Renal Transplantation in HIV-Positive Recipients

Jayme E. Locke · Dorry L. Segev

Published online: 7 January 2010
© Springer Science+Business Media, LLC 2010

Abstract About 1% of all patients with end-stage renal disease in the United States are infected with HIV. With the introduction of highly active antiretroviral therapy (HAART), HIV death rates have declined 80%, and chronic diseases resulting from HIV have replaced opportunistic infections as the leading cause of death among HIV-infected patients. Traditionally, HIV infection has been considered an absolute contraindication to solid-organ transplantation. However, in the context of improved survival, the role for kidney transplantation among HIV-positive patients is currently being revisited. This article discusses long-term outcomes after kidney transplantation in the HAART era and management strategies for the HIV-positive kidney transplant recipient.

Keywords Renal transplantation · Human Immunodeficiency Virus (HIV) · Immunosuppression · Donor selection · Recipient selection

Introduction

Once a universally fatal disease, individuals infected with HIV are now living long productive lives. The HIV epidemic in the United States changed dramatically with the introduction of highly active antiretroviral therapy (HAART). HAART is responsible for an 80% decline in HIV death rates [1, 2], and as a result, chronic diseases resulting from HIV have now replaced opportunistic infections as the leading cause of death among HIV-infected patients [3]. In particular, patients infected with HIV are at risk for developing chronic kidney diseases, such as HIV-associated nephropathy, immune complex diseases, viral-associated glomerulonephritis, and thrombotic microangiopathy [4–7, 8•, 9, 10•, 11].

HIV-associated nephropathy is the most aggressive HIV-related kidney disease and is characterized by rapid progression to end-stage renal disease (ESRD) [12]. The disease is thought to result from direct infection of HIV-1 into renal epithelial cells [13]. HIV-associated nephropathy is now the third leading cause of ESRD among African American patients between the ages of 20 and 64 years [14–16].

Approximately 1% of all patients with ESRD in the United States are infected with HIV [8•, 17], and chronic kidney disease now accounts for more than 10% of HIV-related deaths [7]. Traditionally, HIV infection has been considered an absolute contraindication to solid-organ transplantation. However, in the context of improved survival [18], the role for kidney transplantation among HIV-positive patients is currently being revisited [19]. In the following sections, long-term outcomes after kidney transplantation in the HAART era are discussed and management strategies for the HIV-positive kidney transplant recipient are reviewed.

Selection Criteria

Patient selection criteria continue to evolve over time as experience with transplants in patients with HIV grows. Currently, a US National Institutes of Health-sponsored multicenter trial is actively enrolling HIV-positive ESRD patients. Inclusion and exclusion criteria for enrollment in this trial provide the most up-to-date guidelines for transplanting HIV-positive ESRD patients [20]. Participants are required to meet standard listing criteria for placement on the transplant waiting list; have a CD4 T-cell count ≥200/µL within 16 weeks before transplant; have a low viral load; have an absence of specific patterns of HIV viral resistance; have an
absence of ongoing specific opportunistic infections (eg, chronic cryptosporidiosis, systemic Kaposi sarcoma, or progressive multifocal leukoencephalopathy); and be on a stable antiretroviral treatment regimen for at least 3 months before transplantation (Table 1) [20, 21, 22]. Further, because the percentage of CD4 cells serves as a better predictor of disease progression in children than absolute CD4 count, pediatric participants between 1 and 2 years of age must have 30% CD4 cells and those between 2 and 10 years of age must have 20% CD4 cells [23]. Finally, the prevalence of co-infection of HIV-positive patients with hepatitis B and C viruses (~10% and 30%, respectively) cannot be overlooked [24, 25]. Trial guidelines recommend critical assessment of liver damage among these patients before performing kidney transplantation.

Appropriate donor selection for potential HIV-positive kidney transplant recipients is critical. A recent retrospective review of the United Network for Organ Sharing national registry suggested that in some cases HIV-positive serostatus has a negative long-term effect on kidney graft survival, but that the disparity in outcomes between HIV-positive and HIV-negative recipients may be modified by several factors, including donor age and type (deceased vs living) [26]. Specifically, HIV-positive recipients who received a kidney from a deceased donor under the age of 50 years had graft survival similar to their HIV-negative counterparts. Furthermore, HIV-positive recipients did not seem to tolerate delayed graft function as well as their HIV-negative counterparts, as illustrated by a 20% lower death-censored graft survival at 1 year. The risk for delayed graft function might be reduced among HIV-positive kidney transplant recipients by transplanting live donor kidneys as opposed to deceased donor kidneys, and by limiting the cold ischemic time to less than 16 h when transplanting deceased donor kidney. Interestingly, a recent case report suggested that HIV-positive patients can achieve excellent long-term results with the use of an ABO-incompatible kidney allograft [27].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Recommended selection criteria specific for HIV-positive kidney transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meet standard kidney transplant criteria</td>
<td>Current CD4 count</td>
</tr>
<tr>
<td>Adult recipients:</td>
<td>&gt;200 µL at anytime 16 week before transplant</td>
</tr>
<tr>
<td>Pediatric recipients:</td>
<td>1–2 years: CD4 ≥ 30%</td>
</tr>
<tr>
<td></td>
<td>2–10 years: CD4 ≥ 20%</td>
</tr>
<tr>
<td></td>
<td>10–17 years: CD4 ≥ 10%</td>
</tr>
<tr>
<td>HIV-RNA</td>
<td>≤50 copies/mL</td>
</tr>
<tr>
<td>Established antiretroviral regimen for 3 months before transplant</td>
<td></td>
</tr>
</tbody>
</table>

Outcomes

Patient and Graft Survival

Few large, prospective studies examining patient and graft survival after renal transplantation in HIV-positive patients were published during the HAART era. In 2003, Stock et al. [28] published a prospective study evaluating outcomes from 10 patients with HIV infection who underwent kidney transplantation. Patients in this study received no induction immunosuppression and were maintained on a combination of mycophenolate mofetil (MMF), cyclosporine, and prednisone. This initial series suggested that HIV-positive and HIV-negative kidney transplant recipients might have similar patient and graft survival at 1 year [28]. In 2008, Rolland et al. [29] subsequently published a prospective study of 18 HIV-positive patients transplanted in the setting of interleukin-2 receptor inhibitor induction therapy and a maintenance immunosuppression regimen of steroids, calcineurin inhibitors, and MMF. The results from this study also supported the possibility of similar long-term patient and graft survival among HIV-positive and HIV-negative kidney transplant recipients (Table 2) [29].

During the HAART era, multiple retrospective studies of outcomes after kidney transplantation in HIV-positive patients were also performed, and most have demonstrated similar patient and graft survival among HIV-positive and HIV-negative recipients [14, 30, 31, 32–35]. The largest published retrospective review comes from the Scientific Registry of Transplant Recipients, which examined outcomes from 138 HIV-positive kidney transplant recipients before and after the introduction of HARRT (38 pre-HARRT, 100 post-HAAR) [32]. Results from this US registry analysis provided further evidence that even across centers patient and graft survival rates among HIV-positive kidney transplant recipients transplanted during the HARRT era were similar to those reported from patients without HIV.

Acute Rejection

Rates of acute rejection after renal transplantation in patients with HIV have been reported to be as high as 67% [14, 28, 29, 31, 34–36, 37], and the rate of subclinical rejection seen on protocol biopsies has been reported to be as high as 29% [14]. The etiology of higher rejection rates in HIV-positive kidney transplant recipients is not entirely understood but is likely related to a tendency to limit immunosuppression in this already immunocompromised patient population [28, 38–40]. Recently, two separate studies reported that the use of induction therapy (eg, anti-CD25 antibody or anti-interleukin-2 receptor antibody) may attenuate the high rates of acute rejection.
previously reported among HIV-positive kidney transplant recipients [14, 31]. In addition to lower rejection rates, both studies reported excellent long-term patient and graft survival and, despite the use of induction immunosuppression, demonstrated no progression in the study participants’ HIV disease.

Despite reports of high acute rejection rates among HIV-positive kidney transplant recipients, kidney transplantation remains the gold standard for the treatment of ESRD, even among HIV-positive patients. Although there remains concern over long-term outcomes among HIV-positive kidney transplant recipients, Roefs et al. [41] recently reported excellent long-term graft function in an HIV-positive recipient 13 years out from the original kidney transplant, suggesting that excellent long-term outcomes can be achieved. However, HIV-positive kidney transplant recipients are at higher risk for acute rejection than their HIV-negative counterparts. Research is ongoing to better understand the etiology of the higher acute rejection rates and methods for prevention and treatment in this unique patient population.

### Management

#### Immunosuppression Strategies

There have been concerns about the potential additive effect of immunosuppression agents and HIV on the risk for opportunistic infections and malignancy, and the potential for acceleration of HIV infection in the setting of decreased immune surveillance. However, several studies have demonstrated the ability of calcineurin inhibitors, MMF, and sirolimus to inhibit the replication of HIV in vitro [38–40], and other studies have suggested that progression to AIDS is unaffected or even delayed in patients receiving cyclosporine-based immunosuppression [42]. Mechanistically, MMF depletes guanosine nucleosides that are necessary for the virus life cycle [43, 44], calcineurin inhibitors interfere with HIV pathogenic protein functions [45, 46], and sirolimus decreases the expression of a chemokine receptor found on lymphocytes potentially preventing HIV entry and replication [47, 48].

It also seems that HIV-positive kidney transplant recipients are capable of robust alloimmune responses because they have high rates of acute rejection compared with their HIV-negative counterparts [14, 28, 29, 31, 34, 35, 37]. These data suggest that induction therapy may be necessary in this patient population. Currently, most centers are using interleukin-2 receptor inhibitor induction therapy. Reluctance to use lymphocyte-depleting agents for induction remains, because these agents severely deplete CD4 counts for months [36].

#### Antiretroviral Strategies

Several studies have reported that the risk of progression to AIDS is reduced when patients are maintained on the same HAART regimen they received before transplant [14, 28, 29]. Occasionally, during the peritransplant period, patients are unable to tolerate HAART therapy. Current recommendations are to stop HAART immediately in this setting to avoid development of drug-resistant strains, because the cessation of HAART can be tolerated for several weeks without changes in viral load or CD4 count [19, 28].

Drug interactions are common in the HIV-positive kidney transplant population, because many of the HAART medications are metabolized through the same cytochrome system as common immunosuppressant medications [14, 49, 50]. For example, patients on protease inhibitors receiving cyclosporine-based maintenance immunosuppression have been shown to require only 20% of the standard

### Table 2

Summary of studies examining patient and graft survival among HIV-positive kidney transplant recipients

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Patient, n</th>
<th>Induction</th>
<th>Maintenance</th>
<th>Patient survival</th>
<th>Graft survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stock et al. [28]</td>
<td>10</td>
<td>None</td>
<td>Cyclosporine, MMF, prednisone</td>
<td>100% at 480 days</td>
<td>100% at 480 days</td>
</tr>
<tr>
<td>Roland et al. [33]</td>
<td>26</td>
<td>a</td>
<td>a</td>
<td>92% at 1 year</td>
<td>89% at 1 year</td>
</tr>
<tr>
<td>Pelletier et al. [32]</td>
<td>100</td>
<td>a</td>
<td>a</td>
<td>92% at 1 year</td>
<td>84% at 1 year</td>
</tr>
<tr>
<td>Abbott et al. [30]</td>
<td>47</td>
<td>a</td>
<td>a</td>
<td>95% at 3 years</td>
<td>97.8% at 3 years</td>
</tr>
<tr>
<td>Tan et al. [34]</td>
<td>4</td>
<td>Alemtuzumab</td>
<td>Tacrolimus</td>
<td>100% at 3 years</td>
<td>100% at 3 years</td>
</tr>
<tr>
<td>Kumar et al. [14]</td>
<td>40</td>
<td>Basiliximab</td>
<td>Cyclosporine, sirolimus, prednisone</td>
<td>85% at 1 year</td>
<td>75% at 1 year</td>
</tr>
<tr>
<td>Trullas et al. [35]</td>
<td>3</td>
<td>Thymoglobulin</td>
<td>Sirolimus, MMF, prednisone</td>
<td>100% at 1 year</td>
<td>100% at 1 year</td>
</tr>
<tr>
<td>Gruber et al. [31]</td>
<td>8</td>
<td>IL-2 receptor inhibitor</td>
<td>MMF, cyclosporine, prednisone</td>
<td>100% at 1 year</td>
<td>88% at 1 year</td>
</tr>
<tr>
<td>Roland et al. [29]</td>
<td>18</td>
<td>IL-2 receptor inhibitor</td>
<td>Cyclosporine, MMF, prednisone</td>
<td>94% at 3 years</td>
<td>83% at 3 years</td>
</tr>
</tbody>
</table>

IL-2 interleukin-2; MMF mycophenolate mofetil

a Retrospective study: induction and maintenance immunosuppression regimen unknown

b Survival among deceased donor recipients. Live donor recipient patient survival (95% at 1 year) and graft survival (92% at 1 year)
cyclosporine dose used in HIV-negative kidney transplant recipients. Furthermore, proton pump inhibitors (PPIs) are known to reduce the intestinal absorption of the protease inhibitor atazanavir, a common component of HAART. Most transplant recipients are maintained on PPIs to reduce the incidence of steroid-related gastritis. Therefore, HIV-positive kidney transplant recipients receiving atazanavir-based HAART and who are on PPIs require ritonavir boost therapy to maintain adequate plasma concentrations of atazanavir [51]. Finally, there is now evidence suggesting that the common immunosuppressant medication MMF is antagonistic to the anti-HIV replication effects of zidovudine and stavudine [52]. Therefore, these combinations should be avoided whenever possible.

Conclusions

The introduction of HAART has resulted in an 80% decline in HIV death rates [1, 2], and chronic diseases resulting from HIV have replaced opportunistic infections as the leading cause of death among HIV-infected patients [3]. During the HAART era, multiple studies highlighted the significant progress that has been made toward improving long-term survival among HIV-positive kidney transplant recipients [14, 28, 29•, 30, 31•, 32–35]. Many of these outcomes have been achieved without increases in the incidence of opportunistic infections or acceleration of HIV infection to AIDS; however, higher rates of acute rejection remain a concern. Careful donor and patient selection are paramount to achieve long-term outcomes that are comparable to HIV-negative recipients. Active research is necessary to better define and characterize this unique transplant patient population. Currently, there is an ongoing US National Institutes of Health multicenter trial designed to evaluate the safety and effectiveness of kidney transplantation in HIV-positive patients.

Disclosure  No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

8. • Trullas JC, Barril G, Cofan F, et al.: Prevalence and clinical characteristics of HIV type 1-infected patients receiving dialysis in Spain: results of a Spanish survey in 2006. GESIDA 48/05 study. AIDS Res Hum Retroviruses 2008, 24:1229–1235. This article reports on a survey that was conducted across multiple dialysis centers in Spain. The study estimates that about 0.54% of dialysis patients have HIV. Of those, 61% are coinfected with hepatitis C and only 12% are registered on the kidney transplant waiting list.
23. Rouet F, Inwoley A, Ekouevi DK, et al.: CD4 percentages and total lymphocyte counts as early surrogate markers for pediatric...


