CASE REPORT

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Renal transplantation in an HIV-2 positive recipient in Portugal

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ABSTRACT

The improvement of combined antiretroviral therapy regimens has made solid organ transplantation a therapeutic option for patients with human immunodeficiency virus (HIV) infection. Generally, HIV-2 infection presents a slower clinical progression and immunological degradation than HIV-1. HIV-2 infection treatment can be challenging when a complex immunosuppressive regimen is combined with antiretroviral therapy. The authors report the first case in Portugal of renal transplantation in an HIV-2 patient.

A 54-year-old man from Guinea-Bissau was diagnosed with HIV-2 infection on starting haemodialysis in Portugal in 1998. At diagnosis, HIV infection staging revealed undetectable plasma HIV-2 RNA and T-cell CD_4 counts of 808 cells/µl, with no need for combined antiretroviral therapy during follow-up.

The patient underwent renal transplantation from a deceased donor in March 2011. He developed delayed graft function and started therapy with methylprednisolone and thymoglobulin. The patient gradually recovered renal function and was discharged after two weeks with serum creatinine of 2.3 mg/dL.

The HIV-2 RNA levels remained undetectable, but T-cell CD_4 count decreased to less than 200 cells/µl and combined antiretroviral therapy with abacavir, lamivudine and raltegravir was started. Nine months after transplantation, the patient has a serum creatinine of 1.5 mg/dL and a nonreplicating HIV status.

Key-Words:
Antiretroviral therapy; HIV-2 infection; immunosuppressive therapy; kidney transplantation.

INTRODUCTION

Human immunodeficiency virus type 2 (HIV-2) was first recognised in 1985[1]. Infection with HIV-2 occurs mainly in West Africa but a considerable number of cases have been recognised in Europe, India and the United States[2]. The transmission routes are the same as those for HIV-1, namely sexual, blood-borne exposure (blood transfusion, shared needles) and vertical[3], but HIV-2 has a lower risk of contagion.

HIV-associated nephropathy (HIVAN) occurs in about 7% of patients with HIV-1 infection[4], but this complication has been only rarely reported in HIV-2 infected individuals[5]. Since the introduction of effective combined antiretroviral therapy (cART), promoting immunological recovery and replication suppression, the outcome of HIV patients has improved dramatically, and several studies show that the mortality rate for HIV end-stage renal disease (ESRD) patients is now similar to those without HIV infection. Given this significant improvement in HIV patients' morbidity and mortality, kidney

transplantation has been increasingly considered an alternative treatment for ESRD in this population[6].

CASE REPORT

A 54-year-old hypertensive man from Guinea-Bissau was transferred to Portugal in 1998 due to the need for renal replacement therapy. The presumed cause of ESRD was hypertensive nephropathy. HIV-2 infection was diagnosed when he started chronic haemodialysis in Portugal. During follow-up HIV-2 RNA plasma levels were persistently undetectable and TCD_4 remained › 200 cells/µl, with no need for cART. The patient underwent adequate dialysis, his nutritional status was favourable and no opportunistic infections occurred. He was considered a candidate for a deceased donor kidney and on 23 March 2011 underwent renal transplantation from a 67-year-old deceased donor (death from a cerebrovascular accident). Both the donor and the recipient had the same ABO and Rhesus blood type. The receptor had 4 HLA- mismatches (2 in B and 2 in DR) and a panel reactive antibody (PRA) of 40% with positive anti-MICA (MHC class I- related chain A) antibodies. Cold ischaemia time was 16 hours. There were no episodes of hypotension during or after the surgery. According to our protocol, tacrolimus (0.1-0.15mg/Kg) was given before the surgical procedure, and basiliximab (20mg), mycophenolate mofetil (1g) and methylprednisone (500mg) during surgery. In this case, due to PRA and MICA antibodies, intravenous immunoglobulin (2g/Kg) was used in continuous perfusion during the first 48 hours after the transplantation.

The patient developed severe postoperative oliguria. Doppler ultrasound showed no obstruction, but a high resistivity index (0.8). It was decided not to perform a graft biopsy since the patient developed symptomatic anaemia (7.4g/dL). Although two days after transplantation the patient had a TCD_4 count of 214 cells/µl, it was decided to suspend tacrolimus and to administer a three-day course of methylprednisolone (500mg/day) and a five-day course of thymoglobulin (1.25 mg/Kg/day). After thymoglobulin, HIV-2 RNA plasma levels remained undetectable (‹ 50 cp/ml), but absolute and percentage of TCD_4 count fell to 16 cells/µl (9%). In the week after the transplantation, antiretroviral therapy regimen with two nucleoside reverse transcriptase inhibitors – lamivudine, abacavir – and an integrase inhibitor, raltegravir, were started, with good tolerance.

The patient needed three dialysis sessions, but after one week there was a gradual improvement of urinary output and renal function. Tacrolimus (0.1-0.15 mg/Kg/day) was introduced on the seventh postoperative day. The patient was discharged after two weeks with an improving graft function (serum creatinine of 2.3 mg/dL). Nine months posttransplant, graft function is stable with a serum creatinine of 1.5 mg/dL. Patient is clinically stable and asymptomatic, showing good immunological recovery (TCD_4=294 cells/µl) and undetectable HIV-2 viral load.

DISCUSSION

The burden of renal disease in HIV patients living in Africa is adversely influenced by inadequate socioeconomic and health care infrastructures[7]. The absence of renal replacement therapy in Guinea-Bissau led to the life-saving transfer of the patient to Portugal.

This patient presented with HIV-2 infection since 1998, with long-term nonprogression behaviour, supported by the slow immunological degradation and absence of opportunistic or AIDS-related events. In March 2011, the patient successfully underwent deceased donor kidney transplant. After the surgery the patient presented delayed graft function (DGF) which was probably due to a combination of several factors, namely, expanded criteria donor (ECD) [8] and a cold ischaemia time of 16 hours. However, he also had a PRA of 40% with positive MICA antibodies, known risk factors for acute rejection. One study of the United Network for Organ Sharing database demonstrated a lower death-censored graft survival at one year in patients with HIV-1 and renal transplants from deceased donors older than 50 years of age and with a cold ischaemia time longer than 16 hours[9]. ECD kidneys accounts for about 15% of deceased donor kidneys in the USA and has statistically an estimated graft survival at two years of about 80% compared with a two-year graft survival of 88% in a standard criteria kidney[10]. In some studies[11,12], a trend to higher rejection rates was noted in HIV-1 infected patients. The reason for such rates is unclear,

but dysregulation of the immune system or insufficient immunosuppression are two possible causes[11]. Although graft biopsy was not performed, the authors consider that acute tubular necrosis best explains the cause of the initial oliguria. The transplantation team decided to avoid calcineurin inhibitors (CNI) during the first week and initiate thymoglobulin, in order to avoid nephrotoxicity and achieve adequate immunosuppression.

In the last few years, several retrospective and prospective small studies have shown encouraging results, suggesting that renal transplantation is feasible in adequately selected HIV-infected patients. The results of the largest prospective, nonrandomised trial of kidney transplantation in HIV-1 infected patients have recently been published[12]. The patient and graft survival rates at three years were 88.2 and 73.7% respectively, which were between the reported rates for older-kidney transplant recipients and for all kidney-transplant recipients[13].

The first three months after transplantation remain the most critical period for development of significant complications, and one of the most concerning issues in our patient was the need to use immunosuppressive drugs with higher risk of opportunistic infections and interactions with cART. The administration of a complex immunosuppressive regimen in combination with antiretroviral therapy poses a major challenge since drug interactions resulting in altered exposure to immunosuppressants may be associated with rejection[13]. Contemporary treatment of HIV infection involves the combination of at least three fully active drugs from the currently available classes of antiretroviral medications: nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors and integrase inhibitors. The current antiretroviral regimens considered for *naïve* patients are based on a combination of two nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor, a nonnucleoside reverse transcriptase inhibitor or an integrase inhibitor[14]. Antiretroviral medications are generally used in normal doses and adjusted to the improved kidney function that occurs after the transplantation.

In comparison to HIV-1, more patients with HIV-2 infection present as long-term nonprogressors or slow progressors. Although this could be used to argue for a later TCD_4-driven initiation of cART, it has been demonstrated that immunological recovery on therapy could be slower in HIV-2 than HIV-1 patients[15] and excessive delay in initiating cART may carry long-term negative immunological consequences[16]. Current therapeutic HIV guidelines recommend the initiation of cART in individuals presenting with less than 350 TCD_4 cells/µl or with concurrent morbidities, namely, HIVAN.

Antiretroviral susceptibility can differ significantly between HIV-1 and HIV-2, as HIV-2 is intrinsically resistant to two of the major classes of antiretroviral drugs: NNRTIs and fusion inhibitors. Considering the class of protease inhibitors, indinavir, saquinavir, lopinavir and darunavir are the most efficient molecules in HIV-2 suppression[17]. This patient started antiretroviral therapy regimen based on a triple combination: two NRTI (abacavir and lamivudine), since he presented anaemia and moderate elevated serum creatinine levels, something that would contraindicate the use of zidovudine or tenofovir respectively; and an integrase inhibitor (raltegravir) trying to minimise drug interactions between protease inhibitors and CNI which are also metabolised by the CYP450 pathway[13]. Additionally, abacavir and raltegravir have the advantage of having low urinary excretion, and therefore, no requirement for dose adjustment. Mycophenolate mofetil has inhibitory effects on HIV and is synergistic with abacavir[18]. Lamivudine has only few interactions with micophenolate mofetil.

There are no current recommendations about how to treat rejection episodes in HIV-positive recipients, but these patients are more likely to receive induction therapy[19]. The use of antilymphocyte polyclonal antibodies is controversial, and many authors recommend restricting this therapy for patients at very high immunological risk of rejection[9,20]. Thymoglobulin, an agent frequently used to manage acute rejection, may be associated with marked TCD_4 depletion[6]. Several studies have reported significant decreases in TCD_4 counts in HIV-infected recipients related to the use of thymoglobulin[9,12]. In a study published by Stock *et al.*, the median change in the TCD_4 count from baseline to 1 year was greater in patients who received induction therapy with thymoglobulin than those who did not (-239 *versus* -135 cells per mm^3)[12]. However, these changes were transient and the median change in TCD_4+ count from baseline to three years was not significantly

different between these groups (-57 and -52 cells per mm^3, respectively). Another study[9] also showed that there was no increased risk of opportunistic infections or progression to AIDS or death related to induction therapy. Consistent with this findings, after polyclonal therapy TCD_4 count fell to 16 cells/µl in our recipient, but there were no AIDS-defining diseases or opportunistic infections and the patient experienced immunological recover during follow-up (TCD_4=294 cells/µl).

Clinical trials of cART in HIV-2 are scarce compared the ones available to HIV-1, possibly related to low prevalence and geographic distribution constraints[16]. Until there is better evidence from randomised controlled trials, judgement of what constitutes good care in HIV-2 management must therefore rely on data from small cohort studies and case series, theoretical assertions and parallels with HIV-1 therapeutics. The potential benefits of kidney transplantation in HIV-2 patients must be confirmed by further studies before recommendations can be made for clinical practice.

Conflict of interest statement. None declared.

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