	B3	104	38	93	434	<40	FTC+TDF+LPV/RTV +T20
B	3	44	M	23	A3	12	0	12	119	<40	3TC+TDF+fosAPV
	5	52	M	23	A3	82	41	12	139	<40	3TC+ABC+TDF+ATV
	6	52	M	22	B3	117	82	51	287	<40	TDF+ABC+ATV
	7	45	M	17	B3	180	24	86	506	<40	3TC+ABC+ATV
	8	37	F	16	B3	102	27	38	268	<40	3TC+ABC+ATV
	9	40	M	21	B3	52	4	24	578	<40	AZT+3TC+ATV
	11	39	M	19	C3	84	84	0	268	<40	3TC+ABC+ATV
	12	44	M	21	B3	190	40	24	141	<40	3TC+ABC+ATV

yrs = years; CDC = centers for disease control and prevention classification; NRTI$_s$ = nucleoside reverse transcriptase inhibitors; cum exp = cumulative exposure; NNRTI$_s$ = nonnucleoside reverse transcriptase inhibitors; PI$_s$ = protease inhibitors; ARV = antiretroviral; 3TC = lamivudine; TDF = tenofovir; LPV = lopinavir; RTV = ritonavir; APV = amprenavir; T20 = enfuvirtide; ABC = abacavir; fosAPV = fosamprenavir; ATV = atazanavir; AZT = zidovudine.

Table 1 depicts baseline demographics, HIV clinical history, as well as immuno-virological data and ARV$_s$ at the time of LT$_x$.

After transplantation all patients continued the same pre-LT$_x$ ARV regimen and no therapeutic switch was made. ARV$_s$ were restarted as soon as the liver and the kidney regained normal function in all subjects except one, case no. 1, who had discontinued ARV$_s$ for 24 h only. In 6 subjects, ARV$_s$ were instituted within the first 2 weeks following transplantation; in the remaining 6 patients, the reintroduction was delayed due to the impaired liver function (2 cases), ARF (3 subjects) and instable clinical conditions with inability to take oral medications (1 case). The overall median time to start ARV$_s$ after LT$_x$ was 17.58 days (range = 1–37).

At the time of ARV$_s$ resumption, 9 out of 12 patients (75%) had an undetectable plasma HIV viral load, while 4 (33.3%) had a CD4$^+$ cell count >200 cells/mm^3. Median CD4$^+$ cell count was 163 cells/mm^3 (range = 98–416) in group A and 157.5 cells/mm^3 (range = 30–531) in group B, without any significant difference between the two groups (p-value = 0.86). Moreover, comparing change in CD4$^+$ cell count from baseline, there was no significant difference (similar delta CD4$^+$ cell count) between groups A and B (p-value = 0.61).

Table 2 profiles for each patient immuno-virological data at resumption of ARV$_s$, PI$_s$ dosages, IS regimens, IS dosages and plasma C$_t$ drug levels pre- and post-ARV$_s$ reintroduction with the corresponding IS dosage fold decrease and the elapsed time required to achieve IS levels in therapeutic ranges posttransplant.

Rapid increases in plasma levels of IS were noted 48 h after the resumption of boosted PI$_s$ (vs. unboosted PI$_s$) post-LT$_x$. The median fold decrease in IS dosage required to achieve the IS TW was 7.5 (range = 6–14) in group A and 2.9 (range = 2–4) in group B with a significant difference between the two groups (p-value of 0.0065).

The median time required to achieve IS concentrations within the TW after dose adjustment was 4.5 days (range 0–13) in group A and 3.5 days (range = 0–15) in group B, without a significant difference between the two groups (p-value = 0.93). At the time of IS TW achievement, plasma C$_t$ levels of PI$_s$ were above the MEC in 10 of 12 patients (83.3%). The remaining 2, both receiving unboosted ATV (group B), had plasma C$_t$ values below the MEC (50 ng/mL). During the prolonged post-LT$_x$ follow-up period, all patients in both groups achieved C$_t$ levels above the MEC and none developed drug failure.

Grade III–IV drug-related laboratory toxicities were not observed during the first 48 h after restarting ARV$_s$. Seven patients, 3 belonging to group A (2 treated with LPV/RTV and 1 with APV/RTV) and 4 to group B (one receiving fosAPV and 3 ATV), developed ARF. No significant difference was observed between the two groups in the number of ARF episodes (p-value = 0.57).

These episodes were considered by the investigators to be mainly related to drug–drug interactions between PI$_s$ and IS, leading consequently to toxic plasma C$_t$ levels of IS. In 4 subjects, once FK (case no. 1), CsA (cases nos. 8 and 11) and RPM (case no. 12) dosages were lowered, MDRD significantly increased and the mild ARF resolved in a median time of 31.5 days (range = 4–40) post-LT$_x$. In 2 other

Table 2: Immuno-virological and pharmacokinetic parameters at ARV_s resumption

Group	Case no.	Time to start ARV_s post-LT_x (days)	$CD4^+$ at resumption (cells/mm^3)	HIV viral load at resumption (copies/mL)	PI_s dosages (mg)	PI_s C_t at the time of gain of IS TW (ng/mL)	IS	IS C_t pre-ARV_s (ng/mL)	IS C_t 48h post-ARV_s resumption (ng/mL)	IS C_t at the time of gain of TW (ng/mL)	Time to gain of TW (days)	IS dosages pre-ARV_s (mg/day)	IS dosages at the time of gain of TW (mg/day)	IS dosage fold decrease
A	1	1	132	<40	LPV/RTV 400/100 BID	LPV/RTV = 2618/118	FK	0	19	11	2	2	0.5 3/7	8
	2	11	98	<40	APV/RTV 450/100 BID	APV/RTV = 5293/186	CsA	284	1161	268	7	700	50	14
	4	37	194	<40	LPV/RTV 400/100 BID	LPV/RTV = 8823/276	CsA	241	1884	250	13	300	50	6
	10	29	416	<40	LPV/RTV 400/100 BID	LPV/RTV = 18 858/823	CsA	178	294	294	0	175	25	7
B	3	21	155	332	fosAPV 1400 BID	APV = 689	CsA	431	629	265	7	450	200	2.25
	5	12	65	<40	ATV 400 QD	ATV = 523	CsA	344	587	234	8	550	200	2.75
	6	12	276	27 999	ATV 400 QD	ATV = 468	CsA	161	360	225	3	300	150	2
	7	19	221	>500 000	ATV 400 QD	ATV = 206	CsA	163	219	219	0	250	100	2.5
	8	13	531	<40	ATV 400 QD	ATV = 614	CsA	104	324	286	4	350	100	3.5
	9	25	160	<40	ATV 400 QD	ATV = 50	RPM	9	>30	12	15	4	1	4
	11	13	93	<40	ATV 400 QD	ATV = 50	CsA	212	379	272	1	300	100	3
	12	18	30	<40	ATV 400 QD	ATV = 165	RPM	13	10	10	0	2	0.5	4

ARV_s = antiretroviral drugs; LT_x = liver transplantation; PI_s = protease inhibitors; C_t = trough concentration; IS = immunosuppressive agents; TW = therapeutic window; LPV = lopinavir; RTV = ritonavir; BID = two times daily; FK = tacrolimus; APV = amprenavir; CsA = cyclosporine; fosAPV = fosamprenavir; ATV = atazanavir; QD = once daily; RPM = rapamycine.

patients, the reduction of IS dosages was not sufficient to improve glomerular filtration rates. In these individuals, chronic renal failure developed due to metabolic acidosis. A late recovery of kidney function occurred and was maintained only after switching CsA to FK (case no. 4) or RPM (case no. 3) at week 234 and 20 post-LT_x, respectively. Renal impairment resolved in all subjects except case no. 2. Despite reduction of CsA dosages, this individual developed progressive deterioration of glomerular filtration rate, which was already compromised before transplantation, requiring intermittent hemodialysis until death occurred at week 7 post-LT_x due to cardiac tamponade and multiple organ failure.

Table 3 shows per patient changes in renal function with detailed MDRD values pre- and post-ARV_s resumption, the corresponding measures adopted to normalize glomerular filtration rates and the time necessary to recover kidney function.

Discussion

In this pilot study, we explored the optimization of simultaneous ARV_s and IS management in the early post-LT_x period among HIV-infected persons.

While it is clear that effective IS therapy needs to be initiated at the time of transplantation to avoid acute graft rejection, the optimal timing of ARV_s resumption after surgical procedure is less clear.

Recent data support earlier posttransplant ARV_s initiation in order to prevent the $CD4^+$ cell count decline resulting from recrudescent detectable plasma HIV viral load as well as to decrease the risk of hepatitis C virus relapse that is consequent on the reduced cellular immune function. Moreover, unchecked HIV replication may increase systemic inflammation and thereby enhance cardiovascular disease risk over the long term. Proponents of delayed posttransplant ARV_s reinitiation have justified this approach by asserting that it results in reduced direct ARV_s toxicity on the graft and contributes to avoid the difficult management of drug–drug interactions in the early post-LT_x period when acute rejection is more frequent.

Findings from the current study underscore the importance of PK interactions, rather than ARV_s toxicity, as the major clinical issue at hand for HIV-infected persons in the immediate posttransplant period. Although several factors (male gender, advanced recipient age, pretransplantation hypertension, diabetes mellitus, HCV) are involved in the increasing rate of acute and chronic renal impairment after LT_x (20), the length of exposure to IS and the PK interactions between PI_s and IS represent the main risk factors to be taken into account in HIV-infected population.

Table 3: Changes in renal function post-ARV$_s$ reintroduction and corrective measures

Group	Case no.	MDRD pre-ARV$_s$ (mL/min)	MDRD 48 h post-ARV$_s$ resumption (mL/min)	Δ MDRD (mL/min)	ARF post-ARV$_s$ resumption	Measures adopted to normalize renal function	Time to recover renal function post-LT$_x$ (days)
A	1	138	37	−101	Yes	Lowering FK dosages	4
	2	26.9	6.7	−20.2	Yes	Lowering CsA dosages and hemodialysis	n.a. (death)
	4	89.9	48.5	−41.4	Yes	Switching CsA to FK	1610
	10	80.33	109	+28.6	No	n.a.	n.a.
B	3	87.3	29	−58.3	Yes	Switching CsA to RPM	140
	5	66.7	59.7	−6.9	No	n.a.	n.a.
	6	61.9	89.5	+27.6	No	n.a.	n.a.
	7	88.6	128	+39.3	No	n.a.	n.a
	8	50.7	32.45	−27.3	Yes	Lowering CsA dosages	35
	9	131	134	+3	No	n.a.	n.a.
	11	90.34	77	−13.2	Yes	Lowering CsA dosages	40
	12	85.9	67.1	−18.7	Yes	Lowering RPM dosages	28

MDRD = glomerular filtration rate with the modification of diet in renal disease calculation; ARV$_s$ = antiretroviral drugs; Δ MDRD = difference between MDRD 48 h post-ARV$_s$ resumption and MDRD pre-ARV$_s$; ARF = acute renal failure; FK = tacrolimus; CsA = cyclosporine; n.a. = not applicable; RPM = rapamycine.

In our cohort, a significant number of patients (7 out of 12) developed ARF within 48 h after the resumption of ARV$_s$. Although of multifactorial etiology, these episodes were mainly related to rapid increases in IS plasma C$_t$ levels that occurred as a result of PK interactions with PI$_s$. After lowering IS dosages and/or switching CsA to FK or RPM, renal function was normalized in all subjects except one who died from cardiac tamponade and multiple organ failure despite undergoing hemodialysis.

In conclusion, unboosted PI$_s$, namely fosAPV and ATV, had fewer IS PK interactions and were more manageable and easier to use compared to boosted PI$_s$ in the post-LT$_x$ period.

We encourage early resumption of ARV$_s$ posttransplant, as soon as normal graft function is achieved and IS C$_t$ levels can be stabilized within their TW. Furthermore, we emphasize that PK interactions likely to be encountered are markedly and consistently influenced by RTV boosting, making it possible to predict the interval of IS dosage reduction necessary when concomitantly administering a given PI$_s$ regimen. In particular, our data show that major adjustments were required in both groups to prevent toxic drug levels. However, the necessary fold decrease in IS dosage was higher with boosted PI$_s$ (group A), ranging from 6 to 14, than that with unboosted PI$_s$ (group B), ranging from 2 to 4.

Major limitations of this study include its observational methodology and small sample size, the latter reducing our ability to assess exclusively standardized IS and ARV regimens and to establish any exact dosage recommendation. However, since randomized trials would be complex to design and undertake in this patient population, large observational case series will likely remain our best source of data. Hence, we believe that this study provides valuable information regarding the management of PI$_s$ in the early post-LT$_x$ setting among HIV-infected persons.

Given the extent of drug–drug interactions involved and the interpatient variability likely to be encountered, the routine utilization of therapeutic drug monitoring for both PI$_s$ and IS management in the posttransplant period will be essential to optimize and individualize the care of HIV-infected patients undergoing LT$_x$.

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