Efficacy of a Single Pretransplant Donor-specific Transfusion and Cyclosporin A Administered 24 to 48 Hours Before one-haplotype–Mismatched Living Related Donor Kidney Transplant

CHRISTOPHER B. DAVIES, M.D., J. WESLEY ALEXANDER, M.D., Sc.D., BARRY R. COFER, M.D., M. ROY FIRST, M.D., and TIMOTHY J. SCHROEDER, M.S.

During the 7-year period from March 1984 to June 1991, 86 haploidentical living related kidney recipients were entered into one of three donor-specific transfusion (DST) and cyclosporine treatment protocols: (1) Multiple pretransplant DSTs with cyclosporine begun after transplant, n = 34; (2) Multiple pretransplant DSTs with cyclosporine begun pretransplant, n = 31; and (3) a single DST 24 to 48 hours before transplant with intravenous cyclosporine initiated after the transfusion, n = 21. Triple immunosuppression (prednisone, azathioprine, and cyclosporine) was continued in all groups after transplant. The 1-year patient (97%, 97%, and 93%, p = not significant) and graft (91%, 90%, and 87%, p = not significant) survival were similar for the three groups. No differences were seen in the incidence of rejection at 1 year (61%, 45%, and 60%, p = not significant) or in the incidence of infectious complications (26%, 42%, and 47%, p = not significant). It is concluded that a single DST given 24 to 48 hours before operation followed by pretransplant cyclosporine is as effective as classic DST conditioning of recipients using either pretransplant or post-transplant cyclosporine. The single DST protocol has the advantage of not eliminating any donors because of sensitization and was less costly and easier to administer.

From the University of Cincinnati Medical Center Department of Surgery, Transplantation Division, Cincinnati, Ohio

IN 1973 OPELZ ET AL.[1] REPORTED that random donor blood transfusion before cadaveric renal transplant improved allograft survival. The beneficial effects of blood transfusion were further documented by Salvatierra et al.,[2] who achieved a 38% improvement in 1-year graft survival after giving deliberate donor-specific blood transfusions (DST) before kidney transplants from one-haplotype–mismatched living related donors (LRD). All of the recipients had high responses of their lymphocytes against donor cells in mixed lymphocyte cultures (MLC).

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Address reprint requests to J. Wesley Alexander, M.D., Sc.D., University of Cincinnati Medical Center, Department of Surgery, Transplantation Division, 231 Bethesda Avenue, Cincinnati, OH 45267-0558.

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The protocol of three pretransplant DSTs, however, was complicated by sensitization to the proposed donor in 29% of the pairs.[2] Although this sensitization and elimination of recipients at a higher risk for rejections may in part account for the exemplary results of this study, the loss of 29% of potential donors was a significant disadvantage. Several studies have since demonstrated that the incidence of sensitization can be reduced to 8% to 14% through concurrent administration of azathioprine at the time of the initial transfusion and thereafter.[3–5]

The introduction of cyclosporine resulted in a remarkable increase in survival for both living related and cadaveric renal allograft recipients.[6] With cyclosporine, the graft survival advantage provided by transfusion decreased to approximately 5% in cadaveric transplants and to 2% to 3% in LRD one-haplotype–mismatched transplants when examined at 3 months and 1 year.[7] Similarly, the benefit of DST has been reduced to 3% to 9% in living related kidney recipients.[8,9] In light of the reduced benefits, the burden imposed on the donor and recipient by repeated pretransplant blood transfusions with pretransplant immunosuppression, and donor exclusion because of the persistent 10% incidence of sensitization, many centers have abandoned DST in LRD transplants. Recent studies, however, have suggested that DST can induce a specific suppression of the immune system, allowing a decrease in the requirement for nonspecific immunosuppression over the long term, with a coincident decrease in adverse effects, while maintaining or improving allograft survival.[9,10]

Animal studies have demonstrated synergy between cyclosporine and DST given 24 hours before transplantation with no evidence of sensitization.[11–13] Furthermore, a clinical study treating human cadaveric transplant re-

cipients with a single DST and cyclosporine infusion 24 hours before transplantation resulted in immunologic hyporesponsiveness to the donor (by MLC) and a decrease in severe rejection episodes requiring OKT3 treatment in the first 6 months after transplant.[14]

Since April 1989, we have adopted a protocol of giving a single pretransplant DST 24 to 48 hours before transplantation followed immediately by initiation of a cyclosporine infusion for one-haplotype–mismatched LRD renal transplant recipients to eliminate the sensitization caused by multiple DSTs. The safety and efficacy of this protocol is compared with two prior one-haplotype–mismatched LRD treatment protocols that used multiple pretransplant DSTs and cyclosporine initiated either before or after the transplant.

Materials and Methods

Patients

Eighty-six one-haplotype–mismatched LRD–recipient pairs were prospectively entered into a DST/cyclosporine treatment protocol and underwent transplantation between March 1984 and June 1991. There were no exclusionary criteria. Treatment protocols were approved by the Institutional Review Boards of the University of Cincinnati and The Christ Hospital.

Experimental Groups

Three sequential treatment protocols have been used during this period:

Group 1: Multiple pretransplant DSTs with cyclosporine initiated in the post-transplant period, n = 34. Recipients received approximately 150 mL fresh or stored donor whole blood or packed cells on three separate occasions at 2-week intervals. Three patients received two transfusions, and two patients received six transfusions (each had three stored and three fresh). Two weeks after the last transfusion, recipients underwent a final cross-match and were transplanted shortly thereafter. Recipients who developed a warm B-cell–positive cross-match after the last transfusion (4/34, 12%) were challenged with one or more additional transfusions and transplanted when the cross-match reverted to negative after this challenge. Seventy-one per cent of group 1 patients received continuous azathioprine immunosuppression (1 mg/kg/day initial dose, with adjustments in dosage according to the recipient's white blood cell count) during the period of DST administration. Two patients received buffy coat transfusions with RhoGAM (Ortho Diagnostic, Raritan, NJ) rather than whole blood or packed cells because of Rh incompatibility. Oral cyclosporine was initiated at a dose of 4 mg/kg twice daily after good renal function was established (mean, 5.31 ± 1.5 days after operation), except for one patient who developed severe acute rejection before initiation of cyclosporine.

Group 2: Multiple pretransplant DSTs with pretransplant cyclosporine, n = 31. This group was transfused using a protocol similar to that for group 1. All patients received three transfusions, except for one patient who developed a warm B-cell cross-match (given an additional fresh DST) and a patient whose transplant was delayed because of an upper respiratory tract infection (given a fourth fresh DST). Two patients were given buffy coat transfusions and RhoGAM to prevent Rh sensitization. Eighty-four per cent of the recipients received azathioprine immunosuppression concurrently with DST. Cyclosporine was started the day before transplantation as either an oral dose (4 mg/kg twice daily) (48%) or as a constant intravenous infusion (3 mg/kg/day) (52%). Patients were converted to oral cyclosporine in the post-transplant period as soon as they were able to take oral medications.

Group 3: Single pretransplant DST with pretransplant cyclosporine, n = 21. Recipients were transfused with 250 mL donor whole blood or packed cells 24 to 48 hours before their transplant (mean, 37.7 ± 2.44 hours). Three patients received buffy coat transfusions and RhoGAM. No patient in this group received azathioprine in the pretransplant period. An intravenous infusion of cyclosporine (3 mg/kg/day) was initiated immediately after the completion of DST and continued into the post-transplant period. Cyclosporine levels were measured approximately every 6 hours. At the time of transplantation, cyclosporine levels ranged from 289 to 932 ng/mL (mean, 494 ± 43 ng/mL) by whole blood polyclonal fluorescent polarization immunoassay (FPIA).[15] Conversion to oral cyclosporine was performed as early as possible. As a preliminary study, a subgroup of six patients were also given a single 2.5-mg (4 patients) or 5-mg (2 patients) dose of OKT3 immediately before the DST to assess the efficacy of pretransplant T cell depletion. All patients underwent hemodialysis before the OKT3 administration, but because of the concern regarding ablation of the DST effect, the patients were not pretreated with steroids before the OKT3.

Intraoperative and Post-transplant Immunosuppression

Immunosuppression was maintained after transplant using triple therapy (cyclosporine, azathioprine, and prednisone) in all groups. Cyclosporine was initiated according to treatment protocol. Cyclosporine doses were adjusted to maintain 12-hour whole blood trough levels during the first month at approximately 200 ng/mL, using a high-pressure liquid chromatography assay or 350 to

500 ng/mL by FPIA polyclonal assay. Azathioprine was given in a dose of 3 to 4 mg/kg intravenously in the operating room and then 1.5 mg/kg/day intravenously or orally, adjusted only for leukopenia. Methylprednisolone (Solu Medrol; UpJohn, Kalamazoo, MI) was given in a dose of 250 mg (groups 1 and 2) or 125 mg (group 3) intravenously in the operating room and prednisone (125 mg/day) (groups 1 and 2) or 1.0 mg/kg/day (group 3) was begun orally after transplant, and rapidly tapered to 20 mg/day with a more gradual taper over the first year as rejection episodes allowed. Rejection episodes were identified by a sudden and persistent elevation in serum creatinine and blood urea nitrogen associated with clinical findings of rejection in the absence of other causes of renal dysfunction. Percutaneous biopsy was performed if the diagnosis was in doubt or if rejection episodes failed to respond to initial therapy. Mild rejection episodes were treated initially with bolus injections of methylprednisolone (250 mg intravenously daily for up to 4 days). If there was no response or a worsening of renal function or if the initial biopsy showed moderate or severe acute cellular rejection or any component of acute vascular rejection, therapy was changed to OKT3 (5 mg/day intravenously for 7 to 14 days) or Minnesota antilymphoblast globulin (15–20 mg/kg/day intravenously for 7 to 14 days). In selected instances, refractory rejection in patients with contraindications to further high-dose immunosuppression were treated with local graft irradiation (150 rad/day for 3 days).

Outcome Variables

Treatment complications were compared, including presumptive evidence of cyclosporine nephrotoxicity within the first 14 days, indicated by a rise in creatinine managed by withdrawal or reduction in cyclosporine dose. Graft loss was dated as the time of return to chronic hemodialysis due to loss of graft function or time of transplant nephrectomy. Patient death from any cause was included as a graft loss. Actual and actuarial patient and graft survival were calculated at 1 year. Rejection episodes were compared at 6 months and 1 year. Severe rejection was defined as rejection requiring treatment with OKT3, Minnesota antilymphoblast globulin, or graft irradiation. Infectious complications within the first year were included if they required inpatient or outpatient antimicrobial therapy. Cytomegalovirus (CMV) infections were defined as clinical symptoms characteristic of CMV infection that correlated with an increase in CMV titers or positive CMV cultures.

Statistics

Statistical analysis was performed on the PC SAS system (version 6.04, SAS Institute, Inc., Cary, NC). Comparisons between groups were performed using the chi square test, Fisher's exact test, Wilcoxon rank sum test, t test, or one-way analysis of variance with Duncan's multiple range test, where appropriate. Graft survival curves were calculated using the product-limit survival estimates method (Kaplan-Meier). All means are reported as mean ± standard error of the mean. Significance was accepted if $p < 0.05$.

Results

There were no significant differences between treatment groups on the basis of sex, race, incidence of diabetes, primary disease process, or pretransplant panel-reactive antibody (Table 1). The patient-*versus*-donor MLC was

TABLE 1. *Recipient Characteristics*

	Group 1	Group 2	Group 3	
DST Protocol Cyclosporine	Multiple DST After Transplant	Multiple DST Before Transplant	Single DST Before Transplant	p
N	34	31	21	
Age (mean)	39.3 ± 2.0 yr	39.6 ± 2.1 yr	37.6 ± 2.6 yr	NS
Female	17/34 (50%)	10/31 (32%)	12/21 (57%)	NS
Race				NS
Black	5/34 (15%)	4/31 (13%)	4/21 (19%)	
White	28/34 (82%)	27/31 (87%)	16/21 (76%)	
Asian	1/34 (3%)	(0%)	1/21 (5%)	
Diabetes	12/34 (35%)	13/31 (42%)	6/21 (29%)	NS
Second transplant	1	3	0	NS
PRA (mean)	2.2 ± 2.0%	5.6 ± 1.2%	3.9 ± 2.8%	NS
MLC stimulation index (mean)	9.4 ± 2.8	11.8 ± 2.1	20.3 ± 4.5	<0.05 for 1 *vs.* 3
Third-party transfusions	19/34 (56%)	17/31 (55%)	11/21 (52%)	NS
Mean (units)	5.2 ± 1.7	7.7 ± 2.2	12.5 ± 5	
Median (units)	3	5	4	

DST, donor-specific transfusion; NS, not significant; PRA, panel-reactive antibody; MLC, mixed lymphocyte culture.

TABLE 2. *Donor Demographics*

Characteristic	Group 1	Group 2	Group 3	p
Age (mean)	37.2 ± 2.3 yr	35.4 ± 1.9 yr	33.3 ± 2.8 yr	NS
Female	8/34 (53%)	17/31 (55%)	7/21 (33%)	NS
Relation				NS
Parent	7/34 (20%)	4/31 (13%)	5/21 (24%)	
Sibling	17/34 (50%)	19/31 (61%)	9/21 (43%)	
Offspring	8/34 (24%)	8/31 (26%)	7/21 (33%)	
Other	2/34 (6%)	0%	0%	

NS, not significant.

TABLE 3. *Patient and Graft Survival*

Survival	Group 1	Group 2	Group 3*	p
1-yr patient survival	33/34 (97%)	30/31 (97%)	14/15 (93%)	NS
1-yr graft survival (all causes)	31/34 (91%)	28/31 (90%)	13/15 (87%)	NS
Corrected 1-yr graft survival (excluding death from suicide and allergic reaction)	31/33 (94%)	28/31 (90%)	13/14 (93%)	NS

* Includes only patients with follow-up longer than 1 year.
NS, not significant.

significantly higher in the single-DST group (group 3 *versus* group 1), however. Approximately 55% of the patients from each group received third-party transfusions (Table 1), with a median of 3 to 5 units. Mean follow-up for the three groups varied from 72 ± 1.6 months for group 1 to 14.3 ± 1.6 for group 3. Analysis therefore was confined to the first year for statistical comparisons.

Donor characteristics (Table 2) were similar between groups.

Transplant Outcome

Initial graft function was excellent in all groups. Examination of the serum creatinine during the first 5 days disclosed no significant difference in initial function between groups; all groups had good early function (Fig. 1). The grafts continued to function well through the first year of follow-up, with a mean serum creatinine for all groups remaining below 1.7 mg/dL (Fig. 1). Patient survival at 1 year was uniformly good for all groups (Table 3). Two of the three patients who died within 1 year of transplant died as a result of nonimmunologic events. The single death in group 1 was a patient who committed suicide 18 days after transplant, and the death of a patient in group 3 was due to anaphylactic response to protamine sulfate during cardiac surgery at another institution 88 days after transplant. Both patients died with excellent graft function. One-year graft survival also was similar for all groups. Elimination of graft losses due to nonimmunologic-related deaths allowed for analysis of immunologic graft survival related to treatment protocol (Table 3) and also demonstrated no differences between groups. Actuarial graft survival curves are presented in Figure 2.

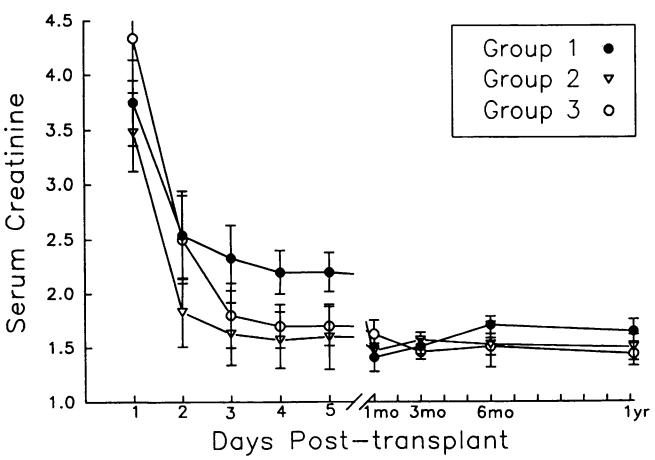

FIG. 1. Graft function.

The prednisone doses for each group over the first year were not significantly different except at 6 months, when the doses for both groups receiving pretransplant cyclosporine were significantly lower. This effect was lost by 1 year (Fig. 3). All patients continued to receive steroids by the end of the first year, but many were subsequently withdrawn from this drug (comparison of groups not possible at this time).

Rejection

There were no hyperacute rejections seen in any of the groups, but all had a similar incidence of early rejections described in DST protocols.[16] Thirty-eight per cent of the recipients in the single-DST group (group 3) had a rejection episode within the first 14 days, compared with 23% in group 2 and 35% in group 1 (p = not significant). All but two of these rejection episodes resolved with antirejection therapy. One patient in group 3 and one in group 1 underwent transplant nephrectomy because of irreversible rejection at postoperative days 7 and 22, respectively. A third patient in group 2 recovered from an initial rejection episode at 13 days, but had two additional rejection episodes in the following 30 days and subsequently lost her graft on post-transplant day 56.

Fifty-two per cent of the patients receiving a single DST (group 3) had a rejection within the first 6 months, compared with 45% for group 2 and 56% for group 1 (Table 4). The rejection episodes in the single-DST group tended to be more severe, because 48% of the patients experienced a severe rejection during this period. This was not statistically different from the other groups, however. The patterns of rejection also were quite similar at 1 year. None

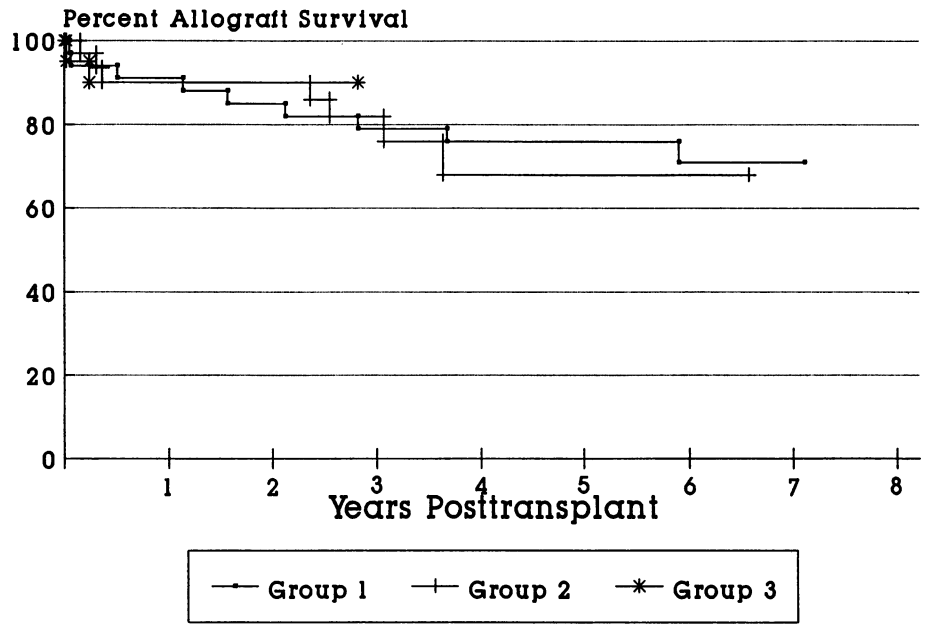

FIG. 2. Actuarial graft survival (no exclusions).

of the groups had a high incidence of patients experiencing more than one episode of severe rejection within the first year. Rejections also tended to occur within a similar time frame for all groups, with no difference in time to first rejection during the first year after transplant. The use of pretransplant azathioprine and conditioning with fresh or stored blood did not significantly impact on rejection. Third-party transfusions tended to improve the freedom from severe rejection in group 3 ($p = 0.08$ by Fisher's exact test; $p = 0.05$ by chi square test), but not in groups 1 or 2.

Examination of the pretransplant immunologic status of the recipient showed no relation between panel-reactive antibody and rejection. Pretransplant MLC, however, was related to the incidence of severe rejection. Patients who experienced a severe rejection within 6 months had a

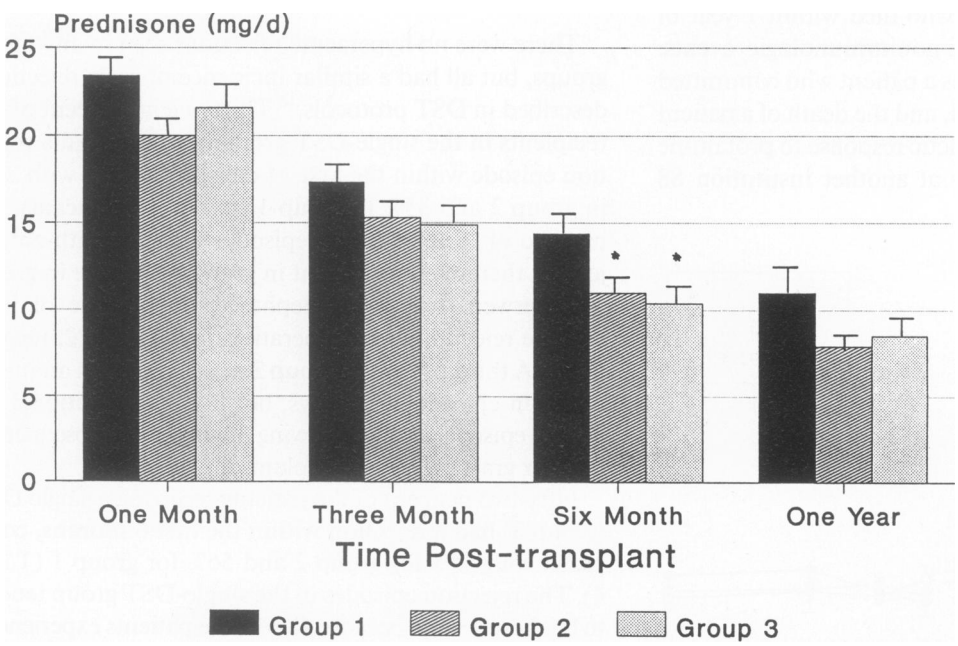

FIG. 3. Prednisone dose.

TABLE 4. *Patients with Rejection Episodes*

	Group 1	Group 2	Group 3	p
Rejection within first 6 months				
Total	19/34 (56%)	14/31 (45%)	11/21 (52%)	NS
Severe	13/34 (38%)	8/31 (26%)	10/21 (48%)	NS
Rejection within first yr				
Total	21/34 (61%)	14/31 (45%)	9/15 (60%)*	NS
Severe	14/34 (41%)	8/31 (26%)	9/15 (60%)*	NS
More than 1 rejection episode first yr				
Total	9/34 (26%)	4/31 (13%)	4/15 (26%)*	NS
Severe	3/34 (9%)	2/31 (6%)	2/15 (15%)*	NS
Time to first rejection (within 1 yr)	50.5 ± 17 days	32.4 ± 13 days	20.9 ± 10.4 days	NS

* Includes only patients with follow-up longer than 1 year.

NS, not significant.

mean stimulation index of 19.8 ± 4, compared with 9.3 ± 1.3 for patients without severe rejection ($p < 0.05$). This relationship also was seen at 1 year with stimulation indices of 18 ± 4 *versus* 8.8 ± 1.2, respectively ($p < 0.05$) (Fig. 4). Similarly, patients with a stimulation index > 20 in their pretransplant MLC were more likely to experience severe rejection at both 6 months and 1 year ($p < 0.05$). None of five patients with a stimulation index > 50 were free from severe rejection at 1 year. Pretransplant MLC did not, however, impact on graft survival or the incidence of mild rejections.

Complications

There was concern that administration of cyclosporine before transplantation might jeopardize allograft function because of vasoconstriction and early cyclosporine toxicity. The groups treated with post-transplant *versus* pretransplant cyclosporine had a comparable incidence of early renal dysfunction that was perceived to be associated with cyclosporine therapy (Table 5). The cyclosporine level at the time of transplant (available only for group 3) did not impact on early function, nor did the route of administration (oral or intravenous) in group 2.

There were no differences in the incidence of bacterial, viral, or fungal infections except for an unexplained significantly higher incidence of CMV infection in group 2 (Table 5). One of the patients from group 2 developed life-threatening CMV infection and a lymphoproliferative disorder and subsequently died. The incidence of malignancy was low during the first year. In addition to the lymphoproliferative disorder in group 2, there were three skin malignancies (1 squamous cell and 2 basal cell carcinomas).

OKT3 Pretreatment

Six of the patients in group 3 were treated with OKT3 in the pretransplant period in addition to a single DST and pretransplant cyclosporine. There was a 33% incidence of rejection in the first 6 months in this subgroup. More importantly, without steroid pretreatment, all of

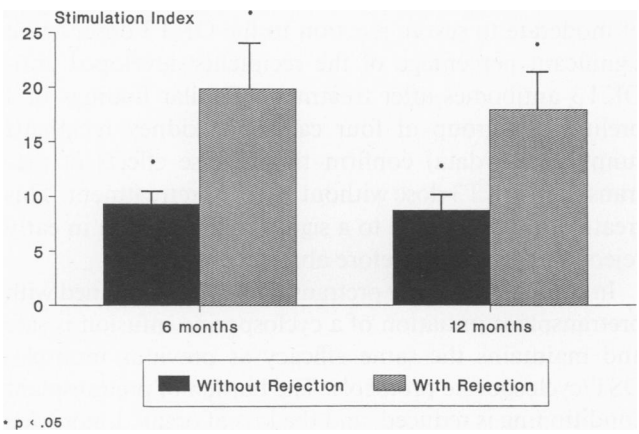

FIG. 4. Relation of pretransplant MLC to severe rejection episodes.

TABLE 5. *Patients With Complications in the First Year*

	Group 1	Group 2	Group 3	p
Infections				
Total	9/34 (26%)	13/31 (42%)	7/15 (47%)*	
Bacterial	7/34 (21%)	7/31 (23%)	6/15 (40%)*	NS
Viral	2/34 (6%)	8/31 (25%)	2/15 (13%)*	NS
Cytomegalovirus	(0%)	5/31 (16%)	(0%)*	NS
Fungal	1/34 (3%)	2/31 (6%)	(0%)*	<0.05
Malignancies	1/34 (3%)	3/31 (10%)	(0%)*	NS
Presumptive CsA toxicity in first 14 days	2/34 (6%)	3/31 (10%)	3/21 (14%)	NS

* Includes only patients with follow-up longer than 1 year.
NS, not significant.

the patients had moderate to severe reactions to the OKT3. One woman required intensive care after OKT3, necessitating a 3-day delay in her transplant. These patients also tended to form anti-OKT3 antibodies. Two of the six developed titers of 1:100 and 1:1,000 after the single dose, and a third patient developed a titer of 1:100 after an 11-day course of OKT3 for early rejection.

Discussion

Since the commercial availability of cyclosporine in late 1983, there has been controversy over the deliberate administration of DST in LRD renal transplant recipients.[17-19] The early benefits of DST on graft and patient survival have been markedly reduced to 3% to 9% by cyclosporine therapy[8,9] and exclusion of approximately 10% of potential donors because of sensitization has continued to occur. Conversely, experimental data have demonstrated repeatedly that cyclosporine and donor antigen, including DST, can prolong allograft survival synergistically.[11-13,20-22] Furthermore, there is the potential that immune modification through DST can decrease the need for continued immunosuppression and the severity of chronic rejection with respect to long-term graft survival in humans. Donor-specific transfusion treatment can induce the development of hyporesponsiveness of donor-specific cytotoxic T-lymphocytes[23,24] and MLC[14,25-27] in human renal allograft recipients. In one-haplotype–mismatched living related kidney recipients, Reed et al.[10] have shown that three DSTs significantly improved freedom from rejection, increased the rejection-free interval, and improved the ability to aggressively withdraw steroids when compared with random donor transfusions. Salvatierra et al.[9] recently described excellent results over the first 4 years in a protocol using DST and Minnesota antilymphoblast globulin/cyclosporine sequential therapy. In this report, DST provided a 9% benefit at 1 year and a 33% enhancement in allograft survival at 4 years over non-DST/Minnesota antilymphoblast globulin/cyclosporine-sequential therapy. The DST group also tended to have lower prednisone doses.

A persistent disadvantage of DST protocols is the occurrence of a high incidence of sensitization. The original DST protocol introduced by Salvatierra et al.[2] in 1980 consisted of three fresh whole blood transfusions at 2-week intervals. This was complicated by a 29% incidence of sensitization, resulting in elimination of these donors. Modifications of this protocol through the use of stored whole blood,[28] a single transfusion 2 weeks before transplant,[29] concurrent azathioprine,[3-5] or cyclosporine[30] has reduced the rate of sensitization to 9%, 4%, 8% to 14%, and 4%, respectively. Although these sensitized patients may successfully undergo transplantation from a different living related or cadaveric donor, this creates a significant reduction in the donor pool. Prolonged pretransplant immunosuppression also may cause bone marrow toxicity and infectious complications. In the current study, all of the patients that received a single DST and cyclosporine 24 to 48 hours before transplantation were transplanted with organs from their initially intended donor. This protocol maintained the excellent graft survival seen in our previous multiple-DST/cyclosporine groups without significantly increasing the incidence of rejection or complication. The relationship of pretransplant MLC to severe rejection episodes suggests that the single-DST/cyclosporine group may have been at a higher risk for severe rejection, yet the protocol maintained a similar profile of rejection episodes. Thus, 10% of potential donors expected to be excluded because of DST sensitization were not eliminated by this protocol and their kidneys were not lost from rejections. The burden on both the donor and recipient also was significantly reduced with regard to the pretransplant commitment to multiple transfusions, the potential risks of prolonged pretransplant immunosuppression, and costs associated with the transfusion therapy and added immunologic testing.

Concern regarding the effect of preoperative administration of intravenous cyclosporine was unfounded. There was no increase in early renal dysfunction or early cyclosporine toxicity from this treatment. Although no relation of cyclosporine level at transplant to early renal dysfunction could be demonstrated in this study, careful adjustment of cyclosporine dosage with frequent monitoring of levels seems warranted. The problem of cyclosporine toxicity has been more evident in cadaveric organs, where cyclosporine appears to potentiate the tubular damage from ischemia and storage.

Pretransplant T-cell depletion through the use of monoclonal antibodies has been shown to augment the transfusion effect induced by a single pretransplant DST.[31] The clinical application of this approach with OKT3 in six patients in this study demonstrated drawbacks associated with this therapy. There was a uniform incidence of moderate to severe reaction to the OKT3 dose, and a significant percentage of the recipients developed anti-OKT3 antibodies after treatment. Similar findings in a preliminary group of four cadaveric kidney recipients (unpublished data) confirm the adverse effects of pretransplant OKT3 dose without steroid pretreatment. This treatment did not lead to a significant reduction in early rejection and was therefore abandoned.

In summary, a single pretransplant DST combined with pretransplant initiation of a cyclosporine infusion is safe and maintains the same efficacy as previous multiple-DST/cyclosporine protocols. The burden of pretransplant conditioning is reduced, and the loss of organ donors due to sensitization is eliminated, therefore increasing the pool of living related donors. Although the major deterrents

to DST have been removed, the long-term benefits of combined DST and cyclosporine administration need to be studied further.

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