Successful outcome of renal transplantation in a child with HIV-associated nephropathy

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ABSTRACT

Classical HIV-associated nephropathy (HIVAN) was first described before the advent of highly active antiretroviral therapy in late stages of HIV disease with high viral load and low CD4 cell count. Renal transplantation has been successful in a large series of carefully selected HIV-infected adults, with patient and renal allograft survival approaching those of non-HIV-infected patients. We report the successful outcome of living related renal transplantation in a vertically transmitted HIV-infected 8-year-old girl with end-stage kidney disease on haemodialysis due to HIVAN. The pretransplant preparations and post-transplant care, with particular emphasis on immunosuppression and avoidance of opportunistic infections, are discussed.

CASE STUDY

Our patient is a vertically transmitted HIV-infected girl: both parents were HIV-positive, and her mother was diagnosed during her last month of pregnancy. She was HIV-negative at birth (on highly sensitive HIV RNA PCR assay) and received zidovudine and lamivudine for 4 weeks. Thereafter, she was lost to follow-up for 5.5 years when she represented with suppurative lymphadenitis and lymphocytic interstitial pneumonitis (LIP). She was HIV PCR-positive (viral load 28 000 copies/mL) but had good CD4 counts (440/mm3; 18%) and was not PCR-positive (viral load <50 copies/mL) but had good CD4 counts (440/mm3; 18%) and was not infected by hepatitis B or hepatitis C. At 8 years of age, she presented with a prolonged illness, suppurative lymphadenitis, and was HIV-infected. Her serum creatinine was 72 μmol/L (estimated glomerular filtration rate 50 mLs/min/1.73 m2) without hypertension or proteinuria. She had an undetectable HIV-1 viral load and CD4 cell count, without hypertension or proteinuria. She was started on zidovudine and lamivudine for 4 weeks. Thereafter, she was then stabilised on haemodialysis due to HIVAN. The pretransplant preparations and post-transplant care, with particular emphasis on immunosuppression and avoidance of opportunistic infections, are discussed.

Presentation with HIVAN

Eleven months later, she presented in anuric renal failure with pulmonary oedema. Her serum creatinine was 760 μmol/L (eGFR 5 mLs/min/1.73 m2) and percutaneous renal biopsy confirmed HIVAN. She required continuous venovenous haemofiltration for 5 days and was then stabilised on haemodialysis. HAART (lopinavir/ritonavir (Kaletra), lamivudine and abacavir) was started and her HIV viral load became undetectable (<50 copies/mL) within 4 weeks.

Work-up for renal transplantation

She had an undetectable HIV-1 viral load and CD4 counts that were consistently above 200 cells/mm3 for >6 months, no concurrent hepatitis B or hepatitis C infection and was stable on HAART for >6 months, thereby fulfilling the criteria for kidney transplantation in patients with HIV disease.1 2

Work-up for living-related renal transplantation from her maternal grandmother was commenced, although there were several modifications to our routine pretransplantation work-up.

Our patient did not receive any live vaccines (no BCG, measles or varicella vaccination). Prophylaxis against opportunistic infections was planned to start at the time of transplant: isoniazid for 6 months post-transplantation for tuberculosis; lifelong co-trimoxazole for Pneumocystis jiroveci prophylaxis and fluconazole for 6 weeks to prevent fungal infections. In view of the underlying LIP it was decided to continue lifelong azithromycin. As both donor and recipient were CMV-negative, valganciclovir was not required. The same HAART regimen was to be continued post-transplantation as this achieved complete and sustained suppression of HIV viral loads (<50 copies/mL). We calculated that she would require 15 medications (22 tablets per day) for the first 3 months post-transplantation. Despite this significant pill burden, her carers refused gastrostomy tube insertion.

In view of preformed antibodies, a historic B-cell-positive crossmatch and the higher risk of rejection that is reported in HIV-positive renal transplant recipients,3 4 we elected to give basiliximab for induction therapy, tacrolimus, mycophenolate mofetil (MMF) and corticosteroids. Ritonavir inhibits the cytochrome P450 system and can result in toxic levels of tacrolimus; fluconazole can also contribute to tacrolimus toxicity. Therefore, we started tacrolimus 6 weeks pretransplantation in order to find the correct dose and achieve steady-state trough tacrolimus levels (aiming for 10–12 mcg/L) on a dose of 0.1 mg once daily four times per week.

Transplant surgery and post-transplant management

The donor was her 56-year-old blood group compatible maternal grandmother with human leucocyte antigen mismatch 1,1,1,1 and was then stabilised on haemodialysis. HAART (lopinavir/ritonavir (Kaletra), lamivudine and abacavir) was started and her HIV viral load became undetectable (<50 copies/mL) within 4 weeks.

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Kaletra required dose adjustments as GFR improved. Therapeutic drug monitoring for tacrolimus and Kaletra were performed twice weekly for 3 months and thereafter every 2–4 weeks due to the complex drug interactions between lamivudine, Kaletra, fluconazole and tacrolimus. Trough mycophenolate levels were monitored weekly due to the interactions between MMF and isoniazid, although trough level monitoring may not be an ideal surrogate marker for the area under the curve.

At 3 months post-transplantation, she developed neutropenia that was not associated with a febrile illness that was thought to be due to MMF therapy and she was changed to azathioprine with a rapid and sustained recovery of her neutrophil count. She had no evidence of opportunistic infection or HIV-associated complications and her LIP remained dormant. At 8 months post-transplantation, she developed EBV reactivation (both donor and recipient were EBV-positive) with a high EBV PCR level; this was managed by reducing her tacrolimus dose, aiming for levels of 6–8 mcg/L.

**Follow-up**

She is now 18 months post-transplant with good renal allograft function (plasma creatinine 60–65 μmol/L; eGFR 78–85 mLs/min/1.73 m²) without donor-specific antibodies. Trough tacrolimus levels are maintained in the range of 6–8 mcg/L on one dose of 0.1 mg tacrolimus on 3 days per week. She has mild but controlled hypertension on amlodipine monotherapy without albuminuria (urine albumin:creatinine ratio of 3.9 mg/mmol).

Her renal transplant shows good perfusion without dilatation and her native kidneys remain unchanged on ultrasound. She has had an undetectable HIV viral load for almost 2 years, good and her native kidneys remain unchanged on ultrasound. She is now 18 months post-transplant with good renal allograft function (plasma creatinine 60–65 μmol/L; eGFR 78–85 mLs/min/1.73 m²) without donor-specific antibodies. Trough tacrolimus levels are maintained in the range of 6–8 mcg/L on one dose of 0.1 mg tacrolimus on 3 days per week. She has mild but controlled hypertension on amlodipine monotherapy without albuminuria (urine albumin:creatinine ratio of 3.9 mg/mmol).

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**DISCUSSION**

This is the first reported case of successful renal transplantation in a child with HIVAN. With the advent of HAART, the prognosis of HIV infection has improved dramatically in children with end-stage kidney disease (ESKD) reported in less than 4% of infected individuals. The presence of HIV infection can no longer be viewed as a contraindication to renal transplantation and there are recent reports on its efficacy and safety in HIV-infected adults.  

Recently, the results of the first prospective multicentre trial of kidney transplantation into HIV-positive adults were published, showing the success and challenges of transplantation into this population. Transplantation in HIV-infected adults is associated with an increased toxicity of immunosuppressive therapy, a higher rate of renal allograft rejection and risk of long-term HIV-associated complications. In this study, 150 carefully selected HIV-infected adults who underwent renal transplantation were prospectively followed up for a median period of 1.3 years. Patient survival rates at 1 and 3 years were 95 and 88% with corresponding renal allograft survival rates of 90 and 74%, respectively, although there was a very high incidence of renal allograft rejection (31% at 1 year and 41% at 3 years), which was associated with deceased donor transplantation, ciclosporin as compared with tacrolimus use and use of antithymocyte globulin at induction. A higher CD4 count and higher trough tacrolimus levels decreased the risk of acute rejection. The results of this study prompted us to encourage living donor renal transplantation, and we opted to use tacrolimus and basiliximab (rather than antithymocyte globulin for induction therapy) together with corticosteroids and MMF. We decided not to use mTOR-inhibitors as their use has been associated with a higher risk for viral-driven cancers and recent experience with their use in HIV-positive adult renal transplant recipients has shown a higher incidence of antibody-mediated rejection compared with calcineurin inhibitors.

Once HIV patients consistently achieve CD4 counts above 200 cells/mm³, they are considered not to have a major T-cell defect and are treated as immunocompetent in terms of peritransplant immunosuppression. The use of tacrolimus can be problematic because of a narrow therapeutic range, a high interindividual variability of trough levels and multiple interactions with combination antiretroviral therapy. A planned living donor transplant allowed us to perform a careful dose-finding study starting tacrolimus 6 weeks pretransplantation with therapeutic drug monitoring of tacrolimus and Kaletra. Given the availability of tacrolimus suspension, we were able to titrate the dose in 0.1 mg (=0.1 mL) amounts to achieve therapeutic drug levels.

Patients with HIVAN may have a higher risk of malignancies in their native kidneys after transplantation, and nephrectomies prior to transplantation have been considered by some experts. We continue to monitor our patient with 6-monthly renal ultrasound scans.

In summary, renal transplantation in carefully selected HIV-positive children is feasible. The HIV disease is well controlled despite immunosuppression. Significant challenges in the form of managing drug interactions, controlling the risk of
opportunistic infections and monitoring for high rejection rates, require careful long-term monitoring.

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Competing interests None.

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