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Case Report

Successful tacrolimus treatment following renal transplant in a HIV-infected patient with raltegravir previously treated with a protease inhibitor based regimen

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Abstract

A HIV positive patient who received a cadaveric renal transplantation developed tacrolimus toxicity as manifest by renal failure and decreased consciousness. This was due to atazanavir and ritonavir therapy for her HIV inhibiting the CYP3A4 hepatic enzyme resulting in accumulation of tacrolimus. Her HIV treatment was switched to raltegravir which is metabolized by UGT1A1 which does not affect tacrolimus. Tacrolimus was then reintroduced, and follow-up at 1 year demonstrated successful immunosuppression and undetectable HIV viral loads.

Keywords: atazanavir; HIV; tacrolimus.

Case presentation

A 53-year-old woman was admitted to hospital for cadaveric right renal transplant. She had maintenance haemodialysis for 6 years following a diagnosis of HIV associated nephropathy and subsequent end stage renal failure. Her previous medical history included secondary hyperparathyroidism, aspergillus sinusitis 6 years previously and mild concentric left ventricular hypertrophy. She was also taking aciclovir prophylaxis for Herpes simplex infection.

HIV viral load was well controlled on abacavir, tenofovir (renal dialysis adjusted dose), atazanavir and ritonavir. She had a CD4 count of 304 cells/mm^3 and an undetectable HIV viral load prior to the transplant. She had no history of prior opportunist infections.

Her HIV infection was first diagnosed in the 1990s and she was treated with what are now, with the benefit of randomised controlled trials, considered suboptimal HIV treatment combinations. After a period of non-adherence she developed low level HIV viraemia requiring a switch in therapy to a protease inhibitor based regimen including atazanavir and ritonavir. Unfortunately, neither genotypic nor phenotypic HIV resistance test was performed on this occasion, nor at her initial HIV diagnosis as this was not considered universal practice at that time.

Her post-transplant immunosuppression consisted of tacrolimus 1.5 mg b.d., prednisolone 20 mg o.d. and myfortic 540 mg b.d. Her renal function improved significantly and her tenofovir frequency was increased to every 72 h. Four days post-transplant she became drowsy with short-term memory impairment and demonstrated a small drop in haemoglobin level with a raised bilirubin. Pre-transplant bilirubin was elevated which is consistent with previously recognised UDP-glucuronosyltransferase (UGT) inhibition due to atazanavir (1). Tacrolimus levels, measured with a modified Water assay at the Toxicology Laboratory rose sharply to values outside the range of the assay (Figure 1). Her renal function deteriorated, requiring haemodialysis once post-transplant. Her wounds were examined under anaesthesia and a biopsy was taken from the transplanted kidney, which demonstrated acute tubular necrosis. Further exploration of the transplant site occurred 5 days later when her serum haemoglobin levels dropped again, and a haematoma was evacuated from the surgical site.

On day 8 post-transplant, the atazanavir/ritonavir combination was switched to the integrase inhibitor raltegravir following discussion with HIV physicians. Following a break of 13 days, tacrolimus was re-introduced and within 5 days, levels were within the therapeutic window.

Raltegravir has a low genetic barrier to resistance compared to the protease inhibitors atazanavir and ritonavir. In the interests of protecting the regimen and preventing future renal toxicity due to tenofovir, the HIV regimen was changed to abacavir, raltegravir and etravirine.

She was discharged 37 days post-surgery to the community and continued to attend HIV follow-up under her local service. One year later, she had no evidence of transplant rejection and continues with the amended antivirals with no detectable HIV viral load.

Discussion

Tacrolimus has a narrow therapeutic window, and has a side effect profile that includes nephrotoxicity and neurotoxicity,

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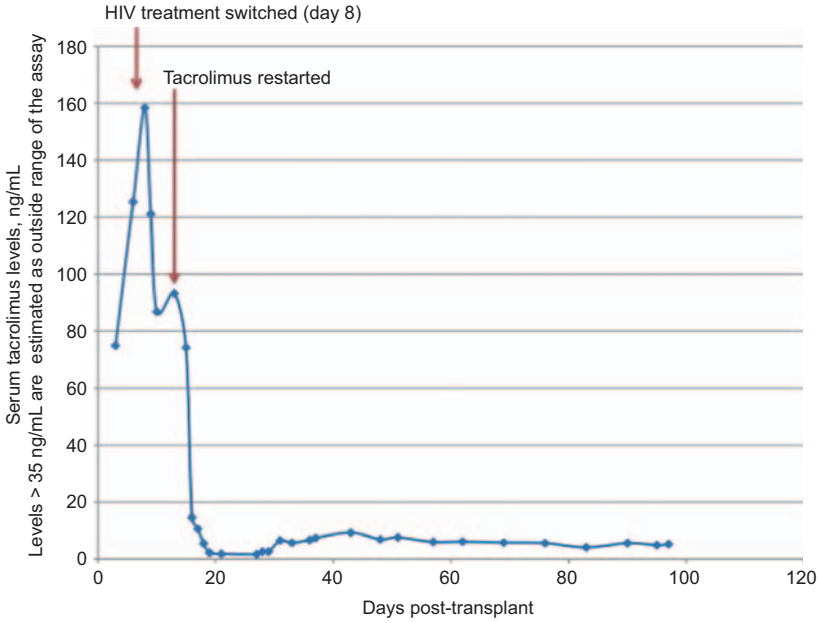

Figure 1 Serum tacrolimus levels post-transplant.

both experienced by the patient. These are dose-dependent and are common at tacrolimus levels >15 ng/mL (2, 3).

Tacrolimus is metabolised by the cytochromes P450 3A4 in the liver, which is a pathway inhibited by protease inhibitors, such as ritonavir and saquinavir (4). Previous case reports have demonstrated the interaction of tacrolimus with lopinavir/ritonavir and saquinavir/ritonavir (2, 3, 5, 6). Significant interactions would be expected with ritonavir alone, although given that the interaction is class-specific there may also be some effect of atazanavir on tacrolimus. Previous research has also demonstrated successful switch of boosted protease inhibitor to raltegravir, as has occurred in this case.

Raltegravir, previously known as MK-0518 is an integrase inhibitor, which is not metabolised by the CYP3A4 enzyme, rather by UGT-1A. This is an enzyme of the glucuronidation pathway which transforms lipophilic molecules into water-soluble metabolites for excretion (7). Raltegravir therefore has no effect on tacrolimus metabolism (8). One concern for the future management of this patient stems from two randomised controlled studies examining patients switched to raltegravir from protease inhibitors with optimised nucleoside backbones who had an undetectable HIV viral load, seen as the standard measure of control of HIV infection (9). The study was terminated early due to treatment failure in the switch arm. This was probably due to the protection by protease inhibitors from previous archived nucleoside reverse transcriptase resistance in the patients who had been treated early in the HIV epidemic with regimens that were probably substandard (7). This patient was also treated in that age group and had never been tested for archived HIV resistance prior to switching therapy, as virological control was achieved on the preceding regimen and therefore resistance testing would not be viable.

Raltegravir is also suggested to have a lower genetic barrier to resistance compared with protease inhibitors, so any failing treatment must be detected early to prevent further resistance to other drug classes.

The authors' concern is that further treatment switches may be challenging due to juggling anticipated viral resistance and pharmacokinetics of dosing regimens with immunosuppressive treatments, such as tacrolimus. Close monitoring of the HIV viral load and collaboration between transplant physicians and their colleagues in HIV medicine is advisable. This is to ensure that hazardous drug-drug interactions and failing HIV treatments are recognised early to ensure appropriate remedy and therefore improve the long-term survival of these patients. As people with HIV have increased survival rates, there will be increasing numbers of HIV-infected people presenting for solid organ transplantation in the future.

Conflict of interest statement

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