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Serum creatinine elevation after switch to dolutegravir in a human immunodeficiency virus-positive kidney transplant recipient

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Abstract

Dolutegravir is a preferred antiretroviral drug for human immunodeficiency virus (HIV)-infected patients following solid organ transplantation. It has potent antiretroviral activity and does not interact with calcineurin inhibitors. We describe a case of an HIV-infected kidney transplant patient, who was noted to have a rising serum creatinine following initiation of dolutegravir. At first an acute rejection episode was suspected, but this finding was later attributed to inhibition of creatinine secretion by dolutegravir. We suggest that an awareness of this potential effect of dolutegravir is important for providers who take care of HIV-positive kidney transplant recipients, in order to prevent potentially unnecessary testing.

Keywords

dolutegravir; kidney transplant; creatinine; human immunodeficiency virus; antiretroviral

Case report

A 56-year-old man with longstanding human immunodeficiency virus (HIV) infection and hypertension developed end-stage kidney disease following a course of ganciclovir to treat cytomegalovirus retinitis. The etiology of his kidney disease was thought to be related to ganciclovir toxicity.

Twelve years later, he underwent successful deceased-donor kidney transplantation. At the time of transplantation, his HIV infection was well controlled with a combination regimen of ritonavir-boosted darunavir and raltegravir. His CD4 count was 450 cell/mm³ with an undetectable viral load. For immunosuppression, he received induction therapy with basiliximab and intravenous immunoglobulin, and then received maintenance immunosuppression with tacrolimus (Tac), mycophenolate mofetil, and oral steroids. He

experienced immediate graft function after transplantation, and his serum creatinine (SCr) was 3.4 mg/dL at the time of discharge. For prophylaxis, he completed a standard 6-month course of sulfamethoxazole-trimethoprim and valganciclovir. His SCr stabilized near 1.5 mg/dL (CKD-EPI: 51.3 mL/min). He required very low doses of maintenance Tac because of significant drug interactions related to his protease inhibitor (PI)-based antiretroviral therapy (ART).

Despite careful monitoring and adjustment of his immunosuppression, interactions with his ART resulted in variable Tac troughs levels, raising the concern that the patient was at risk of developing calcineurin inhibitor (CNI) nephrotoxicity. Based on this concern, at 1 year post-transplant, his ART regimen was changed to an integrase-based regimen (dolutegravir, abacavir, and lamivudine [Triumeq®]) to avoid the interactions associated with PI use. His Tac dosing was closely monitored and adjusted following the change. After the ART changes, the patient's Tac dosing increased from 0.5 mg on every eleventh day to a more standard 5 mg twice a day, and he consistently achieved therapeutic Tac troughs of 5–8 ug/L.

However, 2 weeks after switching ART regimens, the patient's SCr increased to 1.9 mg/dL (glomerular filtration rate [GFR] by CKD-EPI: 38.6 mL/min) from baseline of 1.5 mg/dL (CKD-EPI: 51.3 mL/min). He was admitted for evaluation of elevated creatinine and underwent evaluation for possible rejection. His work up did not reveal infection or obstruction. His serum BK virus polymerase chain reaction was negative and he had no evidence of T- or B-cell panel reactive antibodies.

After his initial work up was found to be unrevealing, he underwent a kidney allograft biopsy. Biopsy pathology revealed tubular epithelial vacuolization and patchy tubular atrophy and fibrosis, which were not consistent with either acute cellular or humoral rejection. In light of the patient's biopsy findings, no anti-rejection therapy was administered. Given the lack of any other identifiable causes, the timing, and continuation of stable laboratory values after the event, the patient's SCr elevation was attributed to dolutegravir. Since then, his creatinine has remained stable at 1.8 mg/dL (CKD-EPI: 41.2 mL/min). His HIV infection has been well controlled after ART change to dolutegravir, and Tac levels have remained stable within our therapeutic targets (Tac trough range 5–7 ng/mL).

Discussion

This case illustrates a potential diagnostic dilemma in an HIV-positive kidney transplant recipient who underwent an ART change to ease immunosuppression dosing, followed by a rise in SCr. An awareness of antiretrovirals that inhibit creatinine secretion is important for providers who take care of HIV-positive kidney transplant recipients, in order to prevent potentially unnecessary hospitalizations and/or kidney allograft biopsies.

Transplantation of HIV-positive patients has become widely accepted and increasingly successful, with rates of graft survival that are similar to those seen in HIV-negative populations (1). With increased demand and positive post-transplant outcomes, organ transplant in HIV-infected patients are expected to increase. According to data from the Scientific Registry of Transplant Recipients (SRTR), the number of HIV transplants

increased significantly in the last decade (2). Two years ago, the HIV Organ Policy Equity (HOPE) act was introduced to allow utilization of HIV infected organs. Once these policy changes become part of standard practice, the number of transplants in HIV-infected patients is expected to increase further.

One of the more challenging aspects of caring for HIV-positive kidney transplant recipients is managing the drug interactions between ART and immunosuppression therapy. (3) Mainly PIs are known to be potent inhibitors of CYP3A and require dramatic dose adjustment with CNIs. Despite close monitoring of CNI levels, cases of CNI-induced nephrotoxicity have been reported, that are thought to be correlated to the altered metabolism and long-term exposure to higher levels of CNI (4, 5). Alternatively, patients who are on both Tac and PIs display unpredictable Tac pharmacokinetics, resulting in persistently lower areas under the curve and, furthermore, may have increased rates of rejection noted in early HIV transplant studies. (6)

Switching ART to a non-PI-based regimen in HIV-positive transplant recipients has become increasingly preferred to avoid such variability in CNI exposure. In HIV-positive patients who are undergoing kidney transplantation, the ideal combination of ART would have limited drug interactions with immunosuppression, lack dose adjustments for augmented renal clearance, and have a favorable side effect profile with a simplified dosing regimen.

Integrase inhibitors represent a newer class of ART that have no interactions with CNI and, therefore, have become preferred ART for transplant recipients. Raltegravir was the first Food and Drug Administration (FDA)-approved agent of this class; however, its low genetic barrier to resistance and inconvenient twice-daily dosing, has precluding long-term use in select populations. Elvitegravir was approved but must be combined with a booster, cobicistat, which limits its use in transplantation, given its inhibition of cytochrome P450 3A. Dolutegravir, which was FDA approved in 2014, has a high genetic barrier to resistance and has once daily dosing. In clinical trials, dolutegravir was well tolerated and it was non-inferior or even superior to other combination ART (7, 8).

Dolutegravir, along with abacavir and lamivudine (Triumeq®) would be an ideal option in a non-treatment experienced patient without complex resistance mutations, although this therapy has not been specifically studied in HIV-positive kidney transplant recipients. Notably, for patients with a GFR < 50 mL/min, lamivudine requires dose adjustment and the individual components in the once-daily single tablet must be divided accordingly. Furthermore, patients with known integrase resistance should receive twice-daily dosing of dolutegravir. Clinical trials evaluating the safety and efficacy of dolutegravir revealed elevated SCr levels within the first 2–4 weeks of treatment with mean increase of 0.1–0.2 mg/dL.

A number of antiretrovirals have been observed to have similar effects on creatinine, including rilpivirine, cobicistat, and ritonavir (8–11). Elevation of creatinine with dolutegravir use has been attributed to the inhibition of the renal organic cation transporter (OCT2) and multidrug and toxin extrusion protein (MATE-2K), which causes a decrease in creatinine secretion. This theory was confirmed in a phase 1 study that demonstrated that,

despite SCr elevation with dolutegravir, GFR showed no change when measured by iothexol clearance (12, 13). In addition, *in vivo* studies indicate abacavir inhibits OCT2, and lamivudine inhibits OCT2, MATE1, and MATE2-K, which may have contributed to the elevation of creatinine (14, 15).

The rise in SCr in our patient was greater than the 0.1–0.2 mg/dL increase noted in HIV-positive patients followed in clinical trials. This larger increase may have been related to the concurrent interaction with abacavir or lamivudine. Another possibility would be the greater effect of creatinine elevation because of diminished GFR in one functioning allograft kidney, as opposed to two native kidneys under normal circumstances.

This case illustrates a potential diagnostic dilemma in an HIV-positive kidney transplant recipient who underwent ART change that was followed by a rise in SCr, where a number of factors might be at play. This report underscores the notion that it is ideal to optimize ART regimens prior to kidney transplantation. We suggest that an awareness of the dynamics of SCr, following a change to a dolutegravir-based ART regimen, is important and caregivers might consider a direct assessment of measured GFR in such patients, when possible.

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