Treatment of ESKD in Acquired Immunodeficiency Syndrome

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ABSTRACT

The prognosis of human immunodeficiency virus (HIV) infection has improved in recent years with the introduction of antiretroviral treatment. While the frequency of AIDS defining events has decreased as a cause of death, mortality from non AID Srelated events including end stage kidney[l] disease has increased[l]. Diseases, unrelated to HIV directly, including immune complex and hepatitis C associated glomerulonephritis, diabetes mellitus, polycystic kidneys and obstructive nephropathy may be encountered. However, HIV-associated nephropathy (HIVAN) is the commonest cause of End stage Kidney Disease (ESKD) in HIV-infected patients[2], and is the third commonest cause of ESKD in black patients in the USA[2]. Presence of HIV infection used to be viewed as a contraindication to transplantation for multiple reasons : concerns for exacerbation of an already immunocompromised state by administration of additional immunosuppressants; the use of a limited supply of donor organs with unknown long-term outcomes; and, the risk of viral transmission to the surgical and medical staff[3]. The main issues in posttransplant period are pharmacokinetic interactions between anti-retrovirals and immunosuppressants, a high rate of acute rejection, the management of hepatitis C virus coinfection, and the high cardiovascular risk after transplantation1.

Keywords : HIV-associated nephropathy, End stage kidney disease.

Introduction :

A few years ago, human immunodeficiency virus (HIV) infection was an absolute contraindication for solid organ transplantation. Renal diseases directly related to HIV infection include HIV-associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy. Although the widespread use of highly active Anti-retroviral therapy (HAART) has decreased the incidence of HIV-related renal disease[4], the overall prevalence of renal disease continues to increase among patients with HIV[1]. The most aggressive HIV-related renal disease is HIVAN, which occurs in approximately 10% of patients with HIV[5]. HIVAN is a collapsing form of focal sclerosing glomerulosclerosis (FSGS) with associated tubular microcysts and interstitial inflammation. It presents with significant proteinuria and can rapidly progress towards the ESKD[6]. Hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation may all be considered as therapeutic options when managing ESKD. Studies have shown that the outcomes are similar in HIV-positive ESKD patients whether they have been treated with HD or PD[7].

Since the early years of the AIDS epidemic, the medical and scientific community has been aware of various renal diseases that develop in patients with HIV[8]. With the advent of and access to HAART for patients of HIV there has been a paradigm shift in the management and outcome of HIV patients[9]. Opportunistic infections are now replaced by chronic diseases like chronic kidney disease, chronic liver disease and malignancies etc. The overall prevalence of renal disease continues to increase among patients with HIV[1]. Potential explanations include inadequate HAART, drug toxicity, increased survival rates leading to an increase in the proportion of elderly patients, and chronic viral co-infections (i.e. viral hepatitis)[10].

Classic HIVAN presents histollogically as collapsing focal segmental glomerulosclerosis and clinically as severe proteinuria, renal failure, and rapid progression to ESKD1. It is most common cause of ESRD in untreated HIV infected black individuals who develop renal disease1. Although the etiology of HIVAN is not completely

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understood, direct infection of HIV-1 of renal epithelial cells is associated with the onset of the disease[3]. HIVAN is currently the third most common etiology of ESKD among African Americans aged 20-64 years after diabetes and hypertension[3]. Co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is also common, and affected patients are at risk of developing viral hepatitis- associated glomerulonephritis.

Acute renal failure can be produced by toxic effects of HAART (eg. Tenofovir, indinavir) or nephrotoxic antimicrobial agents used in treatment of opportunistic infections (eg. Aminoglycosides, amphotericin, foscarnet, trimethoprim-sulfamethoxazole, acyclovir)[1]. Some drugs routinely administered to patients with HIV (i.e. indinavir, atazanavir, sulfadiazine, ciprofloxacin and intravenous aciclovir) can also precipitate in the renal tubular lumen, thereby causing renal failure[10]. Tenofovir and adefovir, which are HAART medications also used in the management of lamivudine-resistant HBV, are potentially nephrotoxic agents. Calcineurin inhibitors (CNIs) used in immunosuppressive therapy, such as ciclosporin and tacrolimus, are nephrotoxic, both directly and, by causing vasoconstriction and increasing blood pressure, indirectly[3]. The toxicity of CNIs can be exacerbated by inhibition of the cytochrome P450 system by other HAART agents such as protease inhibitors (PIs) and agents commonly used for fungal prophylaxis and treatment, such as fluconazole[3]. In addition, some HAART agents can induce insulin resistance, diabetes mellitus, hypertension and hyperlipidemia[11], all of which are major risk factors for ESKD in the US.

Notably, however, survival of patients on dialysis who have HIV has improved in patients whose disease is under control on HAART (e.g., those with high CD4+ T-cell counts) and is now similar to that of patients who are not infected with HIV[12]. Kidney transplantation in patients without HIV is known to result in better survival rates than continuing dialysis[13]. After introducing the new antiretroviral therapy mortality rates of HIV-infected and HIV-seronegative patients in dialysis program became equal. Moreover, the survival rate for HIV-infected patients increased from 56% to 74% in the period of only a decade[14].

In the solid organ transplant in HIV : multi-site study (2009), inclusion criteria included CD4 cell count $\geq$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 ESKD patient with HIV if CD4 cell count is $\geq$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 last three months[15]. In the NIH multicenter prospective trial, opportunistic infections which remain a contraindication for solid organ transplantation in general include chronic cryptosporidiosis, progressive multifocal leukoencephalopathy, and systemic Kaposi's sarcoma, whereas a history of tissue-invasive cytomegalovirus infection is no longer considered a contraindication given the availability of effective therapies[3]. A history of opportunistic infections is no longer considered an automatic exclusion criterion in most European countries and North America, as long as the opportunistic infections can be treated successfully in immunosuppressed patients[3]. Approximately 30% of patients with HIV have hepatitis C co-infection[3] and approximately 10% hepatitis B co-infection[16]. In patients with either co-infection, the extent of liver damage needs to be assessed before consideration for kidney transplantation.

In 2010 Stock and colleagues undertook a prospective study of 150 transplanted HIV-infected patients who had CD4+ T-cell counts of at least 200 / mm^3 and undetectable plasma HIV type 1 RNA levels while being treated with a stable antiretroviral regimen. Patient survival rates at 1 year and 3 years were 94.6 ± 2.0% and 88.2 ± 3.8%. Mean graft survival rates were 90.4% and 73.7%. These rates were very similar to those of older kidney transplant recipients ($\geq$65 years) and those reported for all kidney transplant recipients. The rejection rates in the HIV-infected recipients were unexpectedly

higher when compared with recipients who did not have HIV infection. Patient survival rates at 1 year and 3 years were 94.6 ± 2.0% and 88.2 ± 3.8%. Mean graft survival rates were 90.4% and 73.7%. These rates were very similar to those of older kidney transplant recipients (≥65 years) and those reported for all kidney transplant recipients. The rejection rates in the HIV-infected recipients were unexpectedly higher when compared with recipients who did not have HIV infection[17].

Organ recipients with HIV can mount an alloimmune response[18] and renal transplant recipients with HIV have a higher rejection rate than their counterparts without HIV[18]. For this reason, induction therapy with interleukin 2 receptor inhibitor has been introduced[19]. Nonetheless, most transplantation centers are reluctant to use lymphocyte-depleting agents for induction, as these agents severely deplete CD4+ T cells for several months. Nonetheless, these agents have successfully reversed aggressive rejection in several patients[18]. Many agents currently used for post-transplantation maintenance immunosuppression (e.g. MMF, ciclosporin, tacrolimus, and sirolimus) have anti-retroviral properties. MMF virostatic action is thought to result from the depletion it causes of guanoside nucleosides, which are necessary for the virus lifecycle[20]. Ciclosporin and tacrolimus have well-documented antiretroviral effects through selective inhibition of infected cell growth[21]. These agents interfere with HIV pathogenic protein functions, which ultimately results in the reduction of virus formation[22]. Ciclosporin and tacrolimus can however cause glucose intolerance, which can be exacerbated by administration of sirolimus. Since many patients with renal allografts, particularly those with HIV, experience some degree of renal insufficiency, sirolimus, an inhibitor of the mammalian target of rapamycin and an anti-proliferative agent, has been considered as an alternative to CNI. 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[23]. 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[24]. On the other hand, NNRTIs are CYP3A4 inducers and require 25% higher doses of CNI[24]. Sirolimus also exerts some antiretroviral activity through suppression of T-cell activation, suppression of professional antigen presenting cell function, and disruption of infective virion replication[25]. Sirolimus also decreases the expression of C-C chemokine receptor type 5 on monocytes and lymphocytes, thus potentially preventing the HIV virus from entering these cells and replicating[26].

Conclusion :

Kidney transplantation may be considered as one of treatment options in carefully selected patients with satisfactory controlled HIV infection. The graft and patient survival rates are almost similar between HIV positive and HIV negative renal allograft recipients. Immunosuppressive therapy does not have a negative impact on the course of HIV infection, with no evidence of progression to AIDS and no further OIs and neoplasms.

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