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Renal transplant in human immunodeficiency virus positive dialysis patients; report of four cases in French-speaking sub-Saharan Africa and review of literature

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Abstract

Quality of life and life span have considerably increased in human immunodeficiency virus (HIV) patients over the past years owing to the highly effective antiretroviral therapy. Consequently, the number of patients with end-stage renal disease (ESRD) has increased in dialysis centers. Several teams in the United States as well as in Europe have therefore proposed renal transplantation to this group of patients with encouraging results. From March 2015 to February 2016, four kidney transplantations have been conducted in the very first kidney transplantation program ever in French speaking black Africa. Three male and one female with a mean age of 50.75 years have been transplanted. One of them was HIV-2 positive. Before kidney transplantation, patients have exhibited diverse highly active antiretroviral therapy (HAART) regimen. They all have undetectable viremia and the mean value of the CD4 count was 454.5 cells/μL. Raltegravir, an integrase inhibitor, has systematically been added to the baseline HAART therapy at least 30 days before transplantation. Immunosuppression comprised basiliximab as induction therapy, tacrolimus, sodium mycophenolate and steroids. After a mean time of six months, all the patients are alive with a mean serum creatinine of 1.425±0.263mg/dl, and a mean proteinuria of 0.55±0.29 g/d. We present these results in full, and discuss them according to data retrieved from the literature. The conditions of access of human immunodeficiency virus positive patients to renal transplantation, the immunosuppression and the antiretroviral regimen, graft and patient survival have all been discussed accordingly.

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Introduction

End-stage renal disease (ERSD) is a major complication of human immunodeficiency virus (HIV) infection. Quality of life and life span have considerably increased over the past years in HIV patients in general and those with ESRD treated with dialysis owing to the highly effective antiretroviral therapy (1). As a result, renal transplantation has also been proposed to HIV positive patients with ESRD, while the first results obtained in this area were satisfactory. In a US collaborative study of Stock et al (2) listing HIV positive kidney transplant recipients in the United States from 2003 to 2009, 150 patients had been transplanted. The mean survival of the patient and the graft at 1 and 3 years were 94.6 and 88.2 and 90.4% and 73.7% respectively, comparable to that obtained in the general population.

Key point

The survival of the graft in the transplanted human immunodeficiency virus (HIV)-positive patient depends on at least three factors; the incidence of acute rejection known to be high, the recurrence of the virus on graft whether histological or clinical and the renal toxicity of the antiretrovirals in particular by tenofovir.

It is in this context that we undertook for the first time in French-speaking sub-Saharan Africa where the prevalence of HIV infection is high in dialysis patients, to conduct kidney transplantation to this category of patients. In this study, we first reported the results of patients who benefited from this treatment.

Subsequently, a discussion was made to assess relevance of our prescriptions in comparison with that of the literature regarding to the following items; conditions of graft access, immunosuppression protocol, antiretroviral protocol, graft and patients' survival. Therefore, local guidelines to manage HIV dialyzed patients candidates prior to kidney transplantation could be elaborated.

Case Presentation

From March 2015 to February 2016, four kidney transplantations have been performed in our service of nephrology. The characteristics of the four transplanted HIV patients are presented in Table 1. Three male and one female with a mean age of 50.75 years have been transplanted. One of them was HIV-2 positive. None of our patients had a history of opportunist disease not recommended in transplantation. Before kidney transplantation, patients have exhibited diverse highly active antiretroviral therapy (HAART) regimen for the control of HIV infection. They all have undetectable viremia and the mean value of the CD4 count was 454.5±319.39 cells/µL. Raltegravir, an integrase inhibitor, at the dose of 200mg/day has systematically been added to the baseline HAART therapy at least 30 days before transplantation. All the living kidney donors were related to the recipients and their mean age was 46.25 years (41-58). Epstein-Barr virus (EBV) and cytomegalovirus (CMV) serology tests were positive in IgG in all the donors and recipients. Recipients had all three HLA mismatch with their respective donors. Immunosuppression comprised basiliximab as induction therapy except patient number two who did not receive any treatment for induction. Maintenance therapy was steroids, sodium mycophenolateand tacrolimus started 15 day before transplantationin the patient number 2 who did not receive any treatment for induction and 10 days before transplantation in patient number 4 in order to adapt the residual levels in relation to the interaction with the anti-proteases (Lopinavir/ritonavir).

The postoperative history was simple in patient number 1 and patient number 2, with immediate resumption of diuresis and renal function. In the 2 others, there was a delay in the resumption of diuresis and renal function with the need for transient dialysis in patient No. 3. This delay was secondary to amalposition of the urinary catheter inpatient No. 3 and to a severe tacrolimus toxicity (trough level 40 ng/L in patient No. 4.

After a mean time of 6 months, all the patients are alive with a mean serum creatinine of 1.425±0.263 mg/dL and a mean proteinuria of 0.55±0.29 g/d.

Discussion

Conditions required for HIV dialyzed patients before they could pretend to kidney transplantation

The conditions of access to the renal transplant of HIV positive subjects with an ESRD are well known: absence of history of opportunistic disorders such as progressive multifocal leukoencephalopathy, chronic intestinal cryptosporidiosis, central nervous system primary lymphoma, visceral Kaposi sarcoma, an average CD4 value of >200 cells/µL, and of course an undetectable plasma viral RNA (3,4). All of these conditions have been respected in our patients. But the length of period during which the virus must remain undetectable to prompt surgery is not well delineated, although three months of such a period is generally accepted. Since we add on a systematic basis immediate before surgery raltegravir to our initial antiretroviral protocol that already leads an undetectable viremia, we wonder whether a solely month could not be appropriate. In addition, most immunosuppressants having inhibitory effects on the virus (5). This supports, the idea that this delay can be further reduced. It will nevertheless be necessary to confirm, one month before starting the transplant, the undetectability of the virus. Therefore the deadline of one month could be proposed.

Antiretroviral protocol prior to transplant

The ideal antiretroviral drug for transplant (6) should simultaneously suppress viral replication and have minimal toxicity and interaction with immunosuppressive drugs. The patient No 4 showed renal toxicity in relation

Table 1. Characteristics of the 4 transplanted HIV Patients

Patients	Number 1	Number 2	Number 3	Number 4
Gender	Female	Male	Male	Male
Age (y)	35	63	52	53
Type of HIV	HIV 1	HIV 2	HIV 1	HIV 1
Antiretroviralregimen	Tenofovir, Lamivudine, Efavirenz	Emtricitabine, Tenofovir	Emtricitabine, Efavirenz	Lamivudine, Tenofovir, Lopinavir/Ritonavir
CD4 before transplant (cel/mm^3)	917	400	305	196
Associated comorbidities	None	Hypertension, Type 2 Diabetes Abdominal obesity, Coronary artery disease	Hypertension	Hypertension
Serum creatinine (mg/dL) at 6 months after transplant	1.8	1.2	1.3	1.4
Proteinuria (g/d) at 6 months after transplant	0.77	0.54	0.23	0.66

to an overdose of tacrolimus at the very point that he had a delayed recovery of graft function. Resumption of graft function occurred only after two weeks of interruption of anti-proteases (lopinavir/ritonavir). The non-nucleoside analogues determine a decrease in residual levels (efavirenz, nevirapine), and anti-proteases, an increase in residual levels of anti-calcineurins. Inhibitors of integrases (raltegravir, dolutegravir), fusion inhibitors (enfuvirtide), inhibitors of the cell-entry co-receptor in the cell (CXCR5) (maraviroc), nucleoside analogues of reverse transcriptase interaction with anti-calcineurins have no interaction with anti-calcineurins. There is also no interaction between these antiretrovirals and mycophenolate. Integrase inhibitors, particularly dolutegravir (second-generation integrase inhibitors) are the antiretrovirals of choice, especially since they offer effective and robust suppression of the virus and exhibit a high barrier of resistance. This explains the systematic association of these drugs with the basic antiretroviral regimen of our subjects. Therefore, the dose adjustments of anti-calcineurins with regard to the potential interactions with the antiretrovirals (ARVs) used in the basic protocol are facilitated because any possibility of viral escape is attenuated by the administration of integrase inhibitors. The ideal antiretroviral drug should also have no impact on graft function and do not require dose adjustment. Only nucleoside analogues except abacavir recommend dose adjustment according to the renal graft function. Dolutegravir may require dose adjustment for renal clearances below 30 ml/min.

Immunosuppressive protocol in HIV positive renal transplant recipients

Immunosuppressant drugs have, for the most part, inhibitory properties of viral replication (5) and these drugs are not a source of concern in terms of viral resurgence linked to their use. Most studies have reported a high incidence of acute rejection in HIV-positive transplant patients. Indeed, in a study by Stock et al (2), the acute rejection rate reported was 31% at one year and 41% at 3 years. In another study in the United Kingdom (7) comprising 35 HIV patients in whom 74% of them were black and presenting an optimal control of their viremia, the rate acute rejection was 48% at 1 year. Consequently, it appears indispensable in such subjects to propose a strong immunosuppressive protocol necessarily comprising an induction drug.

The anti-IL2 receptors induction therapy of being more efficient as compared to anti-lymphocyte sera, has been reported in several studies (2,8). The superiority of tacrolimus to cyclosporine in terms of prevention of rejection is also well established. In another study by Gathogo et al (9), the incidence of acute rejection was 21% in tacrolimus group as compared to 58% in the cyclosporine group. This explains why the immunosuppressive protocol used in our transplant patients included mostly an induction therapy including the anti-IL2 receptor and a tacrolimus-based maintenance therapy, except for patient No. 2. The latter was carrying a HIV type 2 strain. As few HIV type 2 patients have been transplanted regarding the literature, this attitude of not being aggressive is more dictated by cautious than particularly based on serious evidence. Indeed, one paper has suggested that induction therapy in such a patient was likely to prompt fatal post- operative complications (10). However, tacrolimus was started fifteen days before the transplantation as a "surrogate" induction therapy in a view to downplay any acute rejection without being too deleterious.

Graft survival in HIV-positive renal transplant recipients

Short-term renal survival in the HIV-positive graft compared with HIV-negative subjects is comparable to that of the general population ranging from 90.4% (2) to 100% at 1 year (11), and from 73.7% (2) to 81% (11) at three years. On the other hand, medium-term survival appears to be lower than that of the general population. Indeed, in a study by Locke et al (12) comparing the survival of HIV-positive grafts with that of HIV-negative subjects in a ratio of 1/10, the graft survival at 5-year was 69.2% versus 75.3% and that of 10 years was 49.8% versus 54.4%.

The survival of the graft in the transplanted HIV-positive patient depends on at least three factors; the incidence of acute rejection known to be high (7,8), the recurrence of the virus on graft whether histological (8) or clinical (13) and the renal toxicity of antiretrovirals in particular by tenofovir (14). The renal toxicity of tenofovir is complex and not yet fully elucidated. It is believed that the accumulation of tenofovir in the tubular cells leading to intracellular mitochondrial toxicity (14). In practice, any protocol involving tenofovir prior to transplant is not modified. But if after renal transplantation tenofovir renal toxicity is suspected, this could prompt to a switch for batcaver. Moreover, the existence of an unsatisfactory graft function whatever the cause may also lead to such an adjustment.

Survival of HIV-positive renal transplant recipients

The survival of the HIV-positive renal transplant patients is comparable to that of the general population. In the study by Stock et al (2), the survival of the HIV-positive renal transplant patients in 1 and 3 years were 94.6% and 88.2% respectively. However, survival in HIV-2 transplanted patients seems more controversial. Few studies were devoted to transplantation in HIV- 2 patients. These studies were related to a few clinical cases and death from severe post-operative opportunistic infections have been reported (10). It is for this reason that patient No2, who is elderly, has not been inducted to minimize the depth of his immunosuppression and thus prevent the emergence of such opportunistic infections.

For the time being, all of our patients are alive and no life-threatening complications have so far been noted after an average follow-up of about six months of transplant.

Conclusion

As a prelude to the renal transplant of HIV positive subjects, there are access conditions to be respected. The antiretroviral protocol should be based on the administration of anti-integrases. Immunosuppression should be potent to minimize the risk of rejection. Graft survival is threatened by high prevalence of rejection, the possibility of recurrence of HIV on the graft and the toxicity of some antiretrovirals. The survival of the patient is threatened by infections, especially since this subject is induced by anti-lymphocytic sera and is a carrier of HIV type 2. In any case, the results of the kidney transplant from living donors of HIV positive subjects are satisfactory, provided that these have been carefully selected. Following transplantation, these patients should be monitored closely by the transplant team and infectious disease specialists for optimal management.

Authors' contribution

KCAN was the patients' treating physician and supervised the manuscript preparation. DAL, PAC and KCAN coordinated information's collection on patients and wrote the manuscript. KAT collaborated in the management of HIV disease in patients. MT and MCG collaborated in the management of patients after transplantation. All authors have read and signed the final manuscript.

Conflicts of interest

The authors declare no conflict of interest

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. All patients gave informed consent regarding these case reports.

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