

Thymoglobulin-Associated Cd4+ T-Cell Depletion and Infection Risk in HIV-Infected Renal Transplant Recipients

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HIV-infected patients are increasingly referred for kidney transplantation, and may be at an increased risk for rejection. Treatment for rejection frequently includes thymoglobulin. We studied thymoglobulin's effect on CD4+ T-cell count, risk of infection and rejection reversal in 20 consecutive HIV-infected kidney recipients. All patients used antiretroviral therapy and opportunistic infection prophylaxis. Maintenance immunosuppression consisted of prednisone, mycophenolate mofetil and cyclosporine. Eleven patients received thymoglobulin (7 for rejection and 4 for delayed/slow graft function) while 9 did not. These two groups were similar in age, gender, race, donor characteristics and immunosuppression. Mean CD4+ T-cell counts remained stable in patients who did not receive thymoglobulin, but became profoundly suppressed in those who did, decreasing from 475 ± 192 to 9 ± 10 cells/ μ L ($p < 0.001$). Recovery time ranged from 3 weeks to 2 years despite effective HIV suppression. Although opportunistic infections were successfully suppressed, low CD4+ T-cell count was associated with increased risk of serious infections requiring hospitalization. Rejection reversed in 6 of 7 patients receiving thymoglobulin. We conclude that thymoglobulin reverses acute rejection in HIV-infected kidney recipients, but produces profound and long-lasting suppression of the CD4+ T-cell count associated with increased risk of infections requiring hospitalization.

Key words: HIV, kidney transplant, rejection, thymoglobulin

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Introduction

As the prognosis for HIV-infected patients has improved, transplantation has become more common, often in the

context of clinical trials (1–3). Early experience with kidney transplantation in patients with HIV infection has shown an unexpectedly high rate of early acute rejection (2,4,5). Treatment for such rejection frequently includes the use of antithymocyte globulin (Thymoglobulin[®], Genzyme Transplant, Cambridge, MA), which contains depleting antibodies against T-cell markers including CD4.

Concerns about the use of thymoglobulin in patients with HIV include prolonged CD4+ T-cell depletion, failure to suppress opportunistic infections, loss of HIV viral control and more rapid progression to AIDS and death. Given that HIV-induced CD4+ T-cell depletion predisposes patients to opportunistic and select nonopportunistic infections, there is concern that thymoglobulin-induced CD4+ T-cell depletion may similarly predispose HIV-infected transplant recipients to greater infection risk. Indeed, in patients without HIV, thymoglobulin produces lymphocyte depletion for as long as 2 years, and may deplete the CD4+ T-cell count for even longer (6–8). Such depletion is associated with increased risk of infection (9–11). In the setting of HIV, the degree and duration of thymoglobulin-induced CD4+ T-cell depletion has not been characterized. Also unknown are the associated infectious risks, as well as the efficacy of thymoglobulin in reversing acute rejection.

In this prospective observational study, we aimed to characterize the effect of thymoglobulin on CD4+ T-cell counts, infection rate, HIV viral suppression and success in reversing acute rejection in HIV-infected kidney transplant recipients. We studied 20 consecutive HIV-infected patients who underwent kidney transplantation at a single center over a 4-year period, and compared the 11 patients who received thymoglobulin with the nine who did not.

Materials and Methods

Study design

All consecutive kidney transplants performed in HIV-infected recipients participating in one of three sequential prospective studies at the University of California, San Francisco between January 1, 2000 and December 31, 2004 were included in this analysis. The third study, NIH 5U10-A140166-05, is currently still enrolling patients. HIV-infected patients who received a combined kidney and liver transplant were excluded. This study was approved by the Committee on Human Research at UCSF and informed consent was obtained.

We collected data on recipient demographics, transplant characteristics, induction therapy, maintenance immunosuppression, highly-active antiretroviral therapy (HAART), rejection therapy and thymoglobulin administration. For each recipient, we also reviewed the CD4+ T-cell count, absolute lymphocyte count, CD4/CD8 T-cell ratio, CD4/total lymphocyte ratio (CD4%) and HIV-1 RNA viral load (by quantitative PCR) before transplantation, before thymoglobulin administration and after transplantation according to the following schedule: weekly ($\times 2$ visits), every other week ($\times 5$ visits), monthly ($\times 2$ visits), every other month ($\times 4$ visits), every 12 weeks (until 3 years post-transplant), then biannually. CD4+ T-cell counts and HIV-1 RNA viral load were also obtained at time of admission for any patient requiring hospitalization.

We compared recipients who received thymoglobulin in their post-transplant course with those who never received thymoglobulin. The two primary outcome measures for this study were the recipient's CD4+ T-cell count over time, and the rate of opportunistic and other serious infections with an identified pathogen (or suspected infections treated empirically with targeted antimicrobial therapy) that were sufficiently severe as to require or prolong hospitalization. AIDS-defining opportunistic infections were defined by standard criteria (12).

Transplant criteria

Inclusion criteria for kidney transplantation into HIV-infected candidates were as follows: first, candidates met standard criteria for placement on the kidney transplant waiting list. Second, candidates had undetectable HIV RNA (using an ultra-sensitive assay) for at least 3 months while on a stable HAART regimen. Third, candidates demonstrated stable CD4+ T-cell counts greater than 200 cells/ μL for at least 6 months. Initially, no patient with a history of opportunistic infection was considered for transplant; however, this criterion was relaxed in April 2002, to include patients with a history of selected opportunistic infections if the candidate had no evidence of active disease.

Exclusion criteria included the following, history of cancer or opportunistic neoplasm (except for treated basal cell carcinoma, cutaneous Kaposi's sarcoma or *in situ* anogenital cancer), prior transplant, pregnancy, significant HIV-related wasting ($>5\%$ weight loss over 3 months), coinfection with hepatitis C with evidence of cirrhosis on liver biopsy, history of chronic intestinal cryptosporidiosis of >1 month duration, history of progressive multifocal leukoencephalopathy or documented resistant fungal infections.

Immunosuppression

All patients received perioperative steroids, mycophenolate mofetil (2–3 g/day), a calcineurin inhibitor (either cyclosporine or tacrolimus), and/or sirolimus. Target cyclosporine and tacrolimus trough levels were 150–200 ng/mL and 8–15 ng/mL, respectively, for the immediate post-transplant period. Sirolimus was initiated in recipients with calcineurin inhibitor toxicity who required a reduction in calcineurin inhibitor dose. Induction therapy with lymphocyte-depleting agents was avoided. After we observed a propensity for early rejection in HIV-infected kidney recipients, we used IL-2 receptor inhibitor induction (Simulect[®], Novartis, Basel, Switzerland) in some recipients.

Thymoglobulin was given for delayed graft function (defined as need for dialysis in the first week after transplant) or slow graft function (defined as creatinine >3 mg/dL on post-operative day 5). We did not initiate calcineurin inhibitors in these circumstances due to poor early graft function. For delayed or slow graft function, thymoglobulin was dosed at 1.5 mg/kg on day 1, followed by 1 mg/kg daily, up to a total dose limit of 6–8 mg/kg.

Antiretroviral therapy

Patients resumed their pre-transplant HAART therapy when an oral diet was started, typically 1 or 2 days after transplant.

Infection prophylaxis

A protocol was developed for the prophylaxis of standard post-transplant opportunistic pathogens as well as other pathogens associated with HIV infection (Table 1). Primary prophylaxis refers to patients with no prior history of the infection. Secondary prophylaxis refers to patients with a suspected or documented history of the infection.

Diagnosis and treatment of rejection

All cases of suspected rejection were evaluated with renal biopsy. Kidney rejection was defined by the NIH supported Cooperative Clinical Trials in Transplantation histological criteria (13). When clinical presentation or histological findings suggested antibody-mediated rejection (i.e. a peritubular-capillary neutrophilic infiltrate or glomerulitis was present), C4d staining was performed and correlated with the presence of donor-specific antibody.

Treatment for acute rejection consisted of 3 days of high-dose methylprednisolone, followed by a prednisone taper, and increased maintenance immunosuppression, which frequently meant switching the recipient from cyclosporine to tacrolimus. Additionally, moderate-to-severe cases of rejection were treated with thymoglobulin on an individualized basis. The decision to use thymoglobulin was based upon three factors: histological severity, degree of organ dysfunction and timing of rejection relative to transplant. In general, cases of rejection which were diagnosed within 3 months of transplant, were histological type II (vascular) or III (necrotizing or transmural arteriolar), or were associated with significant organ dysfunction were treated with thymoglobulin and steroids. The target dose of thymoglobulin for rejection was 6 mg/kg, administered as a single 1.5 mg/kg dose on day 1, followed by 1 mg/kg daily until the target dose was achieved. No patient in this study developed antibody-mediated rejection requiring additional therapy.

Statistical analysis

Thymoglobulin recipient characteristics were compared to nonthymoglobulin recipient characteristics using the Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables.

To characterize the effect of thymoglobulin on the CD4+ T-cell count, individual recipient CD4+ T-cell counts after thymoglobulin dosing, along with the mean CD4+ T-cell count for the entire cohort, were plotted over time and compared with the mean CD4+ T-cell count of recipients who did not receive thymoglobulin. Similar analyses were performed for the total lymphocyte count, CD4/CD8 T-cell ratio, and CD4% counts in HIV-infected patients who received thymoglobulin versus those who did not.

To investigate the effect of thymoglobulin-induced CD4+ T-cell suppression on the risk of serious infections requiring hospitalization, we constructed a mixed-effects regression model with a fixed effect of condition and a random effect of person. In this model, the annualized rate of infections requiring hospitalization while the CD4+ T-cell count was suppressed (less than 200 cells/ μL) was compared to the annualized rate of infections requiring hospitalization after relative CD4+ T-cell count recovery (greater than 200 cells/ μL). The duration of CD4+ T-cell suppression was defined as the number of days from thymoglobulin administration until two consecutive CD4+ T-cell counts were greater than 200 cells/ μL . A least-squares-means approach was used to compare the estimated rates.

To investigate the efficacy of thymoglobulin in reversing moderate-to-severe rejection, we calculated the overall therapeutic success rate, defined as the number of treated episodes with improvement in renal function (evident by a reduction in serum creatinine, or repeated biopsies showing no evidence

Table 1: Opportunistic infection prophylaxis

Pathogen	Indication for prophylaxis	Regimen
<i>Pneumocystis carinii</i> (PCP)	1: All patients indefinitely	Trimethoprim-sulfamethoxazole double-strength 1 tablet daily
<i>Cytomegalovirus</i> (CMV)	2: All patients indefinitely	Valganciclovir 900 mg daily or ganciclovir 1g three times daily
	1: All patients for 3 months	
<i>Candida</i>	2: For 1 month post-transplant or rejection, or when CD4 < 100	Fluconazole 100 mg weekly ¹
	1: All patients for 1 month	
<i>Toxoplasmosis</i>	1: If IgG positive, CD4 < 200	Trimethoprim-sulfamethoxazole double-strength 1 tablet daily
	2: For 1 month post-transplant or rejection, or when CD4 < 200	
<i>Mycobacterium avium complex</i> (MAC)	1: When CD4 < 75	Azithromycin 1200 mg weekly
	2: For 1 month post-transplant or rejection or when CD4 < 75	
<i>Epstein-Barr virus</i> (EBV)	1: When recipient serology is negative and donor serology is positive	Ganciclovir 5 mg/kg IV daily, then 1 g three times daily for 1 year
<i>Cryptococcus, extrapulmonary</i>	1: No therapy	Fluconazole 200 mg daily ^a
	2: For 1 month post-transplant or rejection, or when CD4 < 200	
<i>Histoplasmosis</i>	1: No therapy	Itraconazole 200 mg twice daily ^a
	2: All patients regardless of CD4 count	

1 = indicates primary prophylaxis, when no history of infection with pathogen exists; 2 = indicates secondary prophylaxis, when a history of treated infection with pathogen exists.

^acalcineurin inhibitor and sirolimus dosing must be reduced by at least 50% when azole antifungals used.

of rejection) divided by the total number of episodes. We also investigated the effect of IL-2 receptor antibody induction therapy on the incidence of acute rejection by calculating Kaplan-Meier actuarial rejection-free survival curves, and comparing them using the log-rank test.

Statistical significance was defined as a p-value < 0.05. Data are expressed as mean ± standard deviation. All analyses were performed using SAS, version 9.0 software (SAS Institute, Cary, NC).

Results

Recipient and transplant characteristics

A total of 20 kidney transplants into HIV-infected recipients were performed over the 4-year-study period. Of these, 11 recipients received thymoglobulin during their post-operative course, and 9 did not.

Demographic and transplant characteristics of the thymoglobulin recipients are compared with the other recipients in Table 2. The study population was almost exclusively men aged 40–57 years. Half were African-American, and presumptive HIV-associated nephropathy accounted for 35% of the recipients’ end-stage renal failure. No patient had received a prior transplant, and none were sensitized (defined as PRA >30% at the time of transplant). Just under half (8 of 20) of the study population received a kidney from a living donor, and all met the primary inclusion criteria of CD4+ T-cell count >200 cells/μL and undetectable HIV viral load on a stable HAART regimen at the time of transplant.

Initial immunosuppression consisted of steroids and mycophenolate mofetil in all patients. The majority (17 patients, 85%) eventually received cyclosporine as initial maintenance therapy. No patient received thymoglobulin or other lymphocyte-depleting induction therapy at the time of transplant, although 11 patients received IL-2 receptor antibody induction. No significant differences in recipient demographics, CD4+ T-cell or other lymphocyte counts at transplant, or initial immunosuppression strategy existed between recipients who ultimately required thymoglobulin and those who did not. Follow-up time was similar in these two groups, ranging from 111 to 1704 days (Table 2).

Indications for thymoglobulin use included the following: 7 patients were treated for acute rejection (3 for type I and 4 for type II), 3 for delayed graft function and 1 for slow graft function. The total dose of thymoglobulin ranged from 5.2 to 9.0 mg/kg (mean 7.0 mg/kg).

CD4+ T-cell count, CD4%, CD4/CD8 ratio and total lymphocyte response after thymoglobulin

Individual recipient CD4+ T-cell responses to thymoglobulin, as well as the mean for the entire cohort, are shown in Figure 1. Mean CD4+ T-cell count dropped from 475 ± 192 cells/μL to 9 ± 10 cells/μL within 1 week of therapy (p < 0.001). The CD4+ T-cell recovery time varied widely from patient to patient; time to achieve CD4 > 200 cells/μL averaged 342 days and ranged from 18 days to over 2 years, despite maintenance on effective HAART therapy. No

Table 2: Recipient and transplant characteristics

	Thymoglobulin recipients (n = 11)	Nonthymoglobulin recipients (n = 9)	p-value ^a
Mean age in years (range)	49.2 (41–55)	47.3 (40–57)	0.469
Male gender (%)	11 (100)	8 (89)	0.450
Race			
African American (%)	4 (36)	6 (67)	0.370
Caucasian (%)	7 (64)	3 (33)	
Recipient etiology of renal failure			
HIV-associated nephropathy (%)	5 (45)	2 (22)	0.460
Hypertension (%)	2 (18)	4 (44)	
Other (%)	4 (36)	3 (43)	
Mean PRA ^b at transplant (range)	3.3% (0–29%)	4.2% (0–16%)	0.181
Type of transplant			
Deceased donor (%)	7 (64)	5 (56)	1.000
Living donor (%)	4 (36)	4 (44)	
Recipient lymphocyte counts at transplant			
Mean CD4 count in cells/μL (range)	475 (237–890)	443 (334–734)	0.820
Mean CD4% (range)	26 (15–42)	29 (20–36)	0.360
Mean CD4/CD8 ratio (range)	0.5 (0.2–0.6)	0.7 (0.5–0.8)	0.067
Mean total lymphocyte count (range)	1895 (1090–3560)	1690 (1130–2500)	0.820
Induction therapy			
Thymoglobulin or OKT3 (%)	0 (0)	0 (0)	1.000
IL2-receptor antagonist (Simulect) (%)	7 (64)	4 (44)	0.653
Initial maintenance therapy			
Prednisone (%)	11 (100)	9 (100)	1.000
Mycophenolate mofetil (%)	11 (100)	9 (100)	1.000
Cyclosporine (%)	9 (82)	8 (89)	1.000
Tacrolimus (%)	0 (0)	1 (11)	1.000
Sirolimus (%)	1 (9)	0 (0)	1.000
Number of rejection episodes	7	3	0.370
Mean follow-up in days (range)	764 (111–1456)	965 (111–1704)	0.470

^aMann-Whitney test for continuous variables, Fisher's Exact test for categorical variables.

^bPRA = panel reactive antibody.

CD4 Counts in HIV-infected Kidney Recipients

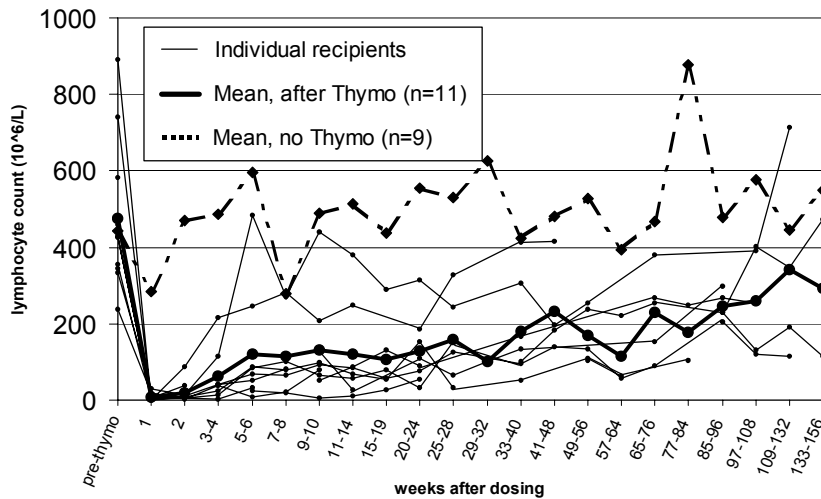


Figure 1: Individual CD4+ T-cell counts versus time after thymoglobulin in HIV-infected kidney transplant recipients are shown. The mean for this cohort (solid bold line) decreased from 475 to 9 cells/μL within 1 week of therapy (p < 0.001). By contrast, HIV-infected kidney recipients who did not receive thymoglobulin displayed stable mean CD4+ T-cell counts (dashed line).

obvious dose-recovery time relationship was present; however, the study was underpowered to detect such a relationship given the small cohort of patients with relatively similar total dose.

In HIV-infected kidney recipients who received thymoglobulin, the mean percentage of CD4+ T-cells to total lymphocytes (CD4%) decreased from 26% ± 9% to 4% ± 3% after dosing (p < 0.001) and recovered by 50% within

8 weeks. Similarly, mean absolute lymphocyte count decreased from 1895 ± 724 cells/ μL to 198 ± 146 cells/ μL , ($p < 0.001$), also recovering by 50% within 8 weeks. No demonstrable change in the mean CD4/CD8 T-cell ratio was observed after thymoglobulin dosing.

By contrast, in HIV-infected kidney recipients who did not receive thymoglobulin, the mean CD4+ T-cell count was stable after transplant (Figure 1), as were the mean percentage of CD4+ T cells to total lymphocytes (CD4%), the mean absolute lymphocyte count, and the mean CD4/CD8 T-cell ratio (data not shown).

Opportunistic and serious infections requiring hospitalization

Only one AIDS-defining opportunistic infection was observed after kidney transplantation in the study population. This was a case of *candida* esophagitis diagnosed 5 months after transplant in a recipient who had received thymoglobulin for Type II rejection. The CD4 count at diagnosis was 76 cells/ μL , and the response to antifungal therapy was rapid.

HIV-infected kidney recipients who received thymoglobulin developed more serious infections requiring hospitalization, during the time their CD4+ T-cell count was suppressed. Ten such infections were observed in six thymoglobulin recipients: *S. aureus* endocarditis with septic embolization, *S. viridans* bacteremia, *pseudomonas* pneumonia with multiorgan failure, *Escherichia coli* urosepsis, culture-negative urosepsis, *enterococcus* bacteremia, polymicrobial nosocomial pneumonia with sepsis, *C. difficile* colitis, diverticulitis and secondary bacterial peritonitis. All but one of these infections occurred when the CD4+ T-cell count was less than 200 cells/ μL . Mean time from thymoglobulin administration to first serious infection was 105 ± 139 days (range 35–382 days). No patient was neutropenic at the time of infection.

Two culture-negative serious infections were included in our analysis. The first case, culture-negative urosepsis, was diagnosed after a patient was presented with fever, hypotension and pyuria. Urine cultures taken after administration of broad-spectrum antibiotics failed to identify a specific pathogen. Response to antibiotics was rapid. The second case, secondary bacterial peritonitis, was diagnosed in a patient with cirrhosis and ascites who presented with abdominal pain. Paracentesis revealed a polymorphonuclear cell count twice the upper limit of normal (corrected count was 507 cells/ μL), but no organism was identified from culture of the ascites, probably as a result of technical error in obtaining ascites for culture. CD4+ T-cell count at the time of diagnosis was 286 cells/ μL . Response to antibiotics was rapid.

Only two serious infections requiring hospitalization were observed in recipients who did not receive thymoglobulin:

pseudomonas pneumonia and *influenza virus B* pneumonia. One of these infections occurred when the CD4+ T-cell count was below 200 cells/ μL (in this case, the CD4+ T-cell count was 25 cells/ μL) after the recipient was treated with steroids for Type I rejection and was receiving a high dose of sirolimus. No cytomegalovirus infections were observed in the study population.

The annualized rate of infections requiring hospitalization in all patients was 1.94 ± 0.48 infections per patient per year when the CD4+ T-cell count was below 200 cells/ μL , and decreased to 0.15 ± 0.37 infections per patient per year when the CD4+ T-cell count was greater than 200 cells/ μL ($p = 0.013$).

HIV viral control

HAART effectively suppressed HIV RNA both in patients who received thymoglobulin and those who did not; only four transient cases of very low level (256–1726 copies/mL) HIV viremia were observed during the follow-up period. The first case (1726 copies/mL) occurred immediately after transplant and before HAART therapy was resumed. After HAART was resumed, HIV viral load became undetectable. The second case (427 copies/mL) occurred 7 months after transplant and was the result of patient non-compliance with HAART. A new HAART regimen was prescribed and HIV viral load dropped below the detectable threshold. The third case (256 copies/mL) occurred when a patient was transiently taken off HAART to recover from a laparotomy for bowel obstruction. The fourth and final case (440 copies/mL) occurred in a recipient on a stable HAART regimen; the HIV RNA assay was repeated and found to be undetectable.

Response to rejection therapy

A total of 10 rejection episodes were observed in the 20 recipients studied. Six of the 7 rejection episodes treated with thymoglobulin and steroids responded to therapy, evidenced by improved renal function and/or a repeat biopsy that showed resolution. One patient with thymoglobulin-refractory rejection developed biopsy-proven type I rejection within 96 h of transplant, characterized by severe organ dysfunction, graft edema and reversal of diastolic arterial flow by graft ultrasound. No technical problems with the venous anastomosis were evident upon re-exploration. The graft went onto develop cortical rupture and venous thrombosis, and was explanted 9 days after the initial transplant. The final pathologic analysis demonstrated severe type II rejection.

Three patients who did not receive thymoglobulin developed mild acute Type I rejection after transplant and were treated with steroids only. All 3 episodes resolved without complications.

A total of 4 rejection episodes occurred in the 11 patients who received IL-2 receptor antibody (Simulect®) induction,

whereas 6 rejection episodes occurred in the 9 patients who did not. No statistically significant difference was present in Kaplan-Meier rejection-free survival between Simulect recipients and non-Simulect recipients ($p = 0.759$ by log-rank test).

Graft and patient survival

In patients who did not receive thymoglobulin, there were no patient deaths and no graft losses. There were two graft losses in the thymoglobulin recipients: one from acute rejection 9 days after transplant (as described above), and the second from patient death from congestive heart failure 5 months after transplant.

Discussion

Patients with HIV were once excluded from solid organ transplantation due to concerns that immunosuppressive therapy would accelerate HIV progression to AIDS and death. Additionally, there was a widely held opinion that the short life expectancy of HIV-infected patients precluded the use of scarce donor organs that could otherwise benefit longer-lived recipients (14). From 1987 to 1997, only 32 kidney transplants were performed in known HIV-seropositive recipients nationally, as reported to the United States Renal Data System (15). At the end of that time period, a survey of U.S. transplant centers revealed that 88% would not transplant a kidney into an asymptomatic HIV-infected patient who was otherwise a good candidate for transplantation (16). The relatively few transplants performed during this period did not reflect demand; from 1993 to 1997 over 3600 HIV-infected patients developed end-stage renal disease, most commonly from HIV-associated nephropathy (17). The vast majority of these patients were young African-Americans (18).

With the advent of HAART in 1996, the morbidity and mortality of HIV disease decreased significantly (19–23). Instead of death from HIV progression to AIDS, HIV-infected patients increasingly survived to develop chronic disease and end-stage organ failure, particularly from liver and kidney disease (24). As these patients were referred for transplantation, several centers began to re-evaluate the feasibility of performing transplants in this patient population (1,2).

Early experience with kidney transplantation into HIV-infected recipients in the HAART-era showed a surprisingly high rate of early acute rejection. We have previously reported outcomes on 26 HIV-infected kidney recipients maintained on cyclosporine-based immunosuppression, of whom 38% developed acute rejection within a mean follow-up of 314 days (2). Subsequent analysis showed that with longer follow-up, up to 70% of these recipients developed at least 1 episode of acute rejection (2). The explanation for this high rate of rejection, which

is more than twice as high as in non-HIV-infected kidney recipients on similar immunosuppression, remains unclear.

Treatment for moderate-to-severe rejection frequently includes thymoglobulin, an agent known to produce lymphocyte depletion associated with increased risk of infection. We have shown in this study that in HIV-infected kidney recipients, thymoglobulin produced a marked suppression of the CD4+ T-cell count with a prolonged recovery despite effective HAART therapy (Figure 1). Although recovery time in our study was similar to that in published reports of non-HIV-infected transplant recipients who received thymoglobulin (i.e. up to 2 years) (7,8), the initial CD4 count was lower and the recovery time was highly variable from patient-to-patient, ranging from 18 days to over 2 years, despite effective HIV viral suppression.

The consequence of such lymphocyte suppression was that majority of HIV-infected thymoglobulin recipients spent significant time with CD4+ T-cell counts below 200 cells/ μ L. Given the well-known association between absolute CD4+ T-cell count and opportunistic infection risk in HIV-infected patients without a transplant, we hypothesized that the amount of time transplant recipients spent with CD4+ T-cell count <200 cells/ μ L would correlate with the risk of infection. Indeed, almost all of the serious infections requiring hospitalization occurred in thymoglobulin recipients, and all but one of these occurred when the CD4+ T-cell count was less than 200 cells/ μ L. Interestingly, only one of these was an AIDS-defining opportunistic infection and others were not infections typically associated with HIV infection. Our mixed-effects regression model confirmed that the annualized risk of serious infections requiring hospitalization while CD4 < 200 cells/ μ L was over 10 times that when CD4 > 200 cells/ μ L. Clinically, this result can be useful to estimate recipient infection risk after thymoglobulin use, since essentially all of the serious infection risk occurred when the CD4+ T-cell count was suppressed below 200 cells/ μ L.

Despite the increased number of serious infections requiring hospitalization, we were successful in suppressing HIV viral replication and opportunistic infections in our study population using HAART and the prophylactic strategy described in Table 1. Say for one case of *candida* esophagitis, no serious or AIDS-defining opportunistic infections were observed. Furthermore, graft survival and graft function were very much acceptable in the study population; most patients enjoyed freedom from dialysis and had minimal complications.

The weaknesses of this study include the small size of the study population and the presence of potential confounders (such as the CD4-suppressing effects of sirolimus and corticosteroids, delayed graft function, increased calcineurin inhibitor levels, rejection itself or other unidentified factors), which could predispose thymoglobulin recipients to increased risk of infection. Although our

comparison of the pre-transplant recipient characteristics (Table 2) suggests that thymoglobulin recipients and non-recipients were similar at the time of transplant, other differences between these patients may also have contributed to the observed difference in infection rate. Future investigation with a study population large enough to construct a multiple predictor model will be necessary to characterize the independent effect of thymoglobulin on serious infection risk. Nevertheless, given the severe and life-threatening infections we observed in the relatively small number of thymoglobulin recipients described in this study, we thought it was important to report these early findings to the transplant community.

A major unresolved question is why HIV-infected kidney recipients reject at a 2-fold rate greater than non-HIV-infected recipients on similar immunosuppression regimens? In the multi-site report on 27 HIV-infected kidney recipients (2), no specific pattern of timing (early vs. late) or type (tubular vs. vascular) of rejection was discernable. Interestingly, high rates of acute rejection have not been observed in HIV-infected liver recipients (2). In this study, we began to use IL-2 receptor inhibition after we observed greater rates of rejection in the HIV kidney population. At this point in our experience, we have been unable to discern a beneficial effect on the incidence of acute rejection; further study with a larger recipient population is required.

In summary, our early experience shows that thymoglobulin is an effective therapy for acute rejection when combined with steroids, reversing rejection in the majority (6 of 7) of patients. Although thymoglobulin can be used safely without development of frequent opportunistic infections or progression to AIDS and death, it produces a profound suppression of the CD4+ T-cell and total lymphocyte count, which places the recipient at risk for serious infections requiring hospitalization. The potential use of the monoclonal anti-CD3 antibody OKT3 could be an alternative agent for the treatment of moderate-to-severe rejection with less long-term T-cell depletion, although its safety has not been reported in the HAART era. In light of these data, we cautiously recommend the use of thymoglobulin for the treatment of moderate-to-severe rejection in the HIV-infected transplant population, with close observation of the CD4+ T-cell count and aggressive evaluation of possible infectious complications until recovery (i.e. CD4 > 200 cells/ μ L) occurs.

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Carter et al.

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