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Calcineurin inhibitor dose-finding before kidney transplantation in HIV patients

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Summary

Kidney transplantation in HIV-infected patients is associated with a higher rate of graft rejection as well as an increased toxicity of the immunosuppressive therapy. Specifically, the use of the calcineurin inhibitor tacrolimus is problematic because of a narrow therapeutic range, a high interindividual variability of trough levels, and multiple interactions with combination antiretroviral therapy (cART). Our objective was to establish the optimal individual immunosuppressive dose for the time after kidney transplantation. We administered a temporary course of immunosuppressive therapy in three HIV-infected patients with end-stage renal disease (ESRD) after wait-listing and prior to transplantation for deceased donor kidney transplantation. Starting with a tacrolimus dose of 1 mg twice daily, the dose was titrated to reach a tacrolimus trough level of 8–12 ng/ml. HIV had been diagnosed 7–14 years prior. All patients had no detectable HIV-1 RNA while on cART. All three patients had been on chronic dialysis for 4, 7, and 10 years. In two patients, the intended tacrolimus trough levels of 8–12 ng/ml were achieved within a month. The required tacrolimus dose ranged from 0.5 mg thrice weekly to 10 mg daily. In one case, ventricular tachycardia occurred, so the immunosuppressive therapy was switched to cyclosporine A. So far, two patients have been transplanted successfully. In summary, dose-finding of immunosuppressive therapy with tacrolimus in patients on cART before renal transplantation is feasible and appears useful to minimize immunosuppressive therapy-related complications in the post-transplantation period.

Introduction

Since the introduction of combination antiretroviral therapy (cART), HIV-related morbidity and mortality have decreased dramatically [1]. However, mortality from non-AIDS-related events in these patients including end-stage renal disease (ESRD) has increased [2]. HIV-infected patients have a 10-fold greater risk for ESRD [2] and HIV-associated renal disease seems to be associated with progression to AIDS and death [3]. The etiology of kidney disease in HIV-infected patients is multifactorial: acute renal failure [4], HIV-associated nephropathy (HIVAN) [5], drug-induced nephropathy [6], mesangioproliferative glomerulonephritis, cryoglobulinemia, amyloidosis, or thrombotic microangiopathy are among the more frequent causes of renal failure [7–9].

Kidney transplantation has evolved as a valid therapeutic option in adequately selected HIV-infected patients [10,11]. Transplant programs usually accept patients with a $CD4^+$ T-cell count above 200 cells/mm^3 and an undetectable HIV-RNA viral load on cART [4,11]. Previous opportunistic diseases are no longer strict exclusion criteria [4].

In recent years, more than 200 HIV-infected patients with ESRD have been transplanted under these conditions. The graft and patient survival has been shown to be similar to HIV-negative patients [4,5,12–15], even though HIV infection is associated with a higher risk of acute rejection episodes [16]. However, pharmacokinetic interaction between antiretroviral drugs and immunosuppressants remains a major issue. Over- or under-dosing of immunosuppressive drugs can lead to increased toxicity or acute rejection [11,17]. Specifically, the use of calcineurin inhibitors (CNI) such as tacrolimus is problematic because of the narrow therapeutic range and high interindividual variability of trough levels. Nonetheless tacrolimus is nowadays considered the CNI of choice because it is associated with fewer acute rejection episodes. The tacrolimus dose needed to reach therapeutic trough levels primarily depends on the cART regime (PI, NNRTI, etc.). CNIs are hepatically metabolized by cytochrome P450 3A4 (CYP3A4) [18]. Drug interactions caused by antiretroviral protease-inhibitors (PIs), especially in ritonavir-boosted regimens, are the main problem in the post-transplant CNI dosing period [19]. PIs are strong inhibitors of CYP3A4, making intensive drug monitoring of immunosuppressive drugs mandatory [13].

Knowledge of the optimal individual tacrolimus dose already before transplantation may provide a significant advantage for post-transplantation management. HIV-infected patients could then be treated with the specific tacrolimus dose required to achieve and maintain optimal therapeutic blood levels of immunosuppressive therapy immediately following kidney transplantation.

To establish the optimal individual immunosuppressant dose at the time of transplantation, we therefore temporarily administered tacrolimus and mycophenolate mofetil (MMF) to three HIV-infected patients with ESRD after they were accepted on the waiting list for deceased donor kidney transplantation in 2010.

Patients and methods

All three patients were male and their age ranged between 43 and 47 years. HIV had been diagnosed between 1996 and 2003. Patients were treated with cART, had an undetectable viral load (plasma HIV-1 RNA <50 copies/ml) and a $CD4^+$ T-cell count greater than 350/μl. ESRD was due to mesangioproliferative glomerulonephritis (IgA-nephropathy) and hypertensive nephrosclerosis and they had been on chronic dialysis for 4, 7, and 10 years, respectively. To determine the optimal individual tacrolimus dose already before kidney transplantation, each patient received a starting dose of 1 mg tacrolimus twice daily. Thereafter, the dose was adjusted to achieve and to maintain tacrolimus trough levels of 8–12 ng/ml. Patient 1 was treated with tacrolimus for 17 days, patient 2 for 41 days (4.5 months before transplantation) and patient 3 for 2 days (6 months before transplantation). Additional immunosuppressive therapy with mycophenolate mofetil was given after stable tacrolimus doses had been reached; the initial dose was 250 mg/day and increased to a maximum of 1000 mg/day. All data were collected retrospectively.

Baseline characteristics of the patients are shown in Table 1.

Results

Both before and after immunosuppressive therapy with tacrolimus, HIV-RNA load was undetectable and $CD4^+$ T-cell counts remained stable. To achieve the target tacrolimus trough level of 8–12 ng/ml, the required doses ranged from 0.5 mg thrice weekly up to a maximum of 10 mg/day.

The highest tacrolimus dose of 10 mg/day was required in patient 1 (Table 2, Fig. 1), treated with efavirenz (EFV), abacavir (ABC), and lamivudine (3TC). In this patient, tacrolimus therapy was associated with mild and transient abdominal pain (Table 2).

Table 1. Demographics and baseline data in 2010.

	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Age	43	45	47
Weight (kg)	66	88	72
HIV diagnosis	2003	1996	2000
CDC stage	B3	B2	B2
cART	EFV, ABC, 3TC	LPVr, SQV, TDF, ABC	LPVr, TDF, 3TC
VL <50 cp/ml stable since	2007	2005	2004
ESRD cause	Hypertensive nephrosclerosis	MSGN (IgA)	Hypertensive nephrosclerosis
Other disorder	HIV-associated thrombocytopenia, hyperlipidemia	Chronic HBV infection, hyperlipidemia	Status post HBV infection

VL, (viral load); cART, combined antiretroviral therapy; CDC, Centers for Disease Control and Prevention; MSGN, mesangioproliferative glomerulonephritis; HBV, Hepatitis B virus; ESRD, end-stage renal disease; EFV, efavirenz; ABC, abacavir; 3TC, lamivudine; SQV, saquinavir; LPVr, lopinavir/ritonavir; TDF, tenofovir.

Table 2. Laboratory data and clinical course of patients.

	Patient 1	Patient 2	Patient 3
CD4 count before dose-finding	741/mm^3	413/mm^3	382/mm^3
CD4 count after dose-finding	740/mm^3	468/mm^3	406/mm^3
Renal replacement therapy	CAPD since 2006	HD since 2003	HD since 2000
Tacrolimus dose (mg/day)	10	0.21	n/a, switched to cyclosporin
Tacrolimus dose (mg/kg/day)	0.15	0.0028	
Adverse reaction	Abdominal pain (transient)	Diarrhea (mild, transient)	Ventricular tachycardia
Outcome	Waiting for transplantation	Successfully transplanted	Successfully transplanted

HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; n/a not available.

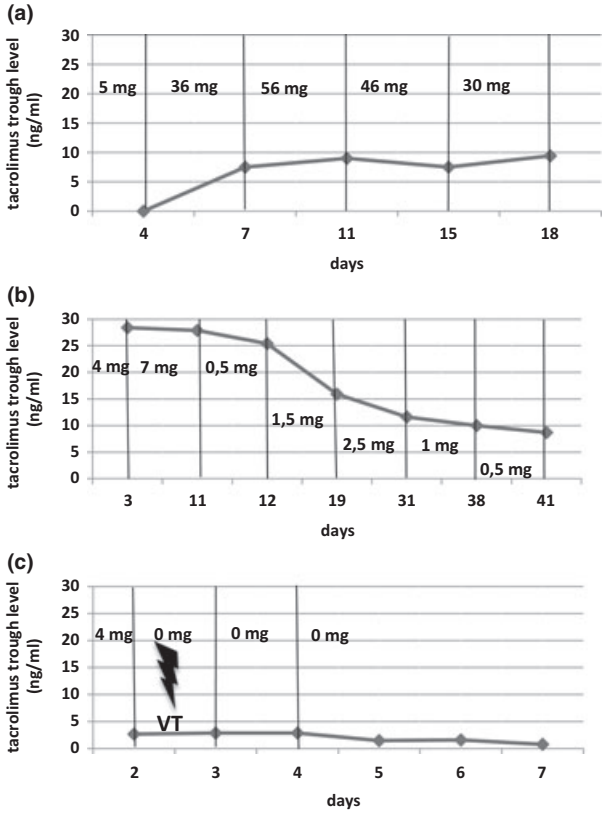

Figure 1 Graphs a–c show tacrolimus trough levels from three patients during tacrolimus dose-titration, treated with: (a) efavirenz (EFV), abacavir (ABC), and lamivudine (3TC) (b) lopinavir/ritonavir (LPVr), saquinavir (SQV), tenofovir (TDF), and ABC (c) LPVr, TDF, and 3TC. VT, ventricular tachycardia. Numbers between the vertical lines show the cumulative dose of tacrolimus (mg) during the time after the previous and before the next tacrolimus level measurement.

Patient 2 required the lowest tacrolimus dose of 0.5 mg thrice weekly (Fig. 1) while on lopinavir/ritonavir (LPVr), saquinavir (SQV), tenofovir (TDF), and ABC. He developed mild, transient diarrhea (Table 2). In the meantime, he has been transplanted successfully. Ten months after kidney transplantation, he presented with a borderline rejection reaction (Banff 3) and was treated with intravenous methylprednisolone (500 mg/day for 3 days). The consecutive 11 month course was uneventful without any sign of rejection. The required tacrolimus dose to achieve and to maintain the optimal trough level of tacrolimus therapy decreased further to 0.5 mg every 5 days after transplantation.

In patients 1 and 2, the target tacrolimus trough level was achieved within a 1-month period and required between 5 and 7 additional clinic visits.

Patient 3 was treated with LPVr, TDF, and 3TC. After 2 days, he developed ventricular tachycardia (Fig. 1) most likely associated with tacrolimus. Therefore, immunosuppressive therapy had to be switched to cyclosporine A. Recently, also this patient has been transplanted successfully.

The MMF dose in all three patients showed little interindividual variability and MMF was well tolerated by all patients. No other serious adverse events, especially no infectious complications were observed during the dose escalation phase.

Discussion

Although overall outcome data in patient and graft survival prove that kidney transplantation is safe in HIV-positive patients with ESRD [4,20–22], some specific problems have been reported in recent clinical trials – such as a high rate of acute rejection and specific drug interactions [16,19].

Especially the interactions of protease inhibitors (strong inhibitors of CYP3A4 [23]) with CNI (metabolized by P450 3A4 [24]) and strategies to supply adequate dosing after transplantation to avoid under- and over-treatment and thus both rejection and toxicity have to be addressed to further improve patient and transplant outcome.

In this small case series, CNI dose-finding before kidney transplantation in HIV-positive patients was applied as a strategy to find the adequate individual oral dose of CNIs to achieve early therapeutic blood levels after transplantation. We identified a wide range of doses required: adjusted to body weight there was a 53.6-fold difference between the highest and the lowest dose of tacrolimus in HIV-infected recipients treated with different cART regimens. In patients

2 and 3, tacrolimus metabolism was significantly inhibited by cART including LPVr. Others have described PI-treated patients needing significantly lower tacrolimus doses to achieve therapeutic blood levels [22,25,26], in one report a tacrolimus dose of even less than 1 mg/week was sufficient to maintain an adequate trough level while on LPVr [18]. Patient 1 was treated with the non-nucleoside reverse transcriptase inhibitor (NNRTI) EFV. He needed higher doses of tacrolimus presumably owing to CYP3A4− induction, an effect that has also been described by others [21].

Therefore, any further changes of cART may require a reassessment and potentially readaptation of the optimal individual tacrolimus dose. The optimal individual tacrolimus dose before transplantation could be achieved within a 1-month period. We also identified intolerance of tacrolimus in one patient (patient 3). Ventricular tachycardia due to tacrolimus therapy required a change of regimen. In contrast to tacrolimus, the MMF dose in all three patients showed little interindividual variability.

Two patients have been successfully transplanted to date. Based on our data, we suggest to perform an individual CNI dose-titration already after wait-listing and prior to transplantation for deceased donor kidney transplantation in HIV-infected patients on cART. This will allow to achieve therapeutic blood levels of immunosuppressants as early as possible post-transplantation. This strategy can minimize complications related to over- or under-immunosuppression in the early post-transplantation period and may identify potential serious adverse reactions. Thereby acute drug toxicity as well as acute rejection rates can be reduced and a long-term graft survival can be improved.

An alternative strategy to avoid interactions may be to change the cART regime prior to transplantation to avoid protease inhibitors in post-transplant drug regimes. A suitable option may be a therapy with integrase inhibitors, e.g., raltegravir or dolutegravir, as they do not interact with CYP3A4 [27]. Changes in antiviral therapy to reduce potential interactions after transplantation and thus facilitate immunosuppressive therapy appear possible, but if intended, such modifications should be considered very carefully and only if this is possible without any disadvantage for the respective patient.

To achieve a better management of cART and immunosuppressive therapy in HIV-infected patients both before and after kidney transplantation, more prospective clinical trials are needed.

Authorship

AP: collected data, analyzed data, wrote the manuscript. US: collected data, analyzed data, revised the manuscript. UlfS, MS, AH and MF: reviewed the manuscript. JF: collected data.

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