Renal transplantation in HIV patients: A series of four cases

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ABSTRACT

Human immunodeficiency virus (HIV) infection in a patient with end-stage renal disease was considered a contraindication for renal transplantation till now despite the advent of highly active antiretroviral therapy with the apprehension that immunosuppression would further jeopardize the already compromised immune status of the patients. Renal transplantation in HIV patients is rare in developing countries including ours. Here we report a series of four cases of renal transplantation in HIV patients.

Key words: End-stage renal disease, highly active antiretroviral therapy, human immunodeficiency virus, immunosuppression

Introduction

With the advent of and access to highly active antiretroviral therapy (HAART) for patients of human immunodeficiency virus (HIV) there has been a paradigm shift in the management and outcome of HIV patients.[1-7] Opportunistic infections are now replaced by chronic diseases like chronic kidney disease, chronic liver disease and malignancies etc.[8] HIV-associated nephropathy (HIVAN) is the most common cause of end-stage renal disease (ESRD) in HIV patients accounting for about 60% cases.[9] Though earlier HIV infection was taken as a contraindication to renal transplantation because of the apprehension of additional immunosuppression, there is now plenty of evidence to its contrary.[5-8,10] Here we report four cases of renal transplantation in HIV patients at our centre.

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.97139

Case Reports

Case 1

A 43-year-old Ugandan male weighing 74 kg was evaluated at our hospital in January 2009 for renal transplantation. He was a known case of HIV infection for the last eight years and was on HAART [abacavir (NRTI) 300 mg BD, efavirenz (NNRTI) 600 mg OD and combination of ritonavir (PI) 100 mg BD and lopinavir 400 mg BD] for the last four years. He was diagnosed to have ESRD in April 2005 with HIV-associated nephropathy (HIVAN) as the possible basic disease. He was on continuous ambulatory peritoneal dialysis (CAPD) till 2007 and then on maintenance hemodialysis. He came to India for renal transplantation with his blood group matched cousin as the prospective kidney donor. Patient had undetectable HIV RNA and CD4 cell count was 403/cmm at the time of renal transplantation. The patient had mild anemia (Hb 10.9 g/dl), normal liver function test, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) were negative and cytomegalovirus (CMV) IgG antibody was positive but IgM antibody was negative. His 24-h urine protein was 3.6 g/day. His urine output was about 500 ml/day. Ultrasonography revealed highly echogenic kidneys with left kidney measuring 9.4 × 3.3 cm^2 and right kidney measuring 9.2 × 3.2 cm^2. His echocardiography was normal and dobutamine stress echocardiography was negative for reversible ischemia. Lymphocytotoxicity cross-match was negative. Investigations did not reveal any evidence of opportunistic infections, malignancy or any AIDS-defining illness. He was well-compliant to HAART.

He was vaccinated for pneumococcus, meningococcus, influenza and hepatitis A. He was already immunized for hepatitis B.

His donor was, a 33-year-old non-diabetic with glomerular filtration rate (GFR) of 114.6 ml/min. Immunosuppression was with tacrolimus 0.075 mg/kg and mycophenolate sodium 360 mg 2 BD a day before the transplantation. Steroid was added after the transplantation with tapering doses till 20 mg OD. At the time of transplantation basiliximab (IL-2 antibody) 20 mg was given and was repeated on the fourth postoperative day. During the immediate postoperative course he developed slow graft function. The tacrolimus level was high. Renal biopsy was deferred as he started improving after optimized doses of tacrolimus. HIV RNA was undetectable and CD4 cell count was 475/ cmm on the seventh postoperative day. He was discharged from the hospital with a creatinine of 1.1 mg% on the tenth postoperative day. In the last follow-up at 2 years and 6 months he had serum creatinine value of 1.1 mg% with tacrolimus level in the therapeutic range with the dose of 0.00625 mg/kg (0.5 mg) every fifth day. HIV RNA was undetectable and CD4 cell count was 443/ cmm.

Case 2

A 50-year-old male from Delhi, hypertensive for the last 25 years was diagnosed to have ESRD. During evaluation for renal transplantion he was found to be HIV-positive and was started on HAART [lamivudine (NRTI) 100 mg 1/2 OD, stavudine (NRTI) 30 mg OD and a combination of ritonavir (PI) 100 mg BD and lopinavir (PI) 400 mg BD] At the time of transplantation, his HIV RNA was found to be <25 copies/ml and CD4 cell count was 400/ cmm. HBsAg and anti HCV were negative, CMV IgG was positive and IgM was negative. The native kidney urine output was 100 ml/day Lymphocytotoxicity cross-match was negative. He did not have any active infection, malignancy or AIDS-defining illness. He was vaccinated similar to the first case. His 45-year-old wife with GFR of 80.5 ml/min was the kidney donor. He was induced with two doses of basiliximab and started on the form of cyclosporine (CsA) 75 mg BD (2 mg/kg) and mycophenolate sodium 72 mg/d. Steroid was added after transplantation with tapering doses till 20 mg OD. On the third postoperative day he developed high-grade fever with high total leukocyte counts which was managed with IV antibiotics. His blood and urine cultures were sterile. His HAART was normalized once he achieved near normal graft function. Cyclosporine dose was adjusted according to the level. His HIV RNA was undetectable and CD4 cell count was 359/ cmm on the seventh postoperative day. He was discharged on the tenth postoperative day with a creatinine of 1.3 mg% with CO level 305 ng/ml, on cyclosporine 25 mg twice a day. He is under regular follow-up since then. In between he had biopsy proven acute cellular rejection which was treated with pulse methylpredenisolone for 3 days followed by increase in the dose of steroid and subsequent slow tapering. He responded well and his serum creatinine came down. In the last follow-up at 15 months he was doing fine with a serum creatinine of 1.3 mg% and CsA in the dose of 0.162 mg/kg/day (25 mg alternate day) and CO level 112 ng/ml. HIV-1 RNA was undetectable and CD4 cell count was 486/ cmm.

Case 3

A 36-year-old male from Uganda was diagnosed to have ESRD with probable etiology of chronic interstial nephritis. He was found to be HIV-positive and was started on HAART {lamivudine (NRTI) 100 mg 1/2 OD, abacavir (NRTI) 300 mg BD and efavirenz (NNRTI) 600 mg OD}. His 24-year old step-brother was found fit as a kidney donor. Patient did not have any active infection, malignancy or AIDS-defining illness and was well-compliant to HAART. He was vaccinated as per protocol. At the time of transplantation, his HIV RNA was undetectable and CD4 cell count was 667/ cmm. He was HBsAg and anti HCV were negative, CMV IgG was positive and IgM was negative. After basiliximab induction, he was given tacrolimus 7 mg BD and mycophenolate sodium 360 mg 2 BD. Steroid was added after transplant with tapering doses till 20 mg OD. On the third postoperative day his serum creatinine started rising with decrease in urine output. His tacrolimus (TAC) trough level was 4.5 ng/ml. Renal biopsy showed mild acute tubular necrosis. He was managed conservatively and his urine output started improving with gradual fall in serum creatinine. HIV RNA was undetectable and CD4 cell count was 359/ cmm on the seventh postoperative day. He was discharged on the 16th postoperative day with tacrolimus 8 mg BD and TAC level of 8.6 ng/ml, with serum creatinine of 1.9 mg/dl. He was doing fine till 10 months post transplant when he started having graft dysfunction. He was subsequently found to have very low TAC trough level and biopsy proven acute humoral rejection. He was treated with 5 sessions of plasma exchange with optimization of his immunosupresssants. However, he was lost follow up since then.

Case 4

A 40-year-old male from Tanzania was a known case of hypertension for 14 years. He was found to have HIV infection in December 2005 when he had some febrile illness and was started on HAART from February 2007 comprising lamivudine (NRTI) 50 mg OD, stavudine (NRTI) 30 mg OD and efavirenz (NNRTI) 600 mg OD. He was diagnosed to have ESRD in February 2007 and

started on hemodialysis. He came to India for renal transplantation with his elder brother as the prospective donor. The HIV RNA was undetectable and CD4 count was 415/cmm. Both he and his donor had the same blood group (B positive). There was HLA haplo-match with the donor and lymphocytotoxicity cross-match was negative. Further investigations did not reveal any evidence of opportunistic infections, malignancy or any AIDS-defining illness with the donor GFR was 118.3 ml/min. He did not receive induction therapy and was started on tacrolimus 5 mg BD and mycophenolate sodium 360 mg 2 BD. Steroid was added after the transplantation with tapering doses till 20 mg OD. The recipient achieved good diuresis postoperatively and his serum creatinine came down to 0.9 mg% on the third postoperative day. HIV RNA was undetectable and CD4 cell count was 418/cmm on the seventh postoperative day. He was discharged on the tenth post operative day with tacrolimus 5 mg PO BD and TAC level of 8.6 ng/ml, with serum creatinine of 0.9 mg/dl.

In the last follow-up at 1 year he had serum creatinine value of 1.1 mg /dl with TAC level 9.1ng/ml with the dose of 0.12 mg/kg (3 mg PO BD).

Discussion

All the four patients had stable HIV disease on HAART regimen with undetectable HIV RNA and CD4 cell count of ≥200/cmm before transplantation. In the solid organ transplant in HIV: multi-site study (2009), inclusion criteria included CD4 cell count ≥200/cmm at any time in the 16 weeks before transplantation and no change in the antiretroviral regimen for three months before transplantation; therefore renal transplantation can be done in an ESRD patient with HIV if CD4cell count is ≥200/cmm at the time of transplant and if there is no change of HAART in the last three months, suggesting adequate antiretroviral therapy for the last three months as were our second and third cases.[11] All four of our patients satisfied the other existing guidelines recommended for HIV patients for renal transplantation and were adequately immunized.[11-13]

In the first case the most probable cause of ESRD was HIVAN. In the second, third and fourth cases, HIV was an association with the most probable causes of ESRD being hypertensive nephrosclerosis, analgesic nephropathy and chronic glomerulonephritis respectively.

Out of four patients three patients were on tacrolimus and one was on cyclosporine while all received MMF and steroid. Basiliximab induction was done in the first three cases like Drexel University, Philadelphia where 40 HIV patients received kidney transplantation using induction with basiliximab.[2] Organ recipients with HIV can mount an alloimmune response and renal transplant recipients with HIV have a higher rejection rate than their counterparts without HIV. For this reason, induction therapy with interleukin 2 receptor inhibitor was introduced.[2,13] The protease inhibitors besides being substrates of CYP (cytochrome P), also act as inhibitors of P-gp, a transmembrane glycoprotein that functions as an energy-dependent efflux pump for a wide variety of structurally unrelated compounds.[2,14,15] Also, MRP1 (multi-drug resistant protein-1) and possibly MRP2 (multi-drug resistant protein-2) are known to be involved in the disposition of PI.[14,15] The calcineurin inhibitor cyclosporine and tacrolimus are also metabolized by liver by CYP3A4 and cyclosporine is also substrate for P-gp and MRP2 transporters thus, when used concurrently with PI the drug levels of calcineurin inhibitor may be increased.[16,17] Usually the dose of CNI is reduced to 85% when the patient is on protease inhibitors as these are very potent inhibitors of CYP3A4 which metabolizes the CNIs.[10,17,18] In our case even up to 8% of normal dose (92% dose reduction) of CsA was enough to keep the drug in the therapeutic levels when protease inhibitors were used as in the second case. On the other hand, nonnucleotide reverse transcriptase inhibitors (NNRTIs) are CYP3A4 inducers and require 25% higher doses of CNI.[10,18,19] In our cases the doses of tacrolimus had to be increased by 50% (1.5 times) when only NNRTI was used as in the third and fourth cases. When PIs and NNRTIs are used together, the dose of CNI is reduced to about 50%.[10,18,19] In our cases even up to 2.5% of normal dose of tacrolimus (97.5% dose reduction) was enough to keep the drug at the therapeutic levels when combination of PIs and NNRTIs were used as in the first case. We could not encounter any acute rejection episodes in any of these patients in the early post operative period. The second patient had evidence of septicemia in the early post operative period and he improved after augmenting the antibiotics coverages.[20] All the patients needed drug monitoring in the immediate postoperative period and were discharged in satisfactory condition. During subsequent follow up second patient had steroid responsive rejection and third patient had steroid resistant rejection may be due to lack of proper follow up at his country which needed plasma exchange similar to an earlier report.[21] The longest follow-up was of 2 years and 6 months' duration and the patient had normal renal function with tacrolimus in the dose of 0.0065 mg/kg (0.5 mg) every fifth day.

To conclude, HIV-positive ESRD patients with stable disease should be given the benefit of kidney transplantation as patient and graft survival are reasonably good with good quality of life. The graft and patient survival rates are almost similar between HIV-positive and HIV-negative

renal allograft recipients.[22,23] There has been no evidence of significant HIV progression and no adverse effect of HIV on allograft function.[23,24]

Acknowledgment

We acknowledge the contribution of our transplant team including doctors, nurses and health workers.

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How to cite this article: Agarwal DK, Hota JK, Nag N, Mehta SN. Renal transplantation in HIV patients: A series of four cases. Indian J Nephrol 2012;22:139-42.

Source of Support: Nil, **Conflict of Interest:** No.