Living Related Donor Renal Transplant in Human Immunodeficiency Virus Infected Patient: Case Reports from Tertiary Care Hospital in Western India

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ABSTRACT

Renal transplantation (TX) in human immunodeficiency virus (HIV) infected patients with end stage renal disease (ESRD) is increasingly performed in developed countries in the era of antiretroviral therapy (ART). Management of HIV infected patients during and post-transplant is very complex and challenging due to drug interaction, infection risk and associated co-infections. We described our experience with living related donor renal TX in three HIV infected patients.

Key words: Human immunodeficiency virus, Renal transplant, Solid organ transplant in human immunodeficiency virus

INTRODUCTION

Introduction of antiretroviral therapy (ART) and use of effective opportunistic infection prophylaxis had transformed human immunodeficiency virus (HIV) in to a chronic manageable infective condition since late nineties. In the era of ART, malignancies (both HIV related and unrelated), chronic liver disease and end stage renal disease (ESRD) becomes important causes of morbidity and mortality.[1-3] The incidence of HIV-related renal disease has decreased but overall prevalence of renal disease continues to increase among patients with HIV, mainly due to drug toxicity, aging population with HIV, metabolic disorders and comorbidities.[4-6] Nearly 4-7% of HIV positive patients demonstrate ESRD.[8] Prevalence of ESRD in HIV infected patients in India is unknown. HIV patient with ESRD on maintenance hemodialysis (HD) has poor CD4 recovery on ART compared with those who received renal transplant.[9] Various retrospective analyses, case reports and small prospective studies data showed good patient and graft survival in HIV infected renal transplant patients.[8-10] Now a day more and more numbers of centers in Europe and USA are performing successful renal transplantation (TX) in HIV infected patients. However management of HIV infected patients during and post-transplant is very complex and challenging due to drug interaction, infection risk and associated co-infections. Co-ordination between transplant and HIV physician is the key for successful TX in HIV infected patients. Renal TX is deferred by many transplant centers in India despite regular HD being more expensive and many centers refuses HD in HIV infected subjects. We are describing living related donor TX in HIV infected patients in India.

CASE REPORTS

Case 1

A 45-year-old Kenyan male HIV infected patient received a renal transplant in January 2006. Patient had type 2 diabetes mellitus since 1997 and hypertension since 2000. ESRD was diagnosed in 2000. He was diagnosed to have HIV infection in 2002, treated with tenofovir 300mg + emtricitabine 200mg once a week and efavirenz 600mg daily and was on regular HD since then. He is on stable ART regimen with CD4 count 254 cells/cmm and plasma HIV RNA was <400 copies/ml before transplant. His serology for hepatitis C, syphilis and hepatitis B surface antigen were negative. Co-trimoxazole prophylaxis was given for 3 months post-transplant.
Dalal, et al.: Renal transplant in HIV

Case 2

A 52-year-old Tanzanian male HIV infected patient received a renal transplant in September 2010. Patient is non-diabetic, hypertensive and diagnosed as chronic kidney disease since 2005. His HIV infection was diagnosed in 1996 and present ART regimen was abacavir + lamivudine + atazanavir/ritonavir (abacavir 600mg/day, lamivudine 300mg, atazanavir300mg + ritonavir100mg daily). His atazanavir/ritonavir was changed to lopinavir/ritonavir before transplant. His CD4 count was 456 cells/cmm and plasma HIV RNA was <400 copies/ml before transplant. His serology for hepatitis C, syphilis and hepatitis B surface antigen were negative. Co-trimoxazole prophylaxis was given for 3 months post-transplant.

Case 3

A 24-year-old Nigerian female HIV infected patient received a renal transplant in May 2012. Patient was diagnosed as hypertension and ESRD in 2009 and was on regular HD since then. Her HIV was diagnosed in 2010 and her present ART regimen consisted of raltegravir + lopinavir/ritonavir (raltegravir 400mg bid, lopinavir/ritonavir 400/100mg bid). Her CD4 count was 226 cells/cmm and plasma HIV RNA was <150 copies/ml before transplant. Her serology for hepatitis B and C and syphilis were negative. She was on co-trimoxazole prophylaxis and continued during post-transplant follow up period.

All three patients received similar immunosuppressive therapy, i.e., induction with basiliximab followed by maintenance with tacrolimus, mycophenolate mofetil (MMF) and prednisolone. Tacrolimus dosage was adjusted according to protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor component of ART. Serum tacrolimus trough level was closely monitored and level was maintained between 7 and 12 ng/ml. None of the patients developed acute rejection or delayed graft function (DGF). All three patients maintained undetectable HIV RNA throughout follow up period. No change in ART was made during the follow-up period.

Donor’s characteristics are described in Table 1.

Post-transplant follow up data for all patients are shown in Table 2.

DISCUSSION

HIV was considered a contraindication to renal transplant in the past pre ART era. Survival of HIV positive ESRD patients improved in the mid to late 1990s, by year 2002, the death rate in HIV positive ESRD patients were comparable to diabetic ESRD patients of the same era.[11-13] British HIV Association published guideline for transplant in HIV infected patients.[14] All three of our patients were satisfying criteria for renal transplant according to BHIVA guideline, e.g., they were on stable ART regimens with CD4 count >200 cells/cmm and undetectable HIV RNA without any opportunistic infections. Various prospective studies as well as analysis of retrospective studies and case reports of HIV positive transplanted patients indicate that patient and graft survival rates are similar to those reported for patients without HIV, although allograft rejection (AR) rates are higher as compare to HIV negative individuals. Rates of acute rejection of renal transplants in patients with HIV range from 13% to 67%, such high rejection

| Table 1: Donor’s characteristics |
|----------------------------------|
| Parameters | Case 1 | Case 2 | Case 3 |
| Relation   | Brother | Brother | Father |
| Age (years)/sex | 38/male | 61/male | 58/male |
| HLA        | 3/6    | 0/6    | 3/6    |
| LCM (lysis) % | 2   | 2     | 70 (reduced to 5% after plasma exchange) |
| CMV IgG    | D+R+   | D+R+   | D+R+   |
| CMV IgM    | D+R+   | D+R+   | D+R+   |

HLA: Human leucocyte antigen; HLA a/b: A compatible locus out of b; CMV: Cytomegalovirus; LCM: Lymphocyte cross match

| Table 2: Post-transplant follow-up |
|-----------------------------------|
| Parameter                     | Case 1 | Case 2 | Case 3 |
| Day of discharge              | 13th   | 11th   | 10th   |
| Serum creatinine <1.5 mg%     | Day 3  | Day 2  | Day 2  |
| Post Tx issues                | Right basal atelectasis, oral thrush | Urinary tract infection | Nil |
| Rejection                     | No     | No     | No     |
| Follow-up                     | 5 years | 3 years | 1.6 year |
| Outcome                       | Serum creatinine 1.1 mg% | Serum creatinine 1.1 mg% | Serum creatinine 1.3 mg% |
| Immunosuppressive therapy     | Died on May 2011 due to CAP | Alive | Alive |
| HIV RNA 6 months post-transplant | Prednisolone 5mg, MMF 19 and tacrolimus 3mg BID | <400 copies/ml | <400 copies/ml |
|                                 | <400 copies/ml | <400 copies/ml | <400 copies/ml |

CAP: Community acquired pneumonia; BID: Twice daily; MMF: Mycophenolate mofetil; HIV: Human immunodeficiency virus; RNA: Ribonucleic acid
rates may be due to immunedysregulation or inadequate immunosuppression in the earlier period.[15-21] UK study reported 44% of patients' AR rate in 1st year. They didn't find an association of any donor's or recipient's parameter for AR. Use of anti CD25 antibody or basiliximab for induction has reduced acute rejection rate in HIV infected patient in 2 different studies.[18,20] In all our patients basiliximab was used for induction followed by tacrolimus, MMF and prednisolone for maintenance, might have prevented acute graft rejection. Co-administration of ART and immunosuppressive therapy is complicated by drug-drug interaction due to agents that induce or inhibit the P-glycoprotein 1 flux transporters and cytochrome P450 3A (CYP3A4) metabolizing enzymes found in the gut and liver. These interactions can lead to unexpected increases or decreases in drug plasma levels of tacrolimus and result in toxic side effects, organ rejection. Ritonavir component of PIs is potent inhibitors of both P-glycoprotein 1 and CYP3A4 activity, resulting in increased levels of circulating cyclosporine, while efavirenz induce CYP3A4 activity and decrease plasma drug levels.[22-24] In two of our patients receiving PI based ART and dose of tacrolimus was reduced to 0.5mg once a week and 0.5mg once every 9th day (adjusted according to tacrolimus trough level), whereas in one patient receiving efavirenz based ART received standard dose of tacrolimus.

Study from Spain by Mazuecos et al. showed that HIV-infected recipients developed more DGF (52% vs. 21%, $P < 0.001$) and 1 and 3-year graft survival was 91.6% and 86.2% in HIV-infected patients and 97.1% and 94.7% in HIV-negative patients ($P = 0.052$).[25] DGF is another frequent early complication in HIV-infected recipients that can affect graft survival. Spanish study suggests using agents like raltegravir in kidney transplant recipient patient to reduce the drug-drug interaction, which could improve outcomes by preventing DGF. In addition to these interactions of PIs with proton pump inhibitors and anesthetic agents like (midazolam, fentanyl) should be kept in mind.

Contrary to the conventional belief that immunosuppression may result in progression of HIV disease, risk of opportunistic infections was not found in studies and many immunosuppressive (MMF, cyclosporine, tacrolimus and sirolimus) have antiretroviral properties and synergy with abacavir.[26-28] Immunosuppressive therapy was well-tolerated and had no deleterious effect on HIV disease or any side-effects in our patients, which is consistently seen with other trials.

Study from UK described transient HIV viremia in four patients, mainly as viral load blips ($<200$ copies/ml), transient declines in CD4 cell counts in many patients and esophageal candidiasis and cutaneous Kaposi sarcoma in one each patients. Other non-opportunistic infectious complications requiring hospitalization were seen in 54% patients including urinary infection, pneumonia, cellulitis and herpes encephalitis.[21] In our case report, none of the patients developed new-onset diabetes, opportunistic or other serious infections, malignancy or evidence of HIV progression. Important concern about transplant in HIV could be infectious complications and their management; including HHV8, herpes group of viruses, malignancies, human papillomavirus related anorectal malignancies, management of chronic hepatitis B and C in post-transplant period.

CONCLUSION

Based on the above cases it can be concluded that renal transplant in HIV infected patients with well-controlled disease is possible. Combined team effort form HIV and infectious disease physician, transplant physician and transplant surgeon is crucial to success of transplant. Careful monitoring of drug dosages, side-effects, AR and adequate control of HIV disease are keys to long-term survival. Kidney TX in HIV-infected patients is a safe and effective treatment option for selected patients with ESRD.
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