Transplant Int (1992) 5 [Suppl 1]: S 129–S 132

TRANSPLANT
International

The course of HIV disease in renal allograft recipients

V. Delaney, N. Sumrani, J. Hong, R. Davis, B. Sommer

Department of Surgery, Division of Transplantation, State University of New York Health Science Center at Brooklyn, New York, USA

Abstract. The clinical course of HIV seropositive renal allograft recipients is ill defined. Thus, a retrospective analysis of mortality, morbidity and graft survival was performed in two groups of HIV-positive patients. Group 1 (nine patients), seropositive for an indefinite period of time prior to transplantation (eight IV drug abusers, one homosexual), all lost their grafts after a mean period of 23 ± 11 months from chronic rejection (six), complicated by focal glomerular sclerosis and nephrotic syndrome in three cases, sepsis (two) and death with a functioning graft (one). Four patients died, two from sepsis, one from Kaposi's sarcoma and one from fluid overload. Of the remaining five patients, all on hemodialysis, one had AIDS and four were asymptomatic after a mean period of 44 months following graft failure. Prolonged hospitalizations for both infections and acute rejection were common. Group 2 (six patients) seroconverted in the perioperative period, and two had functioning allografts at 78 and 100 months post-transplant. Causes of allograft loss, patient death and infection-related complications were similar to those of group 1, but acute rejection was rare. In conclusion, HIV infection in renal allograft recipients was associated with poor allograft survival due mainly to rejection, mostly chronic, often complicated by glomerular sclerosis and nephrotic syndrome. Infectious complications requiring hospitalization were also increased.

Key words: HIV – Transplants – Renal – AIDS – Azathioprine – Cyclosporine

More than 70000 people have died of AIDS in the US since its first description in 1981 [2] and it is estimated that an additional 1–2 million are infected with the causative retrovirus, namely HIV [2]. The latter invades, and ultimately destroys, lymphocytes bearing the T4 receptor leading to a relative preponderance of suppressor, or T8, lymphocytes and the production of destructive immunosuppression involving mainly, but not exclusively, cell-mediated immunity [6]. Thus its victims fall prey to a variety of opportunistic infections or unusual B-cell neoplasms and/or a progressive encephalopathy, often accompanied in the terminal stages by severe emaciation [5]. High-risk groups include homosexual males, bisexual men with multiple partners, infants born to infected mothers, and recipients of virus-contaminated blood and tissue products. The frequency of the latter has decreased considerably since 1985 when routine HIV screening of prospective donors became mandatory [15]. The incubation period of HIV is unknown but variable, with some individuals dying of AIDS within 2 years and others remaining asymptomatic for up to 12 years following infection with the virus [2].

Iatrogenic immunosuppression, as used following solid organ transplantation, in patients harboring the virus was thus considered imprudent with the anticipation of earlier death from lethal immunosuppression [1]. By the same token, rejection may be expected to be diminished in both intensity and frequency [2]. Based on the overriding influence of the former consideration, HIV-positive patients are not now (1990) generally considered suitable candidates for transplantation by most centers throughout Europe and the US, although clear-cut data supporting this conclusion are not available in the literature [2]. The uncertainty arises because of both the difficulty in diagnosing AIDS in immunosuppressed patients, the long and variable incubation period, and the usually imprecise timing of infection with the virus. We thus undertook a review of all known HIV-positive renal transplant recipients in a large urban center in the US in an attempt to clarify the clinical course post-transplant.

Materials and methods

A total of 256 patients who received renal transplants between 1976 and 1985 at the State University of New York Health Science Center at Brooklyn consented to HIV testing. Current sera and sera stored at −70°C from the time of transplantation were obtained from each

Offprint requests to: Nabil Sumrani, Department of Surgery, Division of Transplantation, State University of New York Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 40, Brooklyn, New York 11203, USA

patient and analyzed for the presence of HIV-1 antibodies by enzyme immunoassay (LAV-EIA; Genetic Systems, Seattle Wash.) and confirmed by Western blot (Immunoblot; Biorad, Richmond, Calif.). Of those tested, 17 were seropositive. Maintenance immunosuppression post-transplant consisted of azathioprine–prednisone until 1983 (four patients) when cyclosporine–low-dose prednisone (13 patients) was employed, both according to standard protocols [14]. Acute rejection was diagnosed by standard clinical and histological criteria [7] and treated with intravenous pulse methylprednisolone (250–500 mg/day) followed by polyclonal anti-lymphocyte globulin (Minnesota: 10–15 mg/kg per day) in biopsy-proven non-responders.

The following parameters were analyzed: demographics, mortality, graft survival, morbidity, incidence of rejection.

Results

Demographics (Table 1)

A total of 17 patients were HIV positive. Nine of these were positive at the time of transplantation (group 1), six became positive in the perioperative (0–6 months) period (group 2), and two were negative at the time of transplantation, but seroconverted at an unknown time point between 11 and 13 years, respectively, post-transplant (group 3). Mean follow-up periods for groups 1, 2 and 3 were 60 months (range 15–120), 88 months (range 52–94), and 156 months (range 141–168), respectively. Eight of nine patients in group 1 were intravenous drug users, in contrast to group 2 patients in whom the only identifiable risk factor was blood and/or organ donation. Both patients in group 3 were high-risk individuals [IV drug abuser (1) and homosexual (1)].

Table 1. Demographic details of HIV-seropositive renal transplant recipients

	Group 1	Group 2	Group 3
No. of patients	9	6	2
Mean			
Age (years)	31	40	28
Range	20–37	24–56	22–34
Male/female	8/1	5/1	1/1
Cadaveric	6	5	1
Race			
Asian	0 (0%)	1 (16.7%)	0 (0%)
Black	5 (55.6%)	1 (16.7%)	1 (50%)
Caucasian	0 (0%)	1 (16.7%)	0 (0%)
Hispanic	4 (44.4%)	3 (50%)	1 (50%)
Renal disease			
Focal sclerosis	5	2	0
GN	1	1	1
Diabetes	0	1	0
Unknown/others	3	2	1
Risk for HIV			
IVDA	8	0	1
Homosexuality	1	0	1
Blood/organ	0	6	0
CSA/prednisone	7	6	0
AZA/prednisone	2	0	2
Retransplant	1	0	0
Follow-up (months)	60 (15–120)	88 (52–94)	156 (141–168)

Table 2. Causes and times of death (months) in HIV-seropositive renal allograft recipients

Cause of death	*N*	Group	Survival time post-tx (months)
Gram-negative sepsis	1	1	61
Disseminated mycobacterial avium	1	1	15
Kaposi's sarcoma	1	1	27
Fluid overload, hyperkalemia	1	1	58
Hepatic failure, sepsis	1	2	42
Hepatic failure	1	2	52
Colon cancer	1	2	48
Hepatic failure, sepsis	1	3	144
Hepatic failure, PCP pneumonia	1	3	162

Table 3. Causes of renal allograft loss and graft survival times (months) in HIV-seropositive renal allograft recipients

	Group 1 ($n=9$)	Group 2 ($n=6$)	Group 3 ($n=2$)
No. of surviving allografts	0	2	0
Chronic rejection	(3) 11, 23, 24	(2) 36, 58	(2) 132, 156
Chronic rejection with nephrotic syndrome	(3) 13, 20, 30		
Sepsis	(2) 13, 57	(1) 50	
Death	(1) 27	(1) 57	

Numbers in parentheses are the number of allografts

Mortality (Table 2)

Eight patients died (Table 2) with an overall mortality of 53%. Causes of death in group 1 (four patients) included disseminated *Mycobacterium avium intracellulare* (MAI) infection (1), Gram-negative sepsis (1), cardiorespiratory arrest associated with fluid overload and hyperkalemia (1) and Kaposi's sarcoma (1) at 15, 61, 58 and 27 months post-transplant, respectively. Three patients died in group 2, two of non-A, non-B hepatic failure at 42 and 52 months post-transplant and one of metastatic colon cancer at 48 months. Both patients in group 3 died of liver failure (non-A, non-B), one of whom had concomitant PCP pneumonia, at 162 and 144 months post-transplant, respectively.

Graft survival (Table 3)

All patients in group 1 lost their allografts after a mean period of 23 ± 11 months. Causes of allograft loss included MAI infection of the allograft in association with acute and chronic rejection (1), bacterial sepsis with acute allograft failure superimposed upon chronic rejection as a preterminal event (1), chronic rejection (3), chronic rejection in association with transplant glomerulopathy and/or focal glomerular sclerosis (3, all of whom had nephrotic syndrome) and patient death with a functioning graft (1). Graft survival was 33% in group 2 with a mean follow-up of 89 months (range 78–100). Causes of graft loss included chronic rejection (3) at 36, 50 and 58 months post-trans-

plant, respectively, and patient death with a functioning graft at 57 months. Within this group two patients were alive at the time of writing with functioning allografts, one of whom had biopsy proven chronic rejection with focal glomerular sclerosis and nephrotic syndrome at 80 months post-transplant. The remaining patient had a serum creatinine of 177 μmol/l and minimal proteinuria at 94 months post-transplant. Both patients of group 3 lost their allografts from chronic rejection after 156 and 133 months, respectively.

Morbidity

Infections requiring hospitalization in group 1 included CMV (3), Salmonella (1), recurrent Gram-negative sepsis (2) and MAI (1). Mean hospital stay for allograft-related problems in this group was 11.8 weeks. In group 2 three patients developed unexplained fever in association with pancytopenia with spontaneous evolution 4 to 12 weeks post-transplant. Two patients had transient fever in association with generalized lymphadenopathy (non-specific hyperplasia on biopsy) at 6 and 9 weeks following engraftment. One recipient developed CMV retinitis and one PCP pneumonia. Mean hospital stay for this group was 10.5 weeks. Both patients in group 3 developed AIDS 144 and 162 months post-transplant and within 8 and 11 months following return to dialysis.

At the time of writing a total of six patients were on dialysis, five from group 1 and one from group 2 for a mean period of 44 (range 25–83) months, and two patients had AIDS, but the remaining four were asymptomatic.

Acute rejection was observed in 56% and 17% of group 1 and group 2, respectively.

Discussion

Being a retrospective analysis of a specific sub-group of renal allograft recipients, i.e. those that gave consent for HIV testing, this study has obvious shortcomings. However, since the majority of transplant centers are reluctant to perform renal transplantation in HIV-positive patients and since screening for the virus is now a prerequisite for getting on transplant lists in most countries, this relatively large single-center study presents a possibly unique opportunity to study the natural history of renal transplantation and associated immunosuppression, mainly cyclosporine, in patients with HIV infection.

Patients harboring HIV for unknown periods of time prior to transplantation had a dismal prognosis for allograft survival (Table 3). Surprisingly, from a conceptual stand-point, acute rejection, as diagnosed by standard clinical and histological criteria [7], was common with progression to chronic rejection occurring in the majority, half of whom had glomerular abnormalities in addition. These were suggestive of focal glomerular sclerosis with some features of transplant glomerulopathy [1] and were accompanied by nephrotic range proteinuria. This finding may also represent a recurrence of native glomerular disease, namely focal glomerular sclerosis, the underlying disease in the majority of this particular sub-group (Table 1) and thought to be more prevalent in blacks [9], intravenous drug abusers [3] and patients with AIDS nephropathy [8]. Even the diagnosis of acute rejection may be called into doubt in this group of patients, since interstitial nephritis can be a manifestation of HIV-associated renal involvement [12] in addition to being one of the hallmarks of acute rejection.

Patients who acquired the virus in the perioperative period while under routine heavy immunosuppression often developed a viral syndrome characterized by fever, pancytopenia and tender lymphadenopathy similar to that reported in previous studies [4, 10, 11], thought to represent the viremic phase of the acute HIV infection. In general, patients in this group and the subgroup which acquired the virus in the later postoperative period (group 3) had better allograft survival when compared with group 1 (Table 3).

Sepsis-related deaths (Table 2) and hospitalizations were more frequent than age- and time-controlled non-HIV renal transplant recipients within the same patient population [13], but whether the concomitant administration of immunosuppression accelerated the time of onset of HIV-related infectious complications is impossible to evaluate from the present data. Liver failure, a prominent pre-morbid clinical feature in the present study, was non-A, non-B, usually associated with sepsis and multiorgan failure, although a concomitant hepatitis C infection was not ruled out.

In summary, renal transplantation in HIV-seropositive patients in the present patient population has a poor prognosis for allograft and patient survival and is associated with substantial morbidity and expense related mainly to infection-related complications. For these reasons, and because dialysis is a readily available alternative treatment modality for end-stage renal disease, the latter is probably the therapeutic modality of choice at the present time.

References

1. Cameron JS (1982) Glomerulonephritis in renal transplants. Transplantation 34: 237–240
2. Feduska NJ (1990) Human immunodeficiency virus, AIDS, and organ transplantation. Transplant Rev 4: 93–107
3. Friedman EA, Rao TKS (1983) Why does uremia in heroin abusers occur predominantly in blacks? J Am Med Assoc 250: 2965–2966
4. L'Age-Stehr J, Schwarz A, Offermann G, Langmaack H, Bennhold I, Niedrig M, Koch MA (1985) HTLV-III infection in kidney transplant recipients. Lancet II: 1361–1362
5. Mills J, Masur H (1990) AIDs related infections. Sci Am 66: 50–57
6. Nabel GJ (1988) Activation of human immunodeficiency virus. J Lab Clin Med 111: 495–500
7. Olsen TS (1986) Pathology of allograft rejection. In: Williams GM, Burdick JE, Solez K (eds) Kidney transplant rejection. Diagnosis and treatment. Marcel Dekker, New York, pp 173–197
8. Prado V, Meneses R, Ossa L, Jaffe DJ, Strauss J, Roth D, Bourgoignie JJ (1987) AIDS-related glomerulopathy: occurrence in specific risk groups. Kidney Int 31: 1167–1173
9. Rao TKS, Friedman EA, Nicastri AD (1987) The types of renal disease in the acquired immunodeficiency syndrome. N Engl J Med 316: 1062–1068

10. Rubin RH, Jenkins RL, Shaw BW, Shaffer D, Pearl RH, Erb S, Monaco A, Van Thiel D (1987) The acquired immunodeficiency syndrome and transplantation. Transplantation 44: 1–4
11. Schwarz A, Hoffmann F, L'Age-Stehr, Tegzess AM, Offermann G (1987) Human immunodeficiency virus transmission by organ donation. Transplantation 44: 21–24
12. Seney FD, Burns DK, Silva FG (1990) Acquired immunodeficiency syndrome and the kidney. 16: 1–16
13. Sumrani NB, Hong JH, Hanson P, Butt KMH (1989) Renal transplantation in blacks: impact of immunosuppressive regimes. Transplant Proc 21: 3943–3946
14. Sumrani N, Delaney V, Ding Z, Butt K, Hong J (1990) HLA-identical renal transplants: Impact of cyclosporine on intermediate-term survival and renal function. Am J Kidney Dis 16: 417–422
15. United Network for Organ Sharing (1987) UNOS Policies, Richmond