Transplantation in the times of HIV infection: Thinking outside the box

Muller E, Barday Z, Mendelson M, Kahn D. (Transplant Unit, Department of Surgery; Division of Nephrology, Department of Medicine; Division of Infectious Diseases and HIV Medicine, Department of Medicine; and the Department of Surgery, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa.) HIV-positive-to-HIV-positive kidney transplantation—results at 3 to 5 years. *N Engl J Med* 2015;**372:** 613–20.

SUMMARY

This paper describes the long-term results of kidney transplantation, giving kidneys from HIV-positive deceased donors to carefully selected HIV-positive recipients in Groote Schuur Hospital, Cape Town, South Africa. This was done to find a solution to the needs of renal replacement therapy of HIV-positive individuals with end-stage kidney failure in South Africa. These patients were considered not suitable for kidney transplantation and, therefore, not accepted in dialysis programmes that preferentially accepted candidates who would eventually receive a kidney.

The project was started in 2008. After encouraging results (100% graft survival and patient survival at 1 year),[1] and with the approval of their hospital ethics committee, the authors extended this as a prospective study. The recipients were required to be on antiretoviral therapy (ART), and had a CD4 T-cell count of 200 per cmm or higher and an undetectable plasma HIV RNA at the time of transplantation. All donor kidneys were biopsied at the time of implantation. The recipients received depleting induction with antithymocyte globulin (ATG), and triple immunosuppression with tacrolimus, mycophenolate mofetil and prednisolone. Since the study was funded by Sanofi who market ATG, drugs were purchased at full cost to avoid any conflict of interest. After the transplant, patients were switched to a protease inhibitor-based regimen to ensure suppression of potential donor-virus replication. Since ritonavir is an inhibitor of cytochrome P450 system, a reduction in the dose of tacrolimus was needed to as low as 0.5 mg once every 7–10 days. However, concerns about nephrotoxicity of calcineurine inhibitors (CNI) led to abandoning this approach and return to non-protease inhibitor (PI)-based highly active anti-retroviral therapy (HAART). All patients received lifelong cotrimoxazole and isoniazid prophylaxis and valgancyclovir for 3 months. The CD4 T-cell count and plasma HIV RNA viral load were monitored every 6 months.

The paper describes the result of 27 people who received a transplant between September 2008 and February 2014. The donors were young (mean age 30 years). The patient survival rates were 84% (95% CI 62–94) at 1 year and 3 years and 74% (95% CI 45–89) at 5 years; and graft survival at 1 year was 93% (95% CI 74–98), decreasing to 84% at 3 years and 5 years (95% CI 55–95). These were comparable to the survival rate among HIV-negative patients in their unit. Acute rejection developed in 8% at 1 year and 22% at 3 years. The CD4 counts fell initially, perhaps secondary to the ATG therapy but rose later. The viral load remained undetectable throughout the follow-up period. In three patients, routine allograft biopsies revealed changes typical of early HIV-associated nephropathy, which were not present in the baseline biopsy specimens.

The authors concluded that HIV-positive people can be considered a deceased kidney donor for HIV-positive recipients if they are either ART-naïve or on first-line treatment only with no resistance; have normal serum creatinine and no proteinuria. Donors with active infection, malignancies or possible HIV-associated nephropathy (HIVAN) were not used. Finally, the authors neither use, nor suggest the use of HIV-positive individuals for living kidney donation.

COMMENT

According to a UNAID report, of the 35 million people with HIV worldwide, 25 million live in sub-Saharan Africa.[2]The availability of HAART has made HIV infection into a chronic disease, from an invariably fatal one. However, it has paradoxically increased their chances of developing several chronic diseases. About 10%–20% of HIV-infected individuals will develop chronic kidney disease (CKD) despite treatment.[3] This is more likely where the infection is diagnosed relatively late, as in resource-constrained settings.

The results of this important observational study suggest that kidney transplantation from an HIV-positive donor appears to be an additional treatment option for HIV-infected patients requiring renal-replacement therapy. This study is of particular relevance for communities where the rate of HIV infection is high such as sub-Saharan Africa because a large number of patients with end-stage renal disease will have this infection, as will a proportion of potential deceased donors. In the past, discovery of HIV positive status excluded them from being a donor.[1]

It is well known that HIV-infected patients who are stable on ART have survival rates comparable to non-HIV infected ones on haemo- or peritoneal dialysis.[3] In a series of 150 patients, kidney transplantation in HIV-positive patients using kidneys from non-HIV positive donors had patient and graft survival of 88.2% and 73.7%, respectively, at 3 years.[4]

In spite of the HIV infection, acute rejection rates are higher in HIV-infected transplant recipients, suggesting that their immune system may be 'dysregulated' rather than suppressed. This led the authors to use potent immunosuppression, including ATG induction. This seems to be tolerated well and the infection rates were not higher than expected.

This approach is an example of how we can help improve choices for our patients by 'thinking outside the box' and questioning conventional ideas. The authors were compelled to think on these lines because patients with end-stage renal disease and HIV would be turned down for dialysis, as they were considered unfit for transplantation. The authors need to be congratulated for this approach.

However, a few concerns need to be mentioned. The first is the validity of informed consent from a recipient who has literally no choice. In this study, a strong oversight was maintained by the ethics committee. Similar diligence will be needed if this is to be brought into routine practice. The next issue is the possibility of transmission of a second strain of HIV from the donor kidney leading to potential development of a resistant strain or even emergence of a novel recombinant virus. The kidney has been shown to be reservoir for the virus.[5] Such fears have been belied, as the authors of this study did not notice viral replication on standard testing. This could be unique to South Africa, where the resistance rates are low, and may not apply elsewhere.[6] The authors note emergence of changes suggestive of HIVAN on biopsy in some cases, whether this has anything to do with such an event needs to be investigated. The authors are carrying out sequencing to study this in greater detail.

Drug–drug interactions are potentially troublesome. In this study use of boosted PI-based therapy led to a drastic reduction in requirement for CNI. This was beneficial because it reduced the cost of immunosuppression, but emergence of histological changes

suggestive of CNI-nephrotoxicity led to abandoning this approach.

Such research needs to be brought to the notice of policy-makers. In the USA, the newly signed HIV Organ Policy Equity (HOPE) Act permits both the transplantation of organs from HIV-positive donors to HIV-positive recipients and research related to such transplantation.

While such developments open new opportunities for patients and are welcome, they also place a greater burden of responsibility upon the transplant community. We need to be careful in patient selection and post-transplant monitoring. Issues that require vigil include drug levels, infections and nephrotoxicity.

We have been using organs from individuals with certain infections, such as cytomegalovirus. Drugs to effectively treat hepatitis C infection in kidney transplant recipients are already available, and will present us with the possibility of applying a similar approach. The latter is particularly relevant to India where rates of hepatitis C infection are high.

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