Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African–American recipients of primary cadaver renal transplant

Tomasz Jarzembowski, Fabrizio Panaro, Vandad Raofi, Guanglong Dong, Giuliano Testa, Howard Sankary and Enrico Benedetti

Department of Surgery, Division of Transplantation, University of Illinois at Chicago, Chicago, IL, USA

Keywords
African–Americans, cadaveric kidney transplantation, tacrolimus.

Correspondence
Dr Enrico Benedetti MD, Department of Surgery, Division of Transplantation, University of Illinois at Chicago, 840 S. Wood St., Suite 402 M/C 958, Chicago, IL 60612, USA. Tel.: (312) 996-6771; fax: (312) 413-3483; e-mail: enrico@uic.edu

Received: 2 September 2003
Revised: 28 July 2004
Accepted: 4 October 2004

doi:10.1111/j.1432-2277.2004.00055.x

Summary

The ideal immunosuppressive treatment for African–American kidney transplant recipients has not been established. We performed a long-term prospective randomized trial comparing the results of tacrolimus (TAC) and cyclosporine (CSA) in the African–American population. Thirty-five African–American primary cadaveric renal transplant (CRT) recipients were enrolled in the study. Group I ($n = 14$) received TAC and group II ($n = 21$) received CSA; mean follow up was 78 months. We found no difference in patient/graft survival rates between the groups. Twelve patients in the CSA group were converted to TAC, mostly because of hypercholesterolemia or as a rescue for an acute rejection episode. Significant lower creatinine and cholesterol levels were seen at 1 year post-transplant, but this difference lost significance at 3 and 5 years, possibly because of conversion of most patients from CSA to TAC. In conclusion, African–American recipients of primary CRTs can achieve excellent long-term results with TAC-based immunosuppression.

Introduction

Current united network organ sharing (UNOS) data report 52% 5-year graft survival in African–American (AA) recipients of primary cadaveric renal transplant (CRT), which is markedly lower than in other racial groups [1]. The ideal immunosuppressive treatment for AA primary CRT recipients has not yet been established. Historically, cyclosporine (CSA) and tacrolimus (TAC) are the most commonly used immunosuppressive drugs in CRT. Single and multicentre data demonstrated improved effectiveness of TAC in prevention of acute rejection, normalization of lipid profile and decreasing creatinine level when compared with CSA based immunosuppression [2–5]. Furthermore, TAC superiority to CSA as a rescue therapy agent for rejection has been proven by many international studies [5–7]. However, TAC has been associated with an increased incidence of post-transplant diabetes when compared with CSA in the AA population [3].

We previously published the 1-year results of a prospective randomized trial comparing TAC versus CSA in AA recipients of primary CRT. The initial results showed a similar patient and graft survival but a decreased rejection rate, lower cholesterol levels and lower creatinine in the TAC-treated patients [8].

The purpose of the present study is to report the long-term results of our prospective, randomized trial of TAC versus CSA-based immunosuppression for AA recipients of primary CRT.

Patients and methods

Long-term follow up of this prospective randomized trial includes 35 AA (23 male and 12 female) primary CRT recipients. Patients were enrolled between 1995 and 1997 at the University of Illinois at Chicago Medical Center. The Institutional Review Board approved the study and written informed consent was obtained from all patients.

Patients who refused consent or who were already enrolled in any other studies were excluded. All patients received 7 days of induction therapy with OKT3 (Muromonab CD3; Ortho, Raritan, NJ, USA) at a dose of 5 mg/day starting on postoperative day 1. The patients were randomized into two groups using medical record number. Group I received TAC (Prograf®; Fujisawa USA, Deerfield, IL, USA) and prednisone. Group II received CSA (Neoral®; Novartis Pharmaceuticals, East Hanover, NJ, USA) and prednisone. Both TAC and CSA were administered orally with the initial dose given 6 h prior to transplant. Whole-blood trough target levels were measured by microparticle enzyme immunoassay for TAC. All patients received the same steroid induction and maintenance regimen. Methylprednisolone (500 mg) was given intravenously at induction of anaesthesia and oral prednisone was dosed postoperatively at 1.0 mg/kg/day with a gradual taper to a final maintenance dose of 0.2 mg/kg/day by 6 months. Cytomegalovirus (CMV) seronegative recipients of CMV seropositive graft received oral acyclovir at a dose of 800 mg four times daily for 3 months post-transplant.

All clinically suspected rejection episodes were confirmed by percutaneous allograft biopsy using ultrasound guidance. Acute rejection was treated with a 3-day course of methylprednisolone intravenously at a dose of 500 mg/day. Steroid-resistant rejections were treated with OKT3 or ATG (ATGAM; Upjohn Company, Kalamazoo, MI, USA). CSA-treated patients with acute rejection resistant to antilymphocyte treatment were converted to TAC. Routine clinical follow up included serial assessment of electrolytes, liver function tests, lipid profiles, serum creatinine, coagulation profile and complete blood count. Delayed graft function was defined as the need for haemodialysis post-transplant. Graft loss was defined by graft nephrectomy, return to dialysis or death with a functioning graft.

Patient and graft survival rates, incidence of rejection (acute and chronic), serum cholesterol and creatinine levels were analysed in both groups.

Statistical analysis

Actuarial patient and graft survival rates were calculated by the Kaplan–Meier method. Comparison between CSA and TAC group was carried out by unpaired *t*-test and chi-squared test.

Results

Fourteen patients were randomized to receive TAC plus prednisone (group I), while 21 patients were treated with CSA-based immunosuppression plus prednisone (group II). The two groups were comparable with respect to age, gender, cold ischaemia time and the number of human leucocyte antigen (HLA) mismatches (Table 1).

Overall, 1-year patient and graft survival was the same at 91%. Two patients from group I and one patient from group II died of cardiovascular complications at 3, 6 and 7 months post-transplant respectively. Patient and graft survival were 86% (12 of 14) for the TAC group and 95% (20 of 21) for the CSA group ($P = 0.71$) at 1-year. At 3 and 5 years, patient and graft survival were 78.6% for TAC group and 95.2% for CSA group at both intervals, with $P = 0.1$ and $P = 0.1$ at 3 and 5 years respectively (Fig. 1).

Rejection

No graft was lost because of rejection in either group. During the observation period, there were three (21%) acute rejection episodes documented in group I versus 10 (48%) in group II ($P = 0.22$). One of the two cases of acute rejection in the TAC group was steroid resistant and required OKT3 treatment. Three of the acute rejection episodes in the CSA group were steroid resistant, requiring OKT3. One case of chronic rejection was

Table 1. Patient demographics.

	Group I (tacrolimus)	Group II (cyclosporine)
No. of patients	14	21
Age (years)	44 ± 14	46 ± 11
Male/female ratio	8/6	16/5
Cold ischaemia time	25 ± 8	26 ± 10
Human leucocyte antigen mismatch	3.8 ± 1.2	4.5 ± 1.2

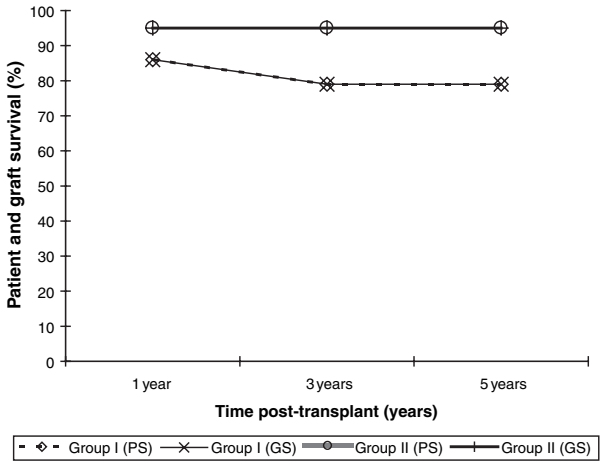

Figure 1 Patient and graft survival at 1,3 and 5 years post-transplant in tacrolimus and cyclosporine group.

Table 2. Creatinine and cholesterol at 1, 3 and 5 years post-transplant.

	Group I (tacrolimus) $n = 14$ (mg/dl)	Group II (cyclosporine) $n = 21$ (mg/dl)	*P*-value
Serum creatinine at			
1 year	1.39	1.94	0.02
3 years	1.68	1.85	NS
5 years	1.87	2.0	NS
Serum cholesterol at			
1 year	198	244	0.03
3 years	195	215	NS
5 years	187	225	NS

documented in the TAC group versus five in the CSA group ($P = 0.41$). Two of these three patients were converted to TAC as rescue for OKT3-resistant rejection. No patient in the TAC group was switched to CSA. Twelve patients (57%) in the CSA group were converted to TAC, mostly because of hypercholesterolemia or as a rescue for acute rejection episode. Ten patients were converted to TAC during the first year post-transplant after their rejection episodes, while the other two were converted to TAC for hypercholesterolemia despite lipid-lowering medical treatment after the initial post-transplant year.

Cholesterol and creatinine

Serum cholesterol and creatinine levels were compared at 1, 3 and 5 years post-transplant (Table 2). Mean creatinine and cholesterol level were significantly lower in the TAC group only at 1 year ($P = 0.02$, $P = 0.03$, respectively) and not significantly different thereafter. However, there was an overall trend of lower cholesterol and creatinine level in the TAC group when compared with the CSA group.

Post-transplant diabetes

The incidence of *de novo* post-transplant diabetes was 21% in the TAC-treated and 19% in the CSA-treated groups ($P = $ NS).

Discussion

African–American primary CRTs have historically experienced a higher incidence of acute rejection and poorer rates of patient and graft survival compared with any other race [1,9–13]. The reasons for this discrepancy have been attributed to HLA mismatching, mismatched Lewis blood group and medical noncompliance related to socioeconomic status [2,14–17]. Furthermore, immunological hyper-responsiveness, pharmacokinetics unique to AA and decreased effectiveness of immunosuppressive agents have all been thought to contribute to poor patient and graft survival rates [16,18–20].

The optimal immunosuppressive regimen for the AA population is still a controversial issue. The literature provides contradictory reports regarding the effectiveness of CSA-based immunosuppression. Some authors report that with the introduction of CSA, patient and graft survival in AA recipients at 1 year has increased, while others showed no change in those rates compared with the pre-CSA era [12,16,21,22]. There is good evidence that the introduction of antilymphocyte induction associated with CSA-based immunosuppresion has significantly improved patient and graft 1-year survival rates in these recipients [9]. Since the introduction of TAC in the mid-1990s, several studies conducted in Europe and the US have shown significant reduction in acute rejection rates, and cholesterol and creatinine levels in TAC-treated renal transplant patients compared with those treated with CSA [3,4,17,22].

Neylan analysed in the subgroup of 104 AA recipients the results of a large randomized clinical trial comparing TAC and CSA in renal transplantation [3]. The author concludes that TAC is more effective than CSA in preventing rejection in AA, but the drug increases the risk of post-transplant diabetes, particularly in this population.

In our previous report, we have shown that there was no difference in patient and graft survival between TAC- and CSA-treated AA primary CRT recipients at 1-year follow up [8]. However, our study documented a trend for decreased incidence of acute and chronic rejection in the TAC-treated patients as well as significantly lower serum cholesterol and creatinine at 1 year.

The long-term follow up of the study herein presented confirms similar patient and graft survival in the two study groups analysed according to the 'intention-to-treat' method. Serum cholesterol and creatinine, albeit lower in TAC-treated patients, are no longer significantly different. However, over time 12 patients (57%) have been converted from CSA to TAC either for rescue therapy for rejection or for severe hypercholesterolemia.

Our data suggest that it is possible to achieve excellent long-term graft survival in AA recipients of primary CRT with a combination of antilymphocyte induction therapy and maintenance with a calcineurin inhibitor, either TAC or CSA. However, TAC-treated patients experience decreased incidence of acute rejection episodes and lower serum cholesterol and creatinine levels in short-term follow up compared with CSA-treated patients. If CSA is chosen as an initial therapy, a liberal policy of conversion to TAC should be considered, especially in the presence

of adverse events such as rejection or hypercholesterolemia, in AA recipients.

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