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Sirolimus improves the two-year outcome of renal allografts in African-American patients

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Abstract The present study evaluated whether the addition of sirolimus to a cyclosporine (CyA)/prednisone (Pred) regimen mitigated the greater proclivity to acute rejection episodes and graft loss characteristic of African-American renal transplant recipients. Using Kaplan-Meier and log-rank tests, African-American renal transplant recipients treated with either CyA/Pred ($n = 90$) or sirolimus/CyA/Pred ($n = 47$) were compared with 120 Caucasian patients treated with sirolimus/CyA/Pred for 2-year rates of patient and graft survival as well as acute rejection episodes. Mean laboratory values were compared using analysis of variance and *F*-tests. Addition of sirolimus to the CyA/Pred regimen reduced the incidence of acute rejection episodes in African-Americans from 43.3% to 19.2% ($P = 0.004$), a value similar to Caucasian patients. The 97.9% 2-year graft survival rate among 47 African-American patients treated with sirolimus/CyA/Pred was significantly higher than the 85.6% rate shown among the 90 CyA/Pred-treated African-American transplant recipients ($P = 0.0479$) and similar to that in Caucasians. The 95.7% patient survival rate among the African-American sirolimus/CyA/Pred group was similar to the 97.8% rate in the African-American CyA/Pred cohort. Interestingly, there was no evident toxicity from the addition of sirolimus. The addition of sirolimus to a CyA-based regimen reduced acute rejection episodes and graft loss experienced by African-American renal transplant recipients.

Keywords Renal transplant · Immunosuppression · Sirolimus · Pharmacokinetics · African-American

Abbrevations *AUC* Area under the concentration-time curve · C_{av} Average concentration · $Cmin_{ss}$ Trough concentration · *CyA* cyclosporine · *Pred* Prednisone

Introduction

African-American renal transplant recipients experience substantially greater rates of acute rejection episodes and allograft failure than Caucasian recipients [3, 6, 8, 9, 20, 26, 36, 37, 38, 43] due to numerous factors. First, African-Americans tend to receive cadaveric allografts bearing a greater number of mismatched donor-recipient HLA and/or Lewis blood group antigens due to the predominance of Caucasian organ donors and to the high degree of polymorphism of antigens among and distinctive for African-Americans [2, 31, 39]. Second, African-Americans display pharmacokinetic and pharmacodynamic risk factors. While the more limited drug absorption [14, 30] characteristic of this group has been at least partly mitigated by the new microemulsion formulation (as opposed to the oil-based version) of cyclosporine (CyA) [23], African-American patients dis-

play more rapid drug clearance rates of CyA [29] and tacrolimus [34] that predispose these transplant recipients to the occurrence of rejection episodes. Although African-Americans, compared with other ethnic groups, exhibit lower clearance rates and smaller volumes of distribution, resulting in higher levels of cortisol [41], they display a pharmacodynamic resistance to methylprednisolone in assays of lymphocyte performance both in the resting and activated states [44]. Furthermore, African-Americans rapidly methylate, and thereby inactivate, azathioprine [4]. Third, African-Americans display a greater incidence of pre-sensitization due to transfusion with Caucasian blood products [25] and to increased allo-reactivity in both nonspecific immune assays and in donor-specific responses of recipient cells in mixed lymphocyte cultures [24]. Thus, effective immunosuppression in African-Americans requires higher doses of antirejection agents, such as steroids, CyA [8, 10], mycophenolate mofetil [33], tacrolimus [34], and OKT3 [27]. A fourth contributing factor to graft loss is the exaggerated vascular reactivity of African-American patients, which leads to a higher incidence and severity of hypertension. Finally, African-Americans show a greater rate of noncompliance to medication regimens [7] disproportionate to that of members of other ethnic groups who also are of lower socioeconomic status [2]. While little can be done to mitigate immunological, genealogical/medical, or social/economic risk factors, new more potent immunosuppressive regimens may improve outcomes for African-American renal transplant recipients.

Sirolimus is a potent new immunosuppressive agent that acts in a fashion complementary to, and probably synergistic with, CyA [12, 16]. Among the 167 primary renal transplant patients of these two ethnic groups treated de novo for more than 2 years with sirolimus/CyA/prednisone (Pred) in Houston, 47 are of African-American descent. The present study reports the results in this sirolimus/CyA/Pred cohort compared with those of 90 African-American transplant recipients treated during this same interval with CyA/Pred and with 120 Caucasian patients receiving sirolimus/CyA/Pred.

Patients and methods

Patient groups and baseline immunosuppressive regimens

This study includes 137 African-American renal allograft recipients who were assigned to two overlapping cohorts based on those that refused (CyA/Pred; $n = 90$) and those that agreed (CyA/Pred/sirolimus; $n = 47$) to enter the clinical trials. The results among African-Americans were compared to the outcomes among a cohort of 120 Caucasian patients who were entered into the same sirolimus clinical trials. All patients received a concentration-controlled regimen whereby CyA doses were selected to obtain target drug concentrations. The concentration-control strategy [18] to individualize dosing of CyA compensated for the otherwise apparent pharmacokinetic differences between the two CyA formulations [17]. The initial CyA dose was selected based upon calculation of the drug clearance rate and relative oral (p.o.) bioavailability using paired pretransplant pharmacokinetic profiles after administration of one intravenous and at least five subsequent p.o. doses of CyA. The clearance and bioavailability parameter estimates were used to estimate the appropriate starting CyA dose that would achieve a 550 ± 50 ng/ml target average concentration (C_{av}); namely, the quotient of the area under the concentration-time curve (AUC) and the dosing interval (in hours) [5, 15]. CyA doses thereafter were adjusted based on C_{av} values calculated from serial pharmacokinetic profiles using an algorithm previously described in detail [18]. Because the regimen was concentration-controlled, there was no difference in the drug exposure among the 33 patients who received the microemulsion formulation (Neoral Novartis, Basel, Switzerland) or the 57 patients who received the gel-capsule formulation (Sandimmune Novartis) or the 47 patients who received the microemulsion formulation of CyA in conjunction with sirolimus. The two cohorts of CyA/Pred-treated patients (Sandimmune and Neoral) were combined into one group for the present analyses since there was no difference in the incidences of acute rejection episodes or graft loss between the cohorts that received either the Sandimmune or the Neoral CyA formulation in conjunction with Pred.

The steroid regimen included an intraoperative bolus injection of 500 mg methylprednisolone, followed by an oral recycling from 200 to 30 mg/day of Pred by day 6, 15 mg/day by day 90, 10 mg/day by day 180, and 7.5 mg/day by day 365 [1]. None of the patients received either induction therapy with antilymphocyte antibodies or maintenance therapy with a nucleoside synthesis inhibitor.

Sirolimus was provided by Wyeth-Ayerst (Radnor, Pa.) either as a solution (5 mg/ml) or a tablet (1 mg) formulation, both of which showed pharmacologic and therapeutic equivalence [22]. After a loading dose three-times greater, the sirolimus doses were stipulated by the various research protocols to be between 0.5 mg/m^2 and 7.0 mg/m^2; the doses were adjusted only in response to clinical or laboratory evidences of toxicity [19]. The Committee for the Protection of Human Subjects at the University of Texas-Houston Health Science Center approved the study protocols, each of which complied with the Helsinki Declaration of 1975. Every patient signed an informed consent document.

Drug measurements

CyA whole-blood concentrations were measured using the fluorescence polarization immunoassay with a selective monoclonal antibody (TDx, Abbott, N. Chicago, Ill.) [28]. The C_{av} targets, derived from previous studies [18], were 550 ± 50 ng/ml during the first month, 500 ± 50 ng/ml during the second and third months, 450 ± 50 ng/ml during months 4 through 6, 400 ± 50 ng/ml from 7 to 12 months, and 350 ± 50 ng/ml thereafter. CyA dosing regimens were modified when an increased serum creatinine value (or other toxicity) was attributed to an adverse reaction to CyA. Sirolimus trough concentration ($Cmin_{ss}$) measurements performed with a validated high-performance liquid chromatography method using ultraviolet detection (LC–UV) selectively estimated the content of parent compound [32]. Since previous data demonstrated an excellent correlation ($r = 0.946$) between $Cmin_{ss}$ and AUC values of sirolimus [45], $Cmin_{ss}$ measurements were utilized as indicators of sirolimus exposure.

Table 1 Demographic features of African-American patients in the cohorts treated with sirolimus/CyA/Pred and CyA/Pred alone (*CyA* cyclosporine, *PRA* panel-reactive antibody, *Pred* prednisone)

Feature	Cohorts		
	African American[a]		Caucasian[a]
	CyA/Pred $n = 90$	Sirolimus/CyA/Pred $n = 47$	Sirolimus/CyA/Pred $n = 120$
Age (mean ± SD; years)[b]	41.7 ± 12.0	40.3 ± 12.9	45.1 ± 13.7[c]
Body weight (mean ± SD; kg)[b]	76.6 ± 15.4	82.7 ± 20.6	77.2 ± 19.7
Body mass index (mean ± SD; kg/m^2)[b]	25.7 ± 4.6	27.0 ± 4.7	26.5 ± 6.0
Pretransplant PRA (mean ± SD; %)[b]	1.8 ± 5.1	2.4 ± 4.2	3.6 ± 8.0
Number of HLA mismatches (mean ± SD)[b]	4.1 ± 1.7	4.7 ± 1.5[d]	4.0 ± 1.6[d]
Gender[e]			
Male (*n*, %)	58 (64.4)	28 (59.6)	72 (60)
Female (*n*, %)	32 (35.6)	19 (40.4)	48 (40)
Donor Source[e]			
Cadaveric donor (*n*, %)	63 (70.0)	35 (74.5)	68 (56.7)[f]
Living donor (*n*, %)	27 (30.0)	12 (25.5)	52 (43.3)
Primary transplant (*n*, %)[e]	77 (85.6)	40 (85.1)	99 (82.5)
Hypertension (*n*, %)[e]	32 (97.0)	45 (95.7)	104 (86.7)
Diabetes (*n*, %)[e]	30 (33.3)	12 (25.5)	27 (22.5)

[a] None of the differences were significant, except as noted
[b] Analysis of variance, unpaired Student's *t*- and *F*-tests
[c] The age difference between the African-American and Caucasian recipients in the sirolimus/CyA/Pred groups was significant, $P = 0.0401$
[d] The difference between the number of HLA mismatches was significant between all groups: $P = 0.0437$ for the African-American cohorts and $P = 0.016$ for the African-American vs Caucasian recipients in the sirolimus/CyA/Pred groups
[e] Fisher's exact and Pearson chi-square tests
[f] The difference in cadaveric donor source between the African-American vs Caucasian recipients in the sirolimus/CyA/Pred groups was significant, $P = 0.035$

Pharmacokinetic measurements

Pharmacokinetic parameters were calculated from drug profiles using noncompartmental methods [11]. CyA profiles included blood samples obtained prior to, as well as at 2, 4, 6, 8, and 12 h after, drug administration. Sirolimus profiles included whole-blood samples collected before drug administration and at 0.5, 1, 2, 4, 6, 10, 14, and 24 h after administration. The trapezoidal rule was used to calculate the AUC. Some protocol-specific studies stipulated slight modifications in the sampling schedule. For the purpose of assessing the impact of ethnic differences on pharmacokinetic parameters, estimates from the 6 African-American patients who underwent concentration profiling were compared to those of 19 demographically matched Caucasian patients (data not shown).

Diagnosis and treatment for rejection

The presence of an acute rejection episode was uniformly confirmed by renal graft biopsy, and the severity was scored according to the Banff 1993 criteria [40]. Mild (Banff grade I) biopsy-proven rejection episodes were treated with steroid pulse therapy alone. Those episodes that were moderate or severe in degree (grades II and III) or that had been refractory to steroid treatment were treated with either OKT3 or ATGAM [1].

Statistical methods

Statistical analyses compared the results in the two treatment groups (sirolimus/CyA/Pred vs CyA/Pred). Fisher's exact test was used to assess differences between categorical demographic features among African-American patients treated with each regimen, including gender, donor source, and pretransplant diagnosis of diabetes. Analysis of variance and unpaired Student's *t*-test was used to compare mean age, body weight, body mass index, number of HLA mismatches, and percentage of panel-reactive antibody. Pharmacokinetic parameters ($Cmin_{ss}$, AUC, C_{av}) after administration of CyA or sirolimus were compared using analysis of variance between African-American and non-African-American renal transplant recipients. Analysis of variance was used to compare the mean values of laboratory parameters. The 2-year patient and graft survival rates as well as the time to biopsy-proven rejection were compared between ethnic groups using Kaplan-Meier and log-rank tests. The severity of acute rejection episodes was compared by chi-square analysis between African-Americans treated with each regimen.

Results

Baseline characteristics

The demographic features of the 47 African-American patients who received sirolimus/CyA/Pred were similar

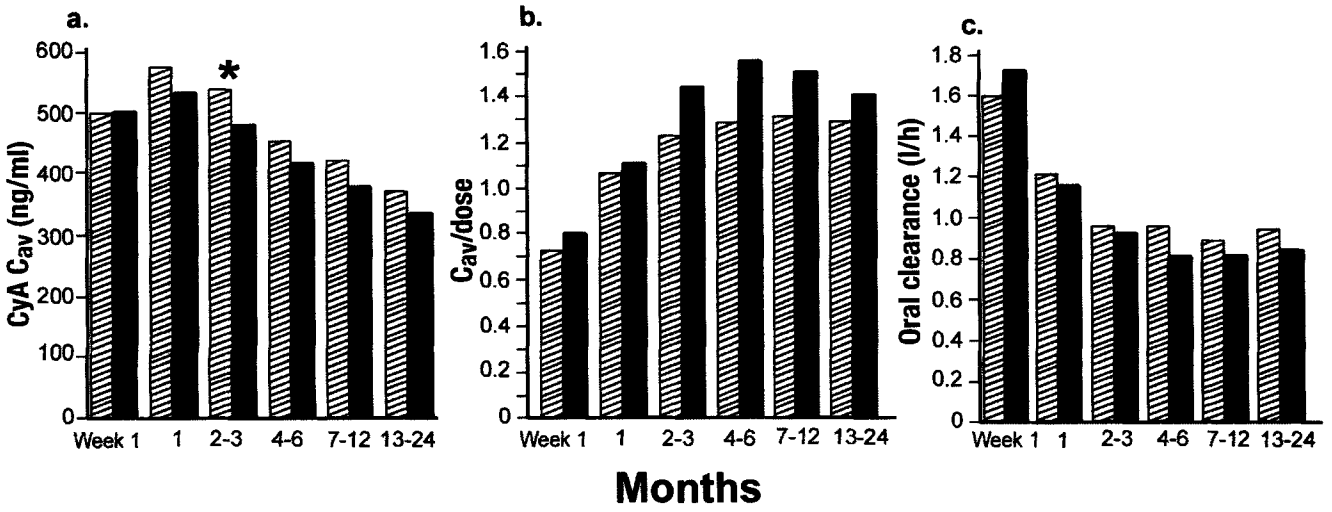

Fig. 1 Cyclosporine (*CyA*) pharmacokinetics in African-American patients treated without (▨) or with (■) sirolimus: **a** CyA average concentration (C_{av}) exposure (ng/ml), **b** normalized exposure (C_{av}/dose), and **c** CyA oral clearance rates (l/h). None of the differences were significant except months 2–3 in panel a (*), $P < 0.01$

Table 2 Comparison of dose-corrected sirolimus pharmacokinetic parameters between African-American and non-African-American patients (*AUC* area under the concentration-time curve, C_{max} maximum concentration, $Cmin_{ss}$ trough concentration, *PK* pharmacokinetic)

Dose-corrected PK parameter (Months 4–6)	Mean ± SD		
	African-American	Caucasian	*P*
$Cmin_{ss}$ (ng/ml)	5.02 ± 3.17	3.36 ± 1.92	NS
C_{max}/mg (ng/ml)	13.15 ± 5.89	9.12 ± 4.47	NS
AUC (ng × hr/ml)	152.75 ± 70.10	120.34 ± 64.72	NS
Clearance (l/h)	0.01 ± 0 .00	0.01 ± 0.01	NS

to the 90 African-American patients treated with CyA/Pred (Table 1) except that the former cohort showed a larger mean number of HLA mismatches. The cohort of Caucasian patients entered into the same sirolimus trials showed similar demographic characteristics as the African-Americans, save for the greater number of living donors and the higher mean age in the former group.

Pharmacokinetic parameters among treatment groups

The mean values of CyA exposure among the African-American renal transplant patients in the two groups were similar except during months 2 and 3, when the observed (Fig. 1 a), but not the dose-corrected (Fig. 1 b), value was significantly higher in the CyA/Pred than in the sirolimus/CyA/Pred cohort. There was no significant difference in the mean oral clearance rates between the patients in the two groups (Fig. 1 c).

Comparison of the steady-state pharmacokinetic parameters of sirolimus, namely, the dose-corrected $Cmin_{ss}$, AUC, and maximum concentration, as well as oral clearance at months 4–6 revealed no significant differences between African-American and Caucasian patients (Table 2). These findings suggest that, in contradistinction to CyA for which ethnic background is an important determinant of pharmacokinetic behavior, ethnicity does not seem to affect sirolimus concentrations.

Acute rejection episodes

At 2 years, the incidence of acute rejection episodes among African-American renal transplant recipients was reduced from 43.3% (39/90) among the CyA/Pred-treated group (Fig. 2 a) to 19.2% (9/47; $P = 0.004$) for the sirolimus/CyA/Pred cohort, which was similar to 20.8% (25/120; $P = 0.93$) among the Caucasian recipients treated with this regimen. In contrast, this limited cohort of patients did not show a significant difference in the occurrence rates of the histopathologic diagnosis of chronic nephropathy (Fig. 2 b). Although the CyA C_{av} was actually lower among patients who did not experience rejection, there was a trend towards a lower sirolimus $Cmin_{ss}$ value measured within 2 weeks prior to acute rejection episode among African-American patients (Table 3); however, the data are limited by the small size of the cohorts.

The 2-year graft survival rate among African-Americans (46/47; 97.9%) was similar to that displayed by Caucasian patients treated with sirolimus/CyA/Pred (110/120; 91.7%) and significantly higher than 85.6% (77/90) for African-American patients treated with

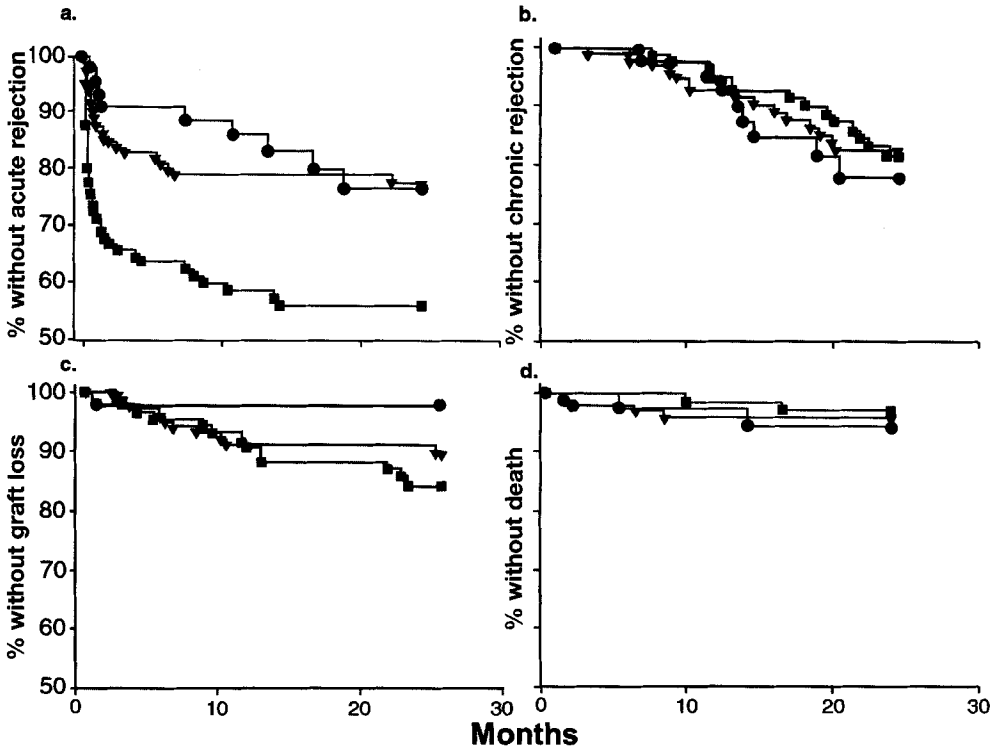

Fig. 2 Comparison of outcomes among African-American patients treated with cyclosporine (*CyA*)/prednisone (*Pred*) (■--■) versus sirolimus/CyA/Pred (●—●) or Caucasian patients treated with sirolimus/CyA/Pred (▼—▼). Cohorts compared using Kaplan-Meier and log-rank tests for: **a** time to acute rejection, African-American CyA/Pred versus the other two cohorts, $P = 0.004$; **b** time to chronic rejection, P = NS; **c** time to graft loss, African-American CyA/Pred versus the other two cohorts, $P = 0.03$; and **d** time to death, P = NS

Table 3 Lack of correlation between CyA or sirolimus $Cmin_{ss}$ and the occurrence of a rejection episode in African-American patients (*$Cmin_{ss}$* trough concentration, *CyA* cyclosporine, *Pred* prednisone)

Cohort	Mean value ± SD		
	No rejection	Rejection	*P*
CyA/$Cmin_{ss}$ (ng/ml)			
CyA/Pred	354.86 ± 100.67	478.75 ± 130.80	0.80
Sirolimus/CyA/Pred	264.91 ± 109.81	430.33 ± 198.0	0.08
Sirolimus $Cmin_{ss}$ (ng/ml)			
Sirolimus/CyA/Pred	10.32 ± 7.77	4.90 ± 4.10	0.61

CyA/Pred (Fig. 2c, $P = 0.048$). Despite the enhanced immunosuppression, patient survival rates among African-Americans in the two treatment groups were not significantly different at 2 years; namely, 95.7% for sirolimus/CyA/Pred compared to 97.8% for CyA/Pred therapy (Fig. 2d) and similar to the Caucasian cohort (96.7%). Thus, the benefit of sirolimus to reduce acute rejection episodes among African-American transplant recipients was not mitigated by a penalty of reduced patient survival rates.

Toxicity

To evaluate the adverse event profiles, the mean values of laboratory parameters were compared among African-American patients treated with versus without sirolimus in combination with CyA and Pred. Fig. 3 shows no significant differences between the mean values of serum cholesterol (mg/dl), triglycerides (mg/dl), creatinine (mg/dl), hemoglobin (g/dl), white blood cells ($n/mm^3 \times 10^{-3}$), or platelets ($n/mm^3 \times 10^{-3}$). In contrast, the African-Americans tended to show less evidence of toxicity than Caucasian patients for hypertriglyceridemia at 1, 3 and 12 months and less leukopenia at 1, 3 and 6 months.

Discussion

African-American recipients experience a higher risk of renal transplant loss owing to a variety of immunological, pharmacological, medical, and socioeconomic factors. Although CyA has revolutionized the overall practice of transplantation, its narrow therapeutic window between immunosuppressive and nephrotoxic drug concentrations is exacerbated among African-Americans who, in addition, show both pharmacokinetic

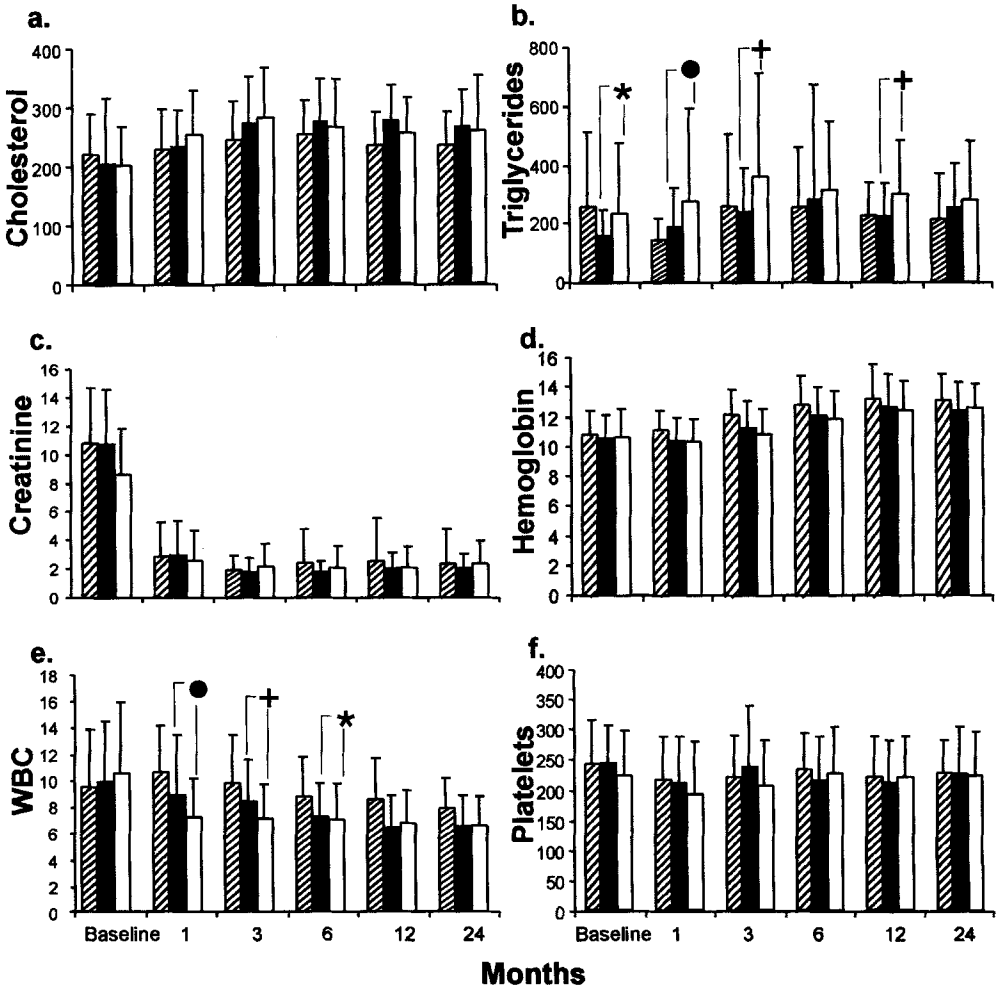

Fig. 3 Comparison of laboratory values between African-American patients receiving cyclosporine (*CyA*)/prednisone (*Pred*) (▨) and those receiving sirolimus/CyA/Pred (■) as well as Caucasians receiving sirolimus/CyA/Pred (□): **a** cholesterol (mg/dl), **b** triglycerides (mg/dl), **c** creatinine (mg/dl), **d** hemoglobin (g/dl), **e** white blood cells (*WBC*) ($n/mm^3 \times 10^{-3}$), and **f** platelets ($n/mm^3 \times 10^{-3}$). Comparisons between African-American and Caucasian patients treated with sirolimus/CyA/Pred: * $P < 0.05$; ● $P = 0.02$; + $P = 0.004$

properties of low drug absorption and rapid clearance rates, as well as greater pharmacodynamic resistance. Thus, despite higher CyA doses, patients of this ethnic background display lower survival rates of both living- and cadaveric-donor transplants. The data reported herein suggest that this risk is overcome by the addition of sirolimus to a concentration-controlled CyA-based regimen.

African-American patients who received sirolimus in addition to CyA/Pred experienced a significantly lower incidence of biopsy-proven acute rejection episodes within 2 years after kidney transplantation, namely, 19.2% compared to 43.3% for CyA/Pred-only patients ($P = 0.004$), and an increased rate of graft survival, namely, 97.9% compared to 85.6% ($P = 0.048$). These findings are notable because African-American patients have tended to experience lower graft survival rates than Caucasian patients when treated with regimens based upon calcineurin inhibitors. Improvements in immunosuppression such as this one are critical because of the difficulty of finding good HLA matches between the predominantly Caucasian donor group and African-American recipients [42]. Notwithstanding the enhanced acute rejection prophylaxis, the addition of sirolimus to a CyA-based regimen did not compromise patient survival among African-American renal transplant recipients.

Furthermore, these benefits were achieved without apparent toxicity as evidenced by less of an increase in serum cholesterol, triglyceride, or creatinine values, or of a decrease in hemoglobin, platelet, or white blood cell counts. The failure to augment hyperlipidemia is an important finding in this patient population owing to their high incidence of concomitant hypertension with left ventricular hypertrophy [21]. Thus, African-American patients show the favorable constellation of responses to sirolimus: enhanced immunosuppression and resistance to drug-induced toxicity. In contrast, African-Americans treated with the higher doses of tacrolimus necessary to obtain a satisfactory clinical effect display a markedly increased incidence of post-transplant diabetes mellitus [35].

Unlike CyA, the pharmacokinetic parameters of sirolimus seem to be similar for both African-American and Caucasian recipients. Thus, sirolimus absorption and clearance rates do not seem to be affected by ethnicity. Interestingly, African-American patients did not show a lower degree of sirolimus exposure on a dose-corrected basis compared with Caucasian patients.

The findings of this study indicate that sirolimus represents a significant addition to the immunosuppressive armamentarium for African-Americans, a group of patients at high risk for acute rejection episodes and graft loss. Although the present limited-sized single-center study did not document a statistically significant improvement in the chronic rejection rate, this issue should be further explored in multicenter trials since several lines of investigation suggest that sirolimus may display several characteristics that may mitigate this most dreaded complication [13].

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References

1. Browne B, Kahan BD (1994) Renal transplantation. In: Kahan BD (ed) Surgical clinics of North America: horizons in transplantation. Saunders, Philadelphia, pp 1097–1116
2. Butkus DE, Meydrech EF, Raju SS (1992) Racial differences in the survival of cadaveric renal allografts: overriding effects of HLA matching and socioeconomic factors. N Engl J Med 327: 840–845
3. Cecka MJ, Terasaki PI (1995) The UNOS scientific renal transplant registry. In: Terasaki PI, Cecka JM (eds) Clinical Transplants. UCLA, Los Angeles, pp 1–18
4. Chocair PR, Duley JA, Simmonds HA, Cameron JS (1992) The importance of thiopurine methyltransferase activity for the use of azathioprine in transplant recipients. Transplantation 53: 1051–1056
5. Chueh SC, Kahan BD (1998) Pretransplant test-dose pharmacokinetic profiles: cyclosporine microemulsion versus corn oil-based soft gel capsule formulation. J Am Soc Nephrol 9: 297–304
6. Dawidson IJ, Coorpender L, Fisher D, Helderman H, Hull A, Palmer B, Peters P, Sagalowsky A, Sandor ZF, Toto R, Reisch J (1990) Impact of race on renal transplant outcome. Transplantation 49: 63–67
7. Didlake RH, Dreyfus KK, Kerman RH, Van Buren CT, Kahan BD (1988) Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. Transplant Proc 20 [Suppl 3]: 63–69
8. Diethelm AG, Blackstone EH, Naftel DC, Hudson SL, Barber WH, Deierhoi MH, Barger BO, Curtis JJ, Luke RG (1988) Important risk factors of allograft survival in cadaveric renal transplantation: a study of 426 patients. Ann Surg 207: 538–548
9. Dunn J, Vathsala A, Golden D, Kerman R, Lawen J, Van Buren CT, Lewis R, Kahan BD (1989) Impact of race on the outcome of renal transplantation under cyclosporine-prednisone. Transplant Proc 21: 3946–3948
10. First MR, Schroeder TJ, Monaco AP, Simpson MA, Curtis JJ, Armenti VT (1996) Cyclosporine bioavailability: dosing implications and impact on clinical outcomes in select transplantation subpopulations. Clin Transplant 10: 55–59
11. Gibaldi M (1991) Biopharmaceutics and clinical pharmacokinetics. Lea and Febiger, Philadelphia
12. Kahan BD (1997) Sirolimus: a new agent for clinical renal transplantation. Transplant Proc 29: 48–50
13. Kahan BD (1998) The role of rapamycin in chronic rejection prophylaxis: a theoretical consideration. Graft 1 [Suppl 2]: 93–96
14. Kahan BD, Kramer WG, Wideman C, Flechner SM, Lorber MI, Van Buren CT (1986) Demographic factors affecting the pharmacokinetics of cyclosporine estimated by radioimmunoassay. Transplantation 41: 459–464
15. Kahan BD, Welsh M, Rutzky L, Lewis R, Knight R, Katz S, Napoli K, Grevel J, Van Buren CT (1992) The ability of pretransplant test-dose pharmacokinetic profiles to reduce early adverse events after renal transplantation. Transplantation 53: 345–51
16. Kahan BD, Tejpal N, Gibbons-Stubbers S, Tu Y, Wang M, Stepkowski S, Chou TC (1993) The synergistic interactions in vitro and in vivo of brequinar sodium with cyclosporine or rapamycin alone and in triple combination. Transplantation 55: 894–900
17. Kahan BD, Dunn J, Fitts C, Van Buren D, Wombolt D, Pollak R, Carson R, Alexander JW, Choc M, Wong R, Hwang DS (1995) Reduced inter- and intra-subject variability in cyclosporine pharmacokinetics in renal transplant recipients treated with a microemulsion formulation in conjunction with fasting, low-fat meals, or high-fat meals. Transplantation 59: 505–511
18. Kahan BD, Welsh M, Rutzky LP (1995) Challenges in cyclosporine therapy: the role of therapeutic drug monitoring by area under the curve monitoring. Ther Drug Monit 17: 621–624
19. Kahan BD, Podbielski J, Napoli KL, Katz SM, Meier-Kriesche H-U, Van Buren CT (1998) Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. Transplantation 66: 1040–1046
20. Kasiske BL, Neylan JF, Riggio RR, Danovitch GM, Kahana L, Alexander SR, White MG (1991) The effect of race on access and outcome in transplantation. N Engl J Med 324: 302–307
21. Kasiske BL, Tortorice KL, Heim-Duthoy KL, Awni WM, Rao KV (1991) The adverse impact of cyclosporine on serum lipids in renal transplant recipients. Am J Kidney Dis 17: 700–707
22. Kelly PA, Napoli KL, Dunne C, Kahan BD (1999) Conversion from liquid to solid sirolimus formulations in stable renal allograft transplant recipients. Biopharm Drug Dispos 20: 249–253
23. Keown P, Niese D (1998) Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in de novo renal transplantation. International Sandimmune/Neoral Study Group. Kidney Int 54: 938–944

24. Kerman RH, Kimball PM, Van Buren CT, Lewis RM, Kahan BD (1991) Possible contribution of pretransplant immune responder status to renal allograft survival differences of black versus white recipients. Transplantation 51: 338–342
25. Kerman RH, Kimball PM, Van Buren CT, Lewis RM, Kahan BD (1991) Stronger immune responsiveness of blacks vs whites may account for renal allograft survival differences. Transplant Proc 23: 380–381
26. Koyama H, Cecka JM, Terasaki PI (1994) Kidney transplants in black recipients. HLA matching and other factors affecting long-term graft survival. Transplantation 57: 1064–1068
27. Light JA, Kelly JL, Aquino A, Neu L, DeNavas L, Williams K (1993) Improving renal transplant outcomes in African-Americans with OKT3 induction therapy. Transplant Proc 25: 2436–2438
28. Lindholm A, Napoli K, Rutzky L, Kahan BD (1992) Specific monoclonal radioimmunoassay and fluorescence polarization immunoassay for trough concentration and area-under-the-curve monitoring of cyclosporine in renal transplantation. Ther Drug Monit 14: 292–300
29. Lindholm A, Welsh M, Alton C, Kahan BD (1992) Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: racial differences in bioavailability. Clin Pharmacol Ther 54: 359–371
30. Lindholm A, Welsh M, Rutzky L, Kahan BD (1993) The adverse impact of high cyclosporine: clearance rates on the incidences of acute rejection and graft loss. Transplantation 55: 985–993
31. Milford EL, Ratner L, Yunis E (1987) Will transplant immunogenetics lead to better graft survival in blacks? Racial variability in the accuray of tissue typing for organ donation: the fourth American workshop. Transplant Proc 19 [Suppl 2]: 30–32
32. Napoli KL, Kahan BD (1996) Routine clinical monitoring of sirolimus (rapamycin) whole-blood concentrations by HPLC with ultraviolet detection. Clin Chem 42: 1943–1948
33. Neylan JF (1997) Immunosuppressive therapy in high-risk transplant patients. Transplantation 64: 1277–1282
34. Neylan JF (1998) Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine. Transplantation 65: 515–523
35. Odocha O, McCauley J, Scantlebury V, Shapiro R, Carroll P, Jordan M, Vivas C, Fung JJ, Starzl TE (1993) Post-transplant diabetes mellitus in African-Americans after renal transplantation under FK506 immunosuppression. Transplant Proc 25: 2433–2444
36. Opelz G, Mickey MR, Terasaki PI (1977) Influence of race on kidney transplant survival. Transplant Proc 9: 137–142
37. Opelz G, Pfarr E, Engelmann A, Kepel E (1989) Kidney graft survival rates in black cyclosporine-treated recipients. Transplant Proc 21: 3918–3920
38. Rostand SG, Kirk KA, Rutsley EA, Pate BA (1982) Racial differences in the incidence of treatment for end-stage renal disease. N Engl J Med 306: 1276–1279
39. Scantlebury V, Gjertson D, Eliasziw M, Terasaki P, Fung J, Shapiro R, Donner A, Starzl TE (1998) Effect of HLA mismatch in African-Americans. Transplantation 65: 586–588
40. Solez K, Axelsen RA, Benediktsson H, Burkick JF, Cohen AH, Colvin RB, Croker BP, Droz D, Dunnill MS, Halloran PF, Häyry P, Jennette JC, Keown PA, Marcussen N, Mihatsch MJ, Moroxumi K, Myers BD, Nast CC, Olsen S, Racusen LC, Ramos E, Rosen S, Sachs DH, Salomon DR, Sanfilippo F, Verani R, Willebrand E von, Yamaguchi Y (1993) International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
41. Tornatore KM, Biocevich DM, Reed KA, Tousley K, Gray V, Singh JP (1995) Post-transplant diabetes mellitus and methylprednisolone pharmacokinetics in African-American and Caucasian renal transplant recipients. Clin Transplantat 9: 289–296
42. Van Buren CT, Kerman RH, Lewis RM, Kahan BD (1988) Exchanging donor kidneys. N Engl J Med 319: 1092–1093
43. Ward HJ, Koyle M, Terasaki PI, Cecka JM (1987) Outcome of renal transplantation in blacks. Transplant Proc 19: 1546–1548
44. Ward M, Lazda VA, Gaddis PJ, Stormoen BM, Smith Y, Fabrega AJ, Pollak R (1993) In vitro response to immunosuppressive agents in blacks. Transplant Proc 25: 2470–2471
45. Zimmerman J, Kahan BD (1997) Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral dose administration. J Clin Pharmacol 37: 405–415