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Variable Tacrolimus Dosing After Protease Inhibitor-Based Antiretroviral Therapy Discontinuation in 2 HIV Patients Post–Kidney Transplantation

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To the Editor:

Recent data support the success of solid organ transplants in human immunodeficiency virus (HIV)-positive patients on suppressive antiretroviral therapy (ART).[1] Significant drug-drug interactions (DDIs) occur between calcineurin inhibitors (CNIs) and ART.[2,3] In a recent study of 332 HIV-positive kidney transplant recipients, a 1.8- and 1.9-fold increased risk of allograft loss and death resulted, respectively, in 88 patients receiving protease inhibitor (PI)-based regimens compared with 244 patients on non-PI-based ART.[4] If possible, eligible HIV-positive recipients should be converted to a non-PI-based regimen prior to or after kidney transplantation.

Tacrolimus is the CNI of choice in HIV-positive renal transplant recipients but has a narrow therapeutic index requiring close drug monitoring to avoid common adverse effects (nephrotoxicity and neurotoxicity) with supratherapeutic concentrations.[2,5] CNI dose conversion after PI discontinuation is variable, with tacrolimus (TAC) dose escalation of 5 to 20 times the original dose.[6,7] We report on 2 HIV-positive renal transplant recipients who were successfully switched from ritonavir (RTV)-boosted ART to dolutegravir or rilpivirine necessitating a 10- to 24-fold TAC dose escalation to maintain therapeutic concentrations.

Patient 1 is a 68-year-old male with HIV/hepatitis B (viral loads [VL] undetectable), deceased donor kidney transplant (DDKT), and hypertension. After 2 years of concurrent mycophenolate mofetil, prednisone, and TAC (0.2 mg weekly) (stable serum creatinine [SCr] 1.16-1.30 mg/dL) with fixed dose combination (FDC) abacavir/lamivudine and twice daily DRV)/RTV/etravirine/raltegravir, ART was simplified to abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg. TAC was empirically adjusted 10-fold with weekly concentrations remaining at goal (5-7 ng/mL; Figure 1). After dolutegravir transition, the SCr increased (2.28 mg/dL), resulting in an allograft biopsy demonstrating no acute rejection but chronic antibody-mediated changes with early transplant glomerulopathy. The SCr has remained stable for the following 2 years.

Patient 2 is a 52-year-old female with HIV (DRV/RTV ART with undetectable VL), hypertension, deep vein thrombosis, and recent DDKT receiving mycophenolic acid, prednisone, and TAC (0.5 mg weekly) (goal trough 6-8 ng/mL; Figure 1). Antiretroviral simplification was recommended with daily FDC abacavir/lamivudine and rilpivirine 25 mg (previous integrase resistance [140A, 148R, 203M] and dual tropic HIV). TAC dose titration stabilized at 6 mg twice daily (24-fold dose escalation). TAC weekly concentrations remained therapeutic with SCr improvement (1.23-1.01 mg/dL) and continued VL suppression at 4 months posttransplant.

A similar report describes a DDKT HIV-positive recipient receiving DRV/RTV/raltegravir.[7] ART simplification to FDC dolutegravir/abacavir/lamivudine necessitated a 20-fold TAC dose increase (0.5 mg every 11th day to 5 mg twice daily) after PI discontinuation. The SCr subsequently rose (+0.4 mg/dL) with a negative biopsy. Dolutegravir's inhibition of organic cationic transporter-2 (OCT-2) in the renal tubule was suspected (similar to Patient 1). Rilpivirine also inhibits OCT-2 and a small SCr rise of 0.1 mg/dL is common but does not result in an alteration in the actual glomerular filtration rate. Additional caution should be given to substituting cobicistat-boosted ART in HIV-positive renal transplant recipients as a probable DDI with TAC exists and resulted in supratherapeutic TAC concentrations (111.2 ng/mL) in one reported case.[8,9]

Recent data suggest hypertension as the primary etiology for the pretransplant chronic kidney disease in HIV-positive renal transplant patients as successful ART results in an almost normal life expectancy.[4] Based on historical

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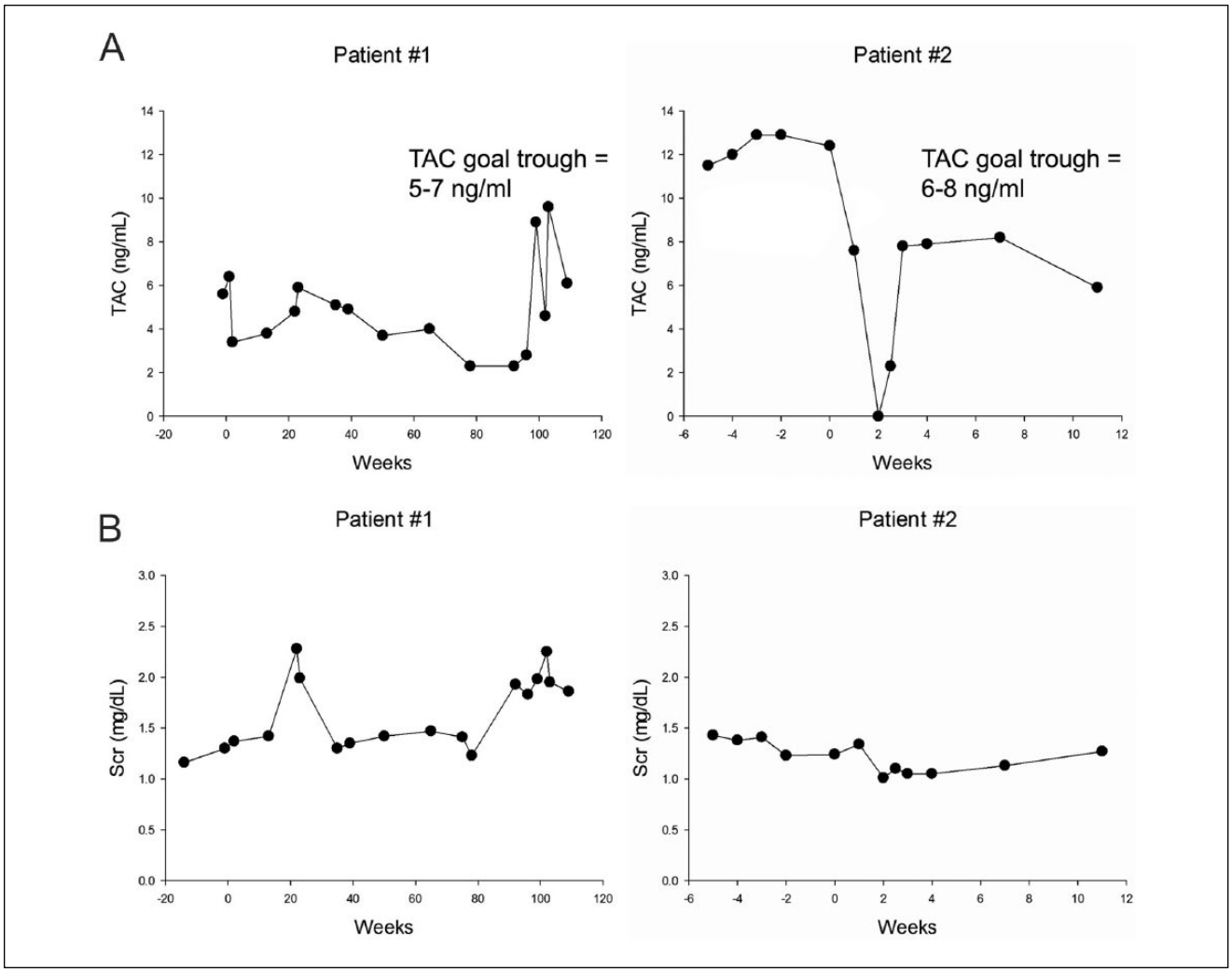

Figure 1. (A) Tacrolimus concentrations and (B) renal function after ART switch to either dolutegravir or rilpivirine therapy.

genotypes and in consultation with an HIV infectious disease specialist, HIV-positive candidates should be switched prior to planned renal transplant as post-allograft ART conversions will require weekly evaluations to maintain therapeutic CNI concentrations and HIV viral rebound (similar to the present cases). RTV or cobicistat-boosted regimens should be changed to ART devoid of cytochrome P450 CNI DDIs (dolutegravir, maraviroc, raltegravir, or rilpivirine or the soon to be approved bictegravir) to prolong allograft survival.[3] If ARV resistance does not allow PI or cobicistat-boosted ART discontinuation, alternative immunosuppressive strategies (belatacept) devoid of CNI DDIs is recommended.[3]

Declaration of Conflicting Interests

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