DOSE OPTIMIZATION OF MYCOPHENOLATE MOFETIL WHEN ADMINISTERED WITH A LOW DOSE OF TACROLIMUS IN CADAVERIC RENAL TRANSPLANT RECIPIENTS

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Background. **Supplementation of immunosuppressive therapy with mycophenolate mofetil (MMF) has been found to reduce the rate of acute rejection in renal transplantation. We report a dose-finding study for MMF when administered in combination with low-dose tacrolimus and corticosteroid prophylaxis in cadaveric renal transplant recipients.**

Methods. **Two hundred thirty-two patients at 16 centers were enrolled in this randomized, parallel-group study. The three treatment groups were tacrolimus and corticosteroids (MMF-0 group, n=82); tacrolimus, corticosteroids, and 1 g of MMF daily (MMF-1 g group, n=79); and tacrolimus, corticosteroids, and 2 g of MMF daily (MMF-2 g group, n=71). Study duration was 6 months, and patients were followed up for patient and graft survival for 12 months.**

Results. **At 6 months posttransplantation, daily doses of 1 g and 2 g of MMF were associated with significantly lower rates of acute rejection compared with tacrolimus alone. The Kaplan-Meier rates were 48.5%, 24.9%, and 22.9%, respectively, for the three treatment groups when acute rejection was determined by clinical criteria (*P*=0.007). At month 12, patient survival rates were 100%, 97.5%, and 97.2% and graft survival rates were 90.2%, 92.4%, and 93.0% for the MMF-0 group, MMF-1 g group, and the MMF-2 g group, respectively. Gastrointestinal adverse events and leukopenia were higher in the MMF groups, especially in the MMF-2 g group (*P*<0.05).**

Conclusions. **Low-dose tacrolimus combined with a MMF dose of 1 g daily and corticosteroids provided an optimized efficacy and safety profile. A higher dose of MMF (2 g) was associated with greater toxicity without a significant improvement in efficacy.**

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Tacrolimus (FK506), a macrolide molecule that is 10- to 100-fold more potent than cyclosporine at inhibiting T-cell activation (*1*), is a relatively new primary immunosuppressant used in solid organ transplantation (*2*). The first experience with the use of tacrolimus in renal transplant patients occurred at the University of Pittsburgh in which studies showed a reduced incidence of acute rejection and a reduced requirement for corticosteroids and antihypertensive medi-

cation compared with cyclosporine (*3, 4*) and no clear benefit for triple therapy with azathioprine (*5, 6*). Preliminary multicenter studies in Europe (*7*), Japan (*8–10*), and the United States (*11*) showed similar results. In phase III, multicenter, randomized studies performed in Europe (448 patients) and in the United States (412 patients), tacrolimus was associated with a significant reduction in the rate of acute rejection and a similar safety profile compared with cyclosporine in patients who received a cadaveric renal transplant (*12, 13*). Tacrolimus is presently licensed as a primary immunosuppressant and rescue agent in liver and renal transplantation in the United States and in European countries.

All immunosuppressant medications are associated with toxicity, and much of the art and science of the clinical management of transplant recipients has been aimed at combining different immunosuppressant medications at a lower dose in an effort to improve the overall efficacy and safety profile. Mycophenolate mofetil (MMF) was developed to supplement cyclosporine administration for prophylactic prevention of allograft rejection. It is a noncompetitive inhibitor of inosine-monophosphate-dehydrogenase, an enzyme that influences the function of lymphocytes via inhibition of purine synthesis. Clinical phase III studies have demonstrated that MMF, in combination with cyclosporine and corticosteroids, significantly reduces the rate of acute rejection relative to placebo or azathioprine after cadaveric renal transplantation (*14–16*). In this study, we report the results of a dose-ranging MMF trial performed in combination with low-dose tacrolimus and low-dose corticosteroid prophylaxis in cadaveric renal transplant recipients.

MATERIALS AND METHODS

Study Design

This randomized, parallel-group, dose-finding study of 6-month duration was conducted at 16 centers in Europe from 13 September 1996 to 8 September 1997. Patients were stratified for previous transplantation and study site and were randomized 1:1:1 to receive tacrolimus and steroids alone or tacrolimus and steroids with one of two different doses of MMF. The protocol was approved by the ethics committee at each center, and the patients gave written informed consent before enrollment.

Patient Selection

Adult patients who were scheduled to receive a single-organ cadaveric renal transplant were eligible for entry. Exclusion criteria were a need for antibody induction therapy, a positive T-cell crossmatch, present or previous malignancies or liver disease, and a recent serious systemic infection or gastrointestinal disorder.

Randomization and Treatment Plan

Each center received 30 sealed envelopes; each contained a randomized treatment allocation from a unique sequence of 30 patient numbers. Treatment allocation was assigned within 6 hours of transplantation. For stratification purposes, patients who had no previous transplant were assigned sequential patient numbers at the lowest number working up, and patients who had a previous transplant were assigned sequential numbers starting at the highest number and working down.

The three treatment groups were (1) tacrolimus and corticosteroids (MMF-0 group); (2) tacrolimus, corticosteroids, and 1 g per day MMF (MMF-1 g group); and (3) tacrolimus, corticosteroids, and 2 g per day MMF (MMF-2 g group). Oral tacrolimus (initial daily dose of 0.2 mg/kg with target blood levels below 15 ng/ml) and MMF were administered in two divided doses per day. Tacrolimus concentrations in whole blood were determined by using a microparticle enzyme immunoassay (IMx, Abbot Laboratories, Abbott Park, IL). Subsequent dosing of tacrolimus could be adjusted for the occurrence of adverse events or rejection.

All patients received maintenance therapy with corticosteroids. The protocol instructed that methylprednisolone be given as a bolus on day 0 (500 mg) and day 1 (125 mg) with oral steroids tapered over time (from 20 mg/day prednisone equivalents [days 2–14] to 5 mg/day at [days 43–90], with later doses at the investigator's discretion).

The type of antirejection therapy, i.e., corticosteroids or antilymphocyte antibodies (muromonab-CD3, antithymocyte globulin), was left to the discretion of the investigator. All other immunosuppressive medications were prohibited during the study.

Clinical Assessments

Episodes of renal dysfunction were evaluated for possible rejection. Investigators were instructed to perform kidney biopsies when rejection was suspected unless the procedure was medically contraindicated. The biopsies were used to aid the investigator in the diagnosis of acute rejection and were subsequently sent to a central blinded histopathologist for evaluation. Other assessments included spontaneously resolving acute rejection, the use of steroids and antibody preparations for the treatment of rejection, refractory acute rejection, chronic rejection, patient survival, and graft survival (graft loss being defined as patients who died or who experienced graft failure). Patients were also assessed for spontaneous adverse events and underwent routine laboratory assessments.

Statistical Analysis

The main efficacy outcome measurement was the time to first acute rejection during the 6-month follow-up. Acute rejection was based on clinical signs and symptoms regardless of whether the episode was treated or confirmed by biopsy. All patients were followed for 6 months after transplantation or until death (main study period) and for 12 months with respect to patient and graft survival. Analysis was intention-to-treat and included all patients who underwent randomization and received at least one dose of tacrolimus. The Kaplan-Meier product-limit estimator was used to prepare descriptive statistics for time-to-event data, and the Wilcoxon test was used for statistical comparisons. Adverse events were analyzed with Fisher's exact test.

RESULTS

Patients

Two hundred and thirty-two patients were enrolled; 82 patients were randomized to the MMF-0 group, 79 to the MMF-1 g group, and 71 to the MMF-2 g group. There were no significant differences in baseline characteristics of the recipients or in donor characteristics among the three treatment groups (Table 1). Fewer patients in the MMF-2 g group were withdrawn from the study than in the MMF-0 group or MMF-1 g group, but reasons for withdrawal were similar among the three treatment groups (Table 1).

Dosing

Mean daily tacrolimus doses and mean whole blood trough concentrations of tacrolimus were similar for the three study groups (Fig. 1). At 3 months, the mean tacrolimus dose was as low as 0.12 mg/kg and the mean level was 10.05 ng/ml. By the end of the 6-month study period, the mean tacrolimus dose decreased to 0.11 mg/kg and blood concentration decreased to 8.7 ng/ml.

TABLE 1. Patient/donor baseline characteristics and reasons for withdrawal from the study[a]

Variable	Tacrolimus		
	Without MMF (N=82)	With 1 g of MMF daily (N=79)	With 2 g of MMF daily (N=71)
Mean age, years	46.6±14.5	46.5±13.3	48.0±13.3
Male gender	44 (53.7)	53 (67.1)	45 (63.4)
Caucasian ethnic origin	77 (93.9)	77 (97.5)	68 (95.8)
Previous transplants	11 (13.4)	10 (12.7)	7 (9.9)
Mean donor age, years	45.6±18.1	45.6±16.0	45.4±16.9
Total HLA (A, B, DR) mismatches	2.6	2.4	2.5
CMV status (recipient/donor)	17 (21.8)	15 (19.5)	19 (27.5)
Withdrawal from study	9 (11.0)	11 (13.9)	6 (8.5)
Reasons for withdrawal			
Irreversible graft failure	7 (8.5)	5 (6.3)	1 (1.4)
Conversion to cyclosporine	2 (2.4)	6 (7.6)	1 (1.4)
Death	0	0 [b]	2 (2.8)
Withdrawal of consent	0	0	1 (1.4)
Severe headache	0	0	1 (1.4)

[a] Data are expressed as number of patients, with percentage in parentheses, except for age, which is reported as mean±SD.
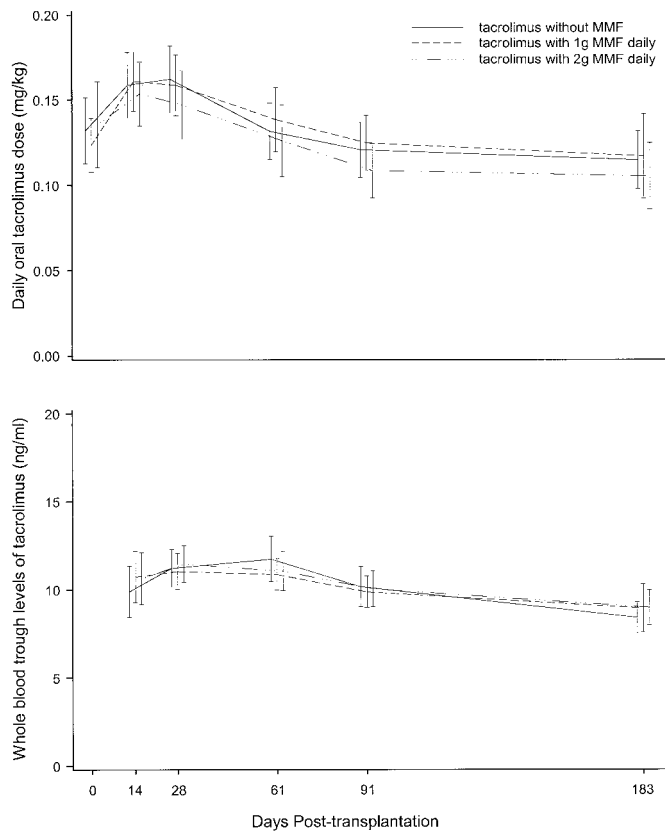[b] Two deaths occurred after withdrawal from the study.

FIGURE 1. Mean daily doses and mean whole blood trough levels of tacrolimus with 95% confidence intervals (n=82, n=79, and n=71 for the three treatment groups, respectively).

FIGURE 2. Mean daily doses of MMF with 95% confidence intervals (n=79 and n=71 for the two treatment groups, respectively).

MMF doses decreased over time, especially in the MMF-2 g study group (Fig. 2). On the basis of an analysis of the first change in the assigned MMF dose, 34 patients (43.0%) in the MMF-1 g group and 46 patients (64.8%) in the MMF-2 g group experienced a MMF dose reduction. The MMF dose decreases were most frequ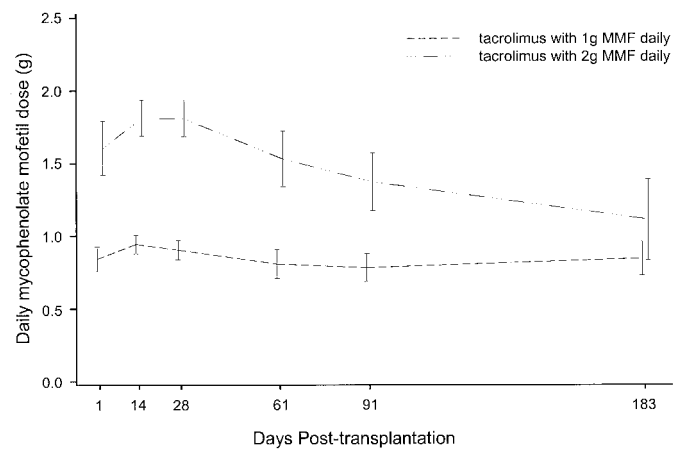ently attributed to gastrointestinal disorders and leukopenia (Table 2). MMF dose increases were experienced by five patients (6.3%) in the MMF-1 g group and none in the MMF-2 g group. MMF dose increases were made on the basis suspected or proven graft rejection. In the MMF-0 group, 18 patients (22.0%) had MMF added to their immunosuppressive regimen. Again, this was done after a diagnosis of graft rejection with the intention to increase maintenance immunosuppression.

Efficacy

Approximately twice as many patients in the MMF-0 treatment group experienced acute rejection, which was determined by clinical signs and symptoms, compared with either of the MMF treatment groups (Table 3). Most first rejection episodes occurred during the first few weeks posttransplantation (Fig. 3). The Kaplan-Meier estimated rate of acute rejection was significantly lower for patients who received MMF ($P=0.007$ for the overall comparison). Pairwise comparisons showed significant differences between the MMF-0 group and MMF-1 g group ($P=0.025$) and between the

TABLE 2. Reasons for first MMF dose reduction[a]

Variable	Tacrolimus	
	With 1 g of MMF daily (N=79)	With 2 g of MMF daily (N=71)
Patients with MMF dose decreases	34 (43.0)	46 (64.8)
Most common reasons for decrease[b]		
Diarrhea	5 (6.3)	14 (19.7)
Other gastrointestinal events[c]	5 (6.3)	7 (9.9)
Leukopenia	6 (7.6)	11 (15.5)
CMV infection	7 (8.9)	1 (1.4)
Anemia	2 (2.5)	1 (1.4)

[a] Data are expressed as number of patients with the percentage in parentheses.

[b] Reasons for MMF dose decrease that affected at least two patients in either treatment group.

[c] Other gastrointestinal events that led to an MMF dose decrease were abdominal pain, gastrointestinal hemorrhage, vomiting, nausea with anorexia and vomiting, and rectal disorder in the MMF-1 g group; and acute abdominal syndrome, dyspepsia with anorexia and diarrhea, gastritis, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal disorder, and nausea in the MMF-2 g group.

TABLE 3. Incidence of acute rejection[a]

Variable	Tacrolimus study group		
	Without MMF (N=82)	With 1 g of MMF daily (N=79)	With 2 g of MMF daily (N=71)
As determined clinically	38 (46.3)	19 (24.1)	16 (22.5)
Spontaneously resolving rejection[b]	2 (2.4)	0	1 (1.4)
Corticosteroid-sensitive rejection	31 (37.8)	15 (19.0)	12 (16.9)
Antibody-sensitive acute rejection	13 (15.9)	5 (6.3)	2 (2.8)
Refractory acute rejection	1 (1.2)	0	1 (1.4)
Blinded central biopsy review	29 (35.4)	12 (15.2)	4 (5.6)
Grade I	11 (13.4)	1 (1.3)	1 (1.4)
Grade II	14 (17.1)	11 (13.9)	3 (4.2)
Grade III	4 (4.9)	0	0
Presumptive acute rejection[c]	3 (3.7)	3 (3.8)	7 (9.9)

[a] Data are expressed as number of patients with at least one event with the percentage in parentheses. Because some patients experienced more than one and different types of rejection, the numbers do not add up.

[b] Spontaneously resolving rejection is defined as an episode of rejection that resolved without corticosteroid or antibody treatment.

[c] Acute rejection as clinically assessed by the investigator for which a biopsy was not available or for which the biopsy material was insufficient for analysis.
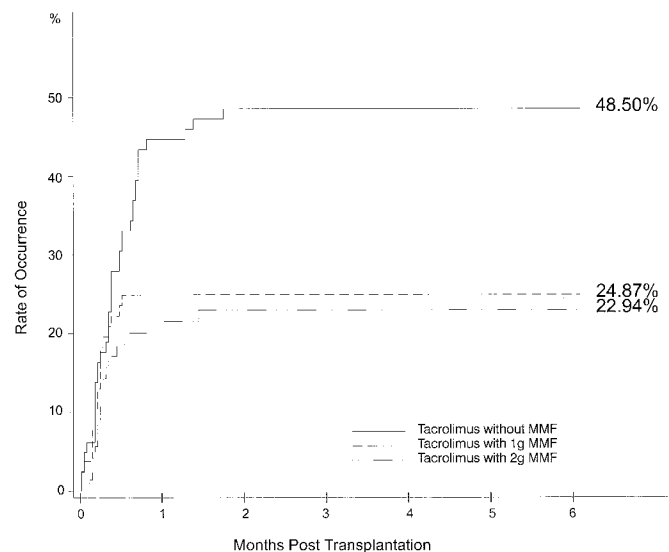

FIGURE 3. Kaplan-Meier estimates of acute rejection based on clinical signs and symptoms.

MMF-0 and the MMF-2 g group (P=0.004) but not between the two groups who received MMF (P=0.597).

The main study results (above) were from data censored at the patient's last visit (the last study visit or the day of withdrawal). Because changes in MMF dosing during the study could potentially affect the outcome, acute rejection was also analyzed using data censored with regard to MMF dose changes. When censoring included the last visit and (1) any dose change, (2) a dose change when it persisted at least 5 days, (3) any dose increase, and (4) a dose increase when it lasted at least 5 days, overall results (statistical significance) were the same as the main analysis.

The number of patients who received treatment with antilymphocyte antibodies was also higher in the patient group who did not receive MMF (Table 3). The Kaplan-Meier estimated rates of freedom from rejection episodes that required antibody therapy showed significant differences among the three treatment groups (P=0.020). Significant differences were also observed between the MMF-0 group and MMF-1 g group (P=0.056) and between the MMF-0 group and MMF-2 g group (P=0.014) but not between the two MMF groups (P=0.522). Antibodies were given as first-line therapy for rejection rather than for

corticosteroid-resistant rejection for five patients in MMF-0 group, two patients in the MMF-1 g group, and one patient in the MMF-2 g group.

The incidence of acute rejection, which was determined by a central blinded biopsy review, was lower in the three treatment groups compared with the incidence of acute rejection determined by clinical criteria. For the patients in the MMF-0 group and the MMF-1 g group, this does reflect the fact that the clinical diagnosis of rejection is not confirmed at histopathological examination of a biopsy sample. However, compliance in obtaining biopsies was low in the MMF-2 g treatment group. No biopsy was available for 44% of patients in the MMF-2 g arm who were determined to have had acute rejection by clinical assessment compared with 16% of such patients in the MMF-1 g treatment group and 8% of such patients in the MMF-0 treatment group.

Serum creatinine levels at 6 months posttransplantation were similar for the three treatment groups, with means of 157 μmol/L (SD 68 μmol/L, n=73) for the MMF-0 group, 142 μmol/L (SD 45 μmol/L, n=68) for the MMF-1 g group, and 145 μmol/L (SD 69 μmol/L, n=65) for the MMF-2 g group.

During the 6-month study period, there were more graft losses in the MMF-0 group and MMF-1 g group than in the MMF-2 g group, but only one graft per treatment group was lost as a result of rejection, and early thrombosis was a frequent reason for graft loss (Table 4). The Kaplan-Meier rates for graft survival at month 6 were 90.2%, 92.4%, and 95.8% for the MMF-0 group, the MMF-1 g group, and the MMF-2 g group, respectively. At month 12, graft survival rates were 90.2%, 92.4%, and 93.0%.

Patient survival rates (Kaplan-Meier) at month 6 and at month 12 were 100%, 97.5%, and 97.2% for the MMF-0 group, MMF-1 g group, and MMF-2 g group, respectively. In the MMF-1 g group, one patient died from cytomegalovirus (CMV) encephalitis and one patient died from cardiac arrest (both deaths occurred after study withdrawal). In the MMF-2 g group, one patient died from a pulmonary embolism and one died from a ruptured thoracic saccular aneurysm. All patients who died were over 60 years of age.

Adverse Events

The most frequently reported adverse events were urinary tract infection, hypertension, and diarrhea. Only diarrhea and leukopenia showed a significant difference among the treatment groups (Table 5); the highest incidence for both events was observed in the MMF-2 g group. CMV infection was higher in the MMF treatment groups, but the differences were not statistically significant (Table 5). Other adverse events such as hypertension (overall 32.8%), increased creatinine (overall 12.1%), tremor (overall 10.8%), and headache (overall 6.0%) showed similar incidences among the three treatment groups.

DISCUSSION

As observed recently for co-administration of MMF and cyclosporine (14–16), the addition of MMF to a low-dose regimen of tacrolimus was associated with a significantly lower rate of acute rejection and significantly reduced the need for antibody-based antirejection therapy during the first 6 months after cadaveric renal transplantation. There was no significant difference between the 1 g and 2 g of MMF groups in the estimated rate of acute rejection. Although many patients' MMF doses were reduced during the study, censoring data at the time of the dose change in the analysis of acute rejection did not alter the overall study findings (17).

The nature and frequency of adverse events associated with MMF in this study, i.e., gastrointestinal adverse events and leukopenia, are consistent with those observed when MMF was co-administered with cyclosporine (14–16). These events seem to be dose-dependent; their incidence was higher and they were the cause of more dose reductions in the MMF-2 g group than the MMF-1 g group. In this study, thrombosis of the renal transplant vessels is given as a reason for graft loss in eight cases. Further analysis showed that the use of organs from non–heart-beating donors did largely contribute to the incidence of these early thrombotic events.

The incidences of other adverse events were particularly low in this study compared with earlier studies. In comparison with the European multicenter study that compared tacrolimus with cyclosporine (12), increased creatinine, toxic nephropathy, tremor, headache, angina, and diabetes mellitus were reduced by 2- to 4-fold in all three treatment groups. The overall incidence of posttransplant diabetes mellitus, which was defined as the sustained need for insulin therapy in previously nondiabetic patients, was 3% (6 of 200 patients) and, thus, remarkably low without significant differences

TABLE 4. Summary of graft losses[a]

Variable	Tacrolimus study group		
	Without MMF (N=82)	With 1 g of MMF daily (N=79)	With 2 g of MMF daily (N=71)
Graft losses (6 months)	8 (9.8)	6 (7.6)	3 (4.2)
Primary cause of graft loss			
Thrombosis	5 (6.1)	3 (3.8)	0
Death	0	0	2 (2.8)
Acute tubular necrosis and rejection	1 (1.2)	1 (1.3)	0
Primary nonfunction	1 (1.2)	1 (1.3)	1 (1.4)
Rejection	0	0	0
Graft lymphoma	1 (1.2)	0	0
Hemorrhage	0	1 (1.3)	0
Graft losses (months 7–12)	0	0	2
Renal artery stenosis (failed PTA)[b]	0	0	1 (1.4)
Transplant nephropathy	0	0	1 (1.4)

[a] Data are expressed as number of patients with the percentage in parentheses.
[b] Abbreviation: PTA-percutaneous transluminal angioplasty.

TABLE 5. Incidence of selected adverse events[a]

Adverse event[b]	Tacrolimus study group		
	Without MMF (N=82)	With 1 g of MMF daily (N=79)	With 2 g of MMF daily (N=71)
Gastrointestinal			
Diarrhea[c]	18 (22.0)	23 (29.1)	30 (42.3)
Gastritis	4 (4.9)	5 (6.3)	5 (7.0)
Hematological			
Anemia	14 (17.1)	15 (19.0)	13 (18.3)
Leukopoenia[c]	5 (6.1)	7 (8.9)	13 (18.3)
Thrombocytopenia	3 (3.7)	2 (2.5)	1 (1.4)
Glucose metabolism			
Diabetes mellitus	5 (6.1)	8 (10.1)	4 (5.6)
Long-term insulin usage[d]	0	2 (3.0)	4 (6.3)

[a] Data are expressed as number of patients with the percentage in parentheses.
[b] Adverse events were coded from investigator terms using a modified COSTART dictionary (coding symbols for thesaurus of adverse reaction terms).
[c] The difference among the three treatment groups was significant at $P<0.05$, Fisher's exact test.
[d] Insulin needed for more than 30 days in patients without pre-existing glucose metabolism disorders (n=70, n=66, and n=64 for the three treatment groups, respectively).

between treatment groups. The incidence of hypertension also decreased in the present study, but to a lesser extent.

The improved safety profile can probably be attributed to the lower dosage of tacrolimus. The earlier European multicenter study used a starting dose of 0.3 mg/kg per day, whereas the present study had a starting daily dose of 0.2 mg/kg per day. The lower dosage and lower target whole blood trough levels were implemented to avoid over-immunosuppression of patients who were to receive MMF; however, this may have sacrificed immunosuppressive coverage in the treatment group who did not receive additional immunosuppression. The rate of acute rejection in the group of patients who received low-dose tacrolimus and corticosteroids alone in the present study was higher than reported previously when a higher tacrolimus dose was used (12). A recent study showed that the risk of acute rejection increases when trough tacrolimus concentrations are low during the early posttransplant period; the authors advised that a trough tacrolimus concentration of 10 ng/ml should be reached by the second to third day posttransplantation to reduce the risk of acute rejection (18).

The central biopsy review data suggest that there may have been some bias in the determination of acute rejection in the MMF-2 g treatment group. No biopsy was available for 44% of patients in the MMF-2 g arm who were determined to have had acute rejection by clinical assessment compared with 16% of such patients in the MMF-1 g treatment group and 8% of such patients in the MMF-0 treatment group. Thus, the incidence of biopsy-proven acute rejection in the MMF-2 g treatment group needs to be interpreted with some caution and may not be reliable, whereas results from the MMF-0 and the MMF-1 g treatment groups mainly reveal the difference between clinical and histopathological diagnosis. Because this was an open study, some bias was unavoidable.

The findings presented here and in other studies suggest that MMF does not affect the absorption of tacrolimus in renal transplant patients and that tacrolimus does not affect the absorption of MMF. Tacrolimus doses and whole blood trough concentrations were proportional during this study. A recent study, based on data from a subset of patients from the present study (ca. 20 from each group), showed no marked differences in pharmacokinetic parameters among the three treatment groups (19). The MMF-1 g and MMF-2 g groups showed mean mycophenolic acid area-under-the-curve (AUC) values of 25 μg·h/ml and 40 μg·h/ml, respectively, but there was considerable overlap in the individual AUC values in the two dosing groups.

We conclude that low-dose tacrolimus (starting dose of 0.2 mg/kg daily) with a low dose of MMF (starting dose of 1 g daily) provides an optimized efficacy and safety profile for cadaveric renal transplant recipients. A higher dose of MMF (2 g daily) is associated with greater toxicity without a significant improvement in efficacy. Because most acute rejection episodes occurred during the early posttransplant period, it would be of value to assess whether MMF can be withdrawn once patients are in stable condition without a compromise in immunosuppressive coverage.

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THE INFLUENCE OF ACUTE REJECTION ON LONG-TERM RENAL ALLOGRAFT SURVIVAL: A COMPARISON OF LIVING AND CADAVERIC DONOR TRANSPLANTATION

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Background. We investigated whether recipients of living donor grafts who suffer an acute rejection progress to graft loss because of chronic rejection at a slower rate than recipients of cadaveric grafts.

Methods. A retrospective review was made of 296 renal transplantations performed at Mount Sinai Hospital. Only grafts functioning for at least 3 months were included in this analysis. Demographic variables of donor and recipient age, race, sex, and serum creatinine at 3 months after transplantation were compared between groups.

Results. Among the acute rejection-free cohort, the estimated 5-year graft survival was 90% for those receiving transplants from living relatives and 88% for those receiving cadaveric transplants (*P*=0.76). However, in grafts with early acute rejection, the 5-year survival was 40% for cadaveric recipients compared with 73% for living related graft recipients (*P*<0.014). Using the proportional hazards model, cadaveric donor source, older donor age, African American recipient race, and elevated 3-month serum creatinine were independent predictors of long-term graft loss caused by chronic rejection. The severity of acute rejection and recipient age had no impact on the risk of graft loss because of chronic rejection.

Conclusion. These data indicate that the benefit of living related transplantation results from the fact that a living related graft progresses from acute to chronic rejection at a slower rate than a cadaveric graft. Furthermore, a cadaveric graft that is free of acute rejection 3 months after transplantation has an equal likelihood of functioning at 5 years as that of a graft from a living related donor.

INTRODUCTION

Living related renal transplantation provides a significant graft survival benefit over cadaveric transplants. Historically, this advantage has been ascribed to better matching between living related grafts, which are shared between first-degree relatives, versus relatively poor histocompatibility matching in cadaveric transplantation. This view is sup-

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ported by evidence showing that the frequency of graft loss caused by chronic rejection is lower among recipients of living related donor grafts than among recipients of cadaveric transplants (*1, 2*).

Most agree that an acute rejection episode is the most important risk factor for the development of chronic rejection (*3*). Recently, a single-center study indicated that, for living donor grafts, an episode of acute rejection is the only significant risk factor for long-term graft loss; whereas, for cadaveric recipients, nonimmunologic factors play an important role (*4*). In this regard, good long-term outcomes with living nonrelated grafts have highlighted the important effect of alloantigen-independent factors in the progression to chronic rejection (*5*). Such factors include cold ischemic preservation injury and older donor age, which seem to act in concert with early acute rejection episodes in accelerating the progression to long-term graft loss in cadaveric transplantation (*6, 7*).

In this study, we sought to determine whether recipients of living donor grafts who suffer an acute rejection progress to graft loss because of chronic rejection at a slower rate than recipients of cadaveric grafts. This would indicate that long-term graft loss among cadaveric grafts is accelerated by alloantigen-independent injuries that are avoided by living related donor transplantation.

METHODS

We reviewed data on 296 patients who underwent renal transplantation at Mount Sinai Hospital between January 1991 and February 1998. Of these patients, 142 received cadaveric grafts and 154 received grafts from living donors (related, 128; nonrelated, 26). To study long-term survival, only primary grafts that functioned for at least 3 months were included in this analysis. Recipients of cadaveric kidneys from donors younger than 18 years were excluded. Because there were only five recipients of living nonrelated grafts with at least 5 years of follow-up, and only eight recipients of living nonrelated grafts suffered an acute rejection episode, data on recipients of living nonrelated grafts were excluded from statistical analysis.

Patients were retrospectively stratified into four groups: recipients of grafts from living related donors or cadaveric donors, with or without acute rejection in the first 3 months. Demographic variables of donor and recipient age, race, sex, and serum creatinine 3 months after transplantation were compared between groups. Graft loss

because of chronic rejection was defined clinically by a slow progressive deterioration in renal function, either confirmed by biopsy or in which all other causes of allograft loss were excluded. Graft survival was calculated by first censoring for death with a functioning graft and then censoring for all causes of graft failure with the exception of chronic rejection. Five-year graft survival was calculated for all four groups.

From 1991 through 1995, all living donor recipients received cyclosporine and prednisone immunosuppression; in 1996, mycophenolate mofetil was added to this regimen. From 1991 through 1995, all cadaveric recipients received OKT3 induction and cyclosporine and prednisone maintenance immunosuppression; starting in 1996, antibody induction was used only for patients with delayed initial graft function and mycophenolate mofetil was added to the maintenance protocol.

The majority of acute rejections were diagnosed by core biopsy. All mild to moderate rejections were treated with pulse steroids. Both severe and steroid-resistant rejections were treated with either OKT3 or antithymocyte globulin.

Demographic variables were compared using the chi-square test and the Wilcoxon rank-sum test. Graft survival was calculated using the Kaplan-Meier product-limit method and compared using the log-rank test. Probabilities of graft survival and freedom from chronic rejection at 5 years were compared using the z-test. The joint influence on graft survival of several factors taken together was analyzed with the Cox proportional hazards model.

RESULTS

Twenty-seven grafts were lost in the first 3 months after transplantation and excluded from further evaluation. Twenty-two (13%) cadaveric grafts were lost; 10 to initial nonfunction, 7 to death, 3 to acute rejection, and 2 to infection. Five (4%) living donor grafts were lost; two to nonfunction, two to death, and one to noncompliance.

Demographic characteristics of the study group are outlined in Table 1. The median recipient age of living related graft recipients was younger than that of cadaveric recipients (30 vs. 47 years) and there were fewer African Americans in the living related group than in the cadaveric group (16.4% vs. 27.5%). Nevertheless, the history of acute rejection within the first 3 months of transplantation was equivalent between the two groups (25.8% vs. 29.6%), as was the need for antibody treatment (63.4% vs. 45.2%).

TABLE 1. **Demographics of patients with functioning grafts 3 months after transplantation**

	Living related donor n=128	Cadaveric donor n=142	*P*
Median donor age (range)	37.5 (18–65)	36.5 (18–71)	ns
Median recipient age (range)	30 (1–75)	47 (5–77)	0.001
Recipient race (% African American)	16.4	27.5	0.03
Percent acute rejections in first 3 months	25.8	29.6	ns
Percent steroid resistant rejections	63.6	45.2	ns
3 month serum creatinine (mg/dl)	1.6 (0.4–5.3)	1.65 (0.6–4.9)	ns

TABLE 2. **Graft losses 3 months after transplantation**

	Living related donors n=18 (%)	Cadaveric donors n=32 (%)
Death with functioning graft	5 (28)	6 (19)
Chronic rejection	6 (33)	22 (69)
Recurrent disease	0	2 (6)
Malignancy	1 (6)	1 (3)
Noncompliance	4 (22)	0
Miscellaneous	2 (11)	1 (3)

FIGURE 1. Actuarial death-censored long-term graft survival, cadaveric versus living related donors, $P<0.03$.
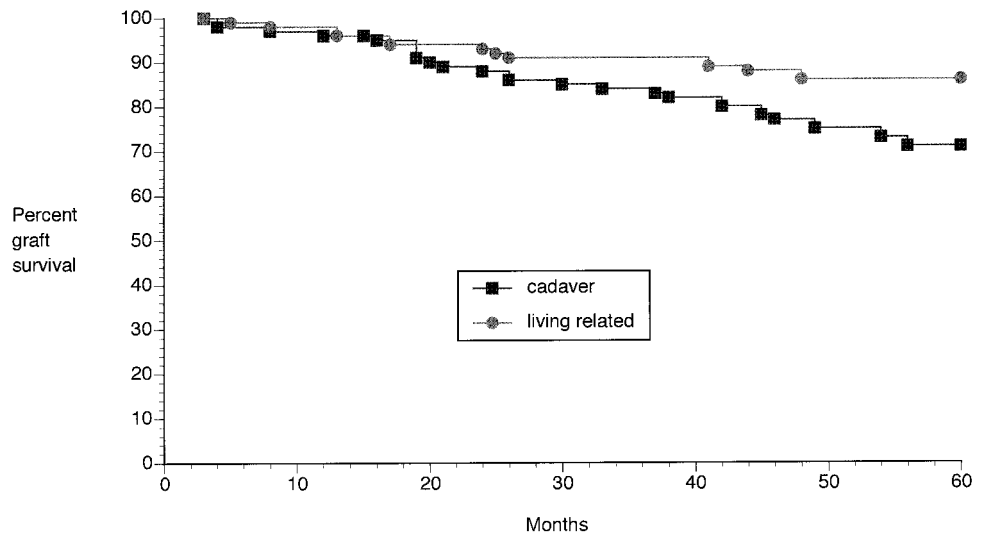
Acute rejection was confirmed by biopsy in 68 (91%) patients. Additionally, early renal function, defined by the 3-month median serum creatinine, was comparable between groups (1.6 vs. 1.65 mg/dl).

There were 51 graft losses during the study period, as shown in Table 2. Chronic rejection was the most common cause of graft loss in both groups. Of the 28 graft losses ascribed to chronic rejection, 23 (82%) were confirmed by biopsy.

The overall death-censored actuarial graft survival is shown in Figure 1, indicating a significant benefit to living related compared with cadaveric transplantation ($P<0.03$, log-rank test). At 5 years, the living related group exhibited an 86% graft survival compared with 71% for the cadaveric group ($P=0.02$, Table 3). We examined graft loss to chronic rejection alone, in which all other causes of graft loss were censored. Five years after transplantation, the living related grafts showed a 92% freedom from graft loss to chronic rejection, compared with 74% for cadaveric grafts (Table 3, $P=0.002$)

Among patients who were free of acute rejection, there was no significant difference in death-censored long-term graft survival between living related and cadaveric recipients (Fig. 2). The risk of graft loss at 5 years was equivalent between the living related and cadaveric groups (90% vs. 88%, $P=0.76$, Table 3). Freedom from graft loss to chronic rejection was similarly equivalent between the groups (96% vs. 91%, $P=0.32$, Table 3).

Among grafts that had suffered an acute rejection within the first 3 months after transplantation, the difference in overall survival between living donor grafts and cadaveric

TABLE 3. Probability of 5-year freedom from graft loss, given function 3 months after transplantation and censoring for patient death[a]

	Loss from all causes			Loss from chronic rejection		
	Cadaver	Living related	Living nonrelated	Cadaver	Living related	Living nonrelated
All patients						
Number of patients	142	128	26	142	128	26
Number of failures	26	13	1	22	6	0
Probability of survival at 5 years (standard error)	0.71 (0.05)	0.86 (0.04)	0.91 (0.09)	0.74 (0.05)	0.92 (0.06)	1
P value (cadaver vs. living related, z-test)	0.02			0.002		
Rejection-free cohort						
Number of patients	100	95	18	100	95	18
Number of failures	7	6	1	5	2	0
Probability of survival at 5 years (standard error)	0.88 (0.05)	0.90 (0.04)	0.83 (0.15)	0.91 (0.04)	0.96 (0.03)	1
P value (cadaver vs. living related, z-test)	0.76			0.32		
Acute rejection cohort						
Number of patients	42	33	8	42	33	8
Number of failures	19	7	0	17	4	0
Probability of survival at 5 years (standard error)	0.4 (0.09)	0.73 (0.10)	1	0.43 (0.10)	0.81 (0.10)	1
P value (cadaver vs. living related, z-test)	0.014			0.007		

[a] Statistical analysis of living nonrelated group was omitted given the small sample size.
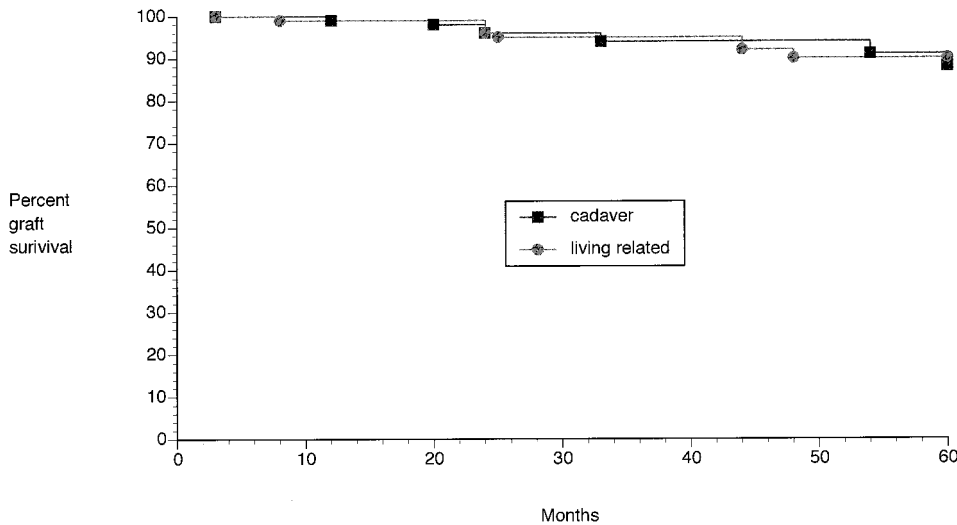
FIGURE 2. **Actuarial death-censored long-term graft survival of acute rejection-free grafts, cadaveric versus living related donors, *P*=not significant.**

grafts approached statistical significance (*P*<0.07, log-rank test, Fig. 3). The cumulative difference at 5 years was statistically significant (cadaveric graft survival 40%; living related graft survival 73%, *P*<0.014, z-test, Table 3). We calculated the risk of graft loss to chronic rejection at 5 years after transplantation, again censoring all causes of graft loss other than chronic rejection. As shown in Table 3, there was a 5-year chronic rejection-free survival of 81% for living related grafts compared with 41% for the cadaveric group (*P*=0.007, z-test).

For recipients who suffered an acute rejection within the first 3 months after transplantation, four factors were identified as independent predictors of graft loss because of chronic rejection: cadaveric donor source (*P*=0.03), elevated 3-month serum creatinine level (*P*=0.0001), older donor age (*P*=0.01), and African American recipient race (*P*=0.035), Table 4. The independent influence of donor source, when each of the remaining three factors is taken into account, is shown in Figures 4, 5, and 6.

For illustrative purposes, we divided patients into two groups according to donor age (greater than or less than 50 years) and calculated the chronic rejection-free graft survival

(Fig. 4). Overall graft survival among cadaveric graft recipients was poorer than among recipients of living related donors, regardless of whether the donor was older or younger than 50 years. Thus, although older donor age was a risk factor for graft loss, it did not fully explain the difference in graft survival between cadaveric and living related recipients that had suffered a previous acute rejection.

When chronic rejection-free graft survival was compared between African American recipients and non-African Americans, living donor recipients exhibited better chronic rejection-free survival than cadaveric recipients, irrespective of recipient race (Fig. 5).

Of all factors studied, early renal function was the most sensitive predictor of long-term graft loss (*P*<0.0001). As shown in Figure 6, among graft recipients with a serum creatinine less than 2 mg/dl 3 months after transplantation, there were no graft losses to chronic rejection within the first 5 years after transplantation. On the contrary, when the creatinine was greater than 2 mg/dl, long-term graft survival for both groups was diminished.

Neither the severity of acute rejection, defined by the need for antibody therapy, or older recipient age, studied as a
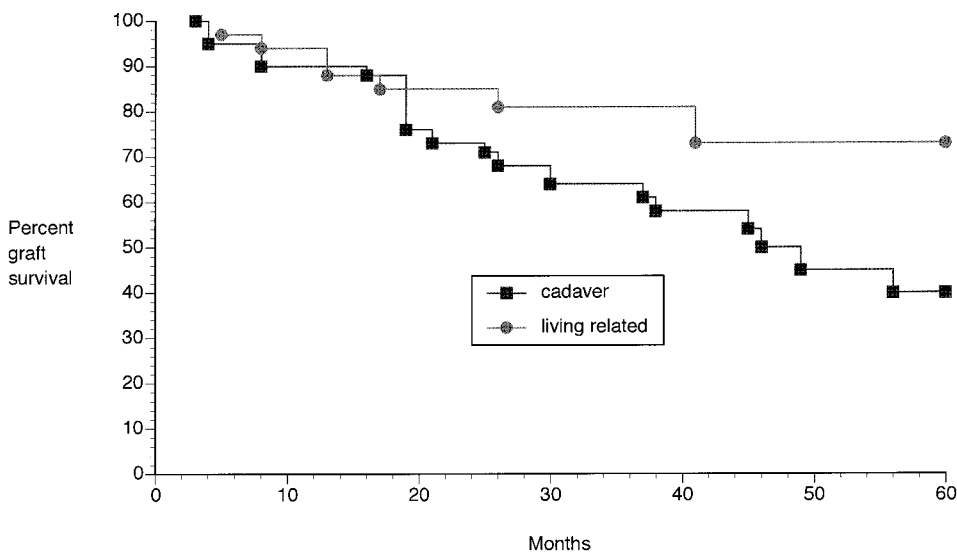

FIGURE 3. **Actuarial death-censored long-term graft survival of acute-rejection cohort, living related versus cadaveric donors, *P*<0.07.**

TABLE 4. Impact of donor and recipient variables on long-term graft loss due to chronic rejection for renal allografts with acute rejection within the first 3 months after transplantation

Variable	Relative risk	*P*
Cadaveric donor	4.401	0.0299
Elevated 3-month serum creatinine[a]	4.134	0.0001
Older donor age[b]	1.047	0.0107
African American recipient race	4.072	0.0351

[a] Relative increased risk for each increase of 0.1 mg/dl of serum creatinine.

[b] Relative increased risk for each year of age.

continuous variable, were independent risk factors for graft loss to chronic rejection, using the proportional hazards model.

During the period of study, living nonrelated transplantation became increasingly more common, resulting in a cohort of 26 patients with excellent long-term survival (Table 3). For this group, the overall risk of graft loss at 5 years after transplantation was only 9%. In fact, among the rejection-free cohort (n=18), the estimated 5 year graft survival was 83%; and among the acute rejecters (n=8), the estimated survival was 100%. Because of the small numbers in these groups, we could not make statistical comparisons with the cadaveric or living related groups.

DISCUSSION

This study suggests that the long-term survival advantage of receiving a living related renal graft versus a cadaveric transplant is restricted to those recipients who have suffered an acute rejection. Despite the fact that the incidence of acute rejection in the first 3 months after transplantation was comparable between groups, the likelihood of progressing to graft loss at 5 years was greater among cadaveric grafts with acute rejection than among living related grafts with acute rejection. Conversely, the recipient of a cadaveric renal graft that was rejection-free within the first 3-month period was as likely as a recipient of a living related allograft to have function 5 years later. This finding highlights the important interaction of alloantigen-dependent and -independent factors.

The recipient of a living related allograft begins with three important advantages over a cadaveric recipient: the likeli-
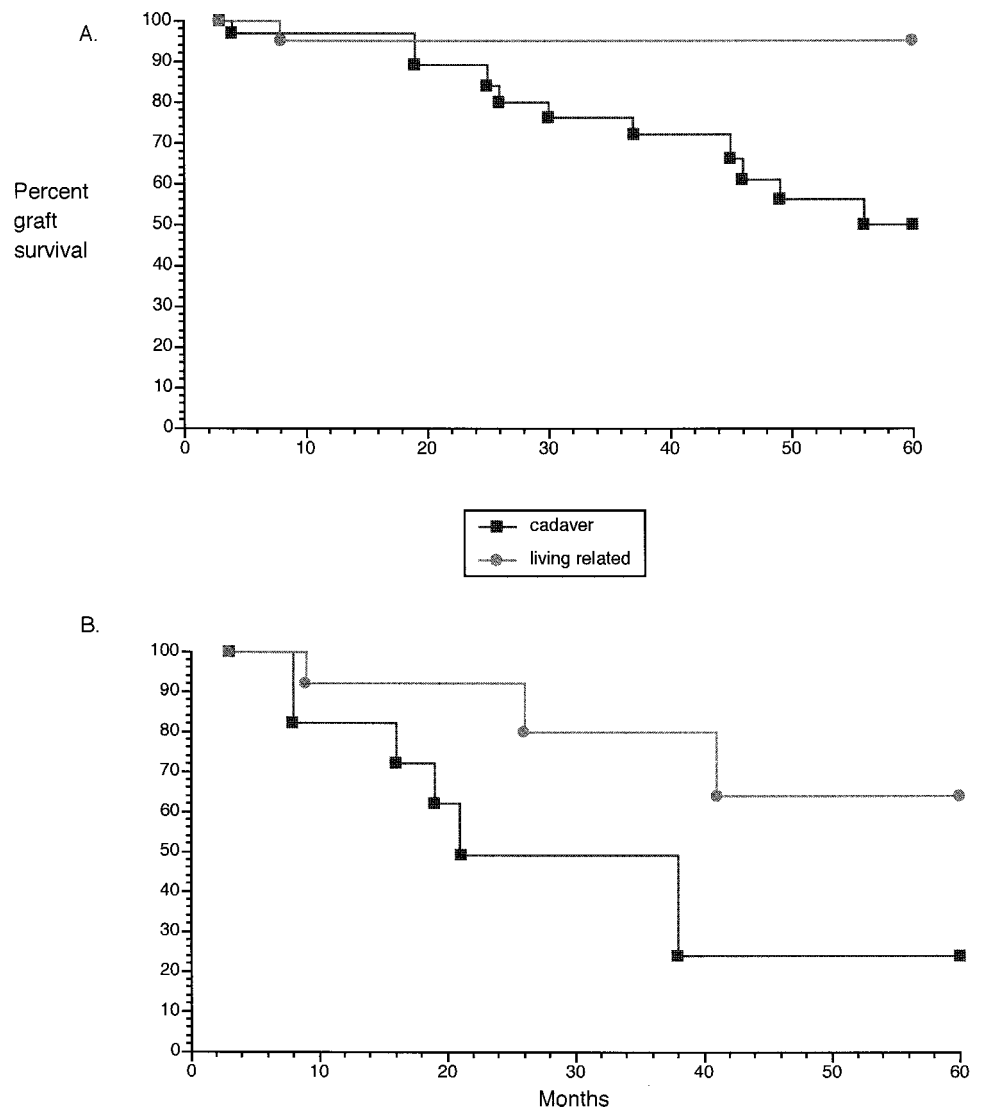

FIGURE 4. Chronic rejection-free graft survival of acute rejection cohort stratified by donor age. (A) donors <50 years old, (B) donors >50 years old.
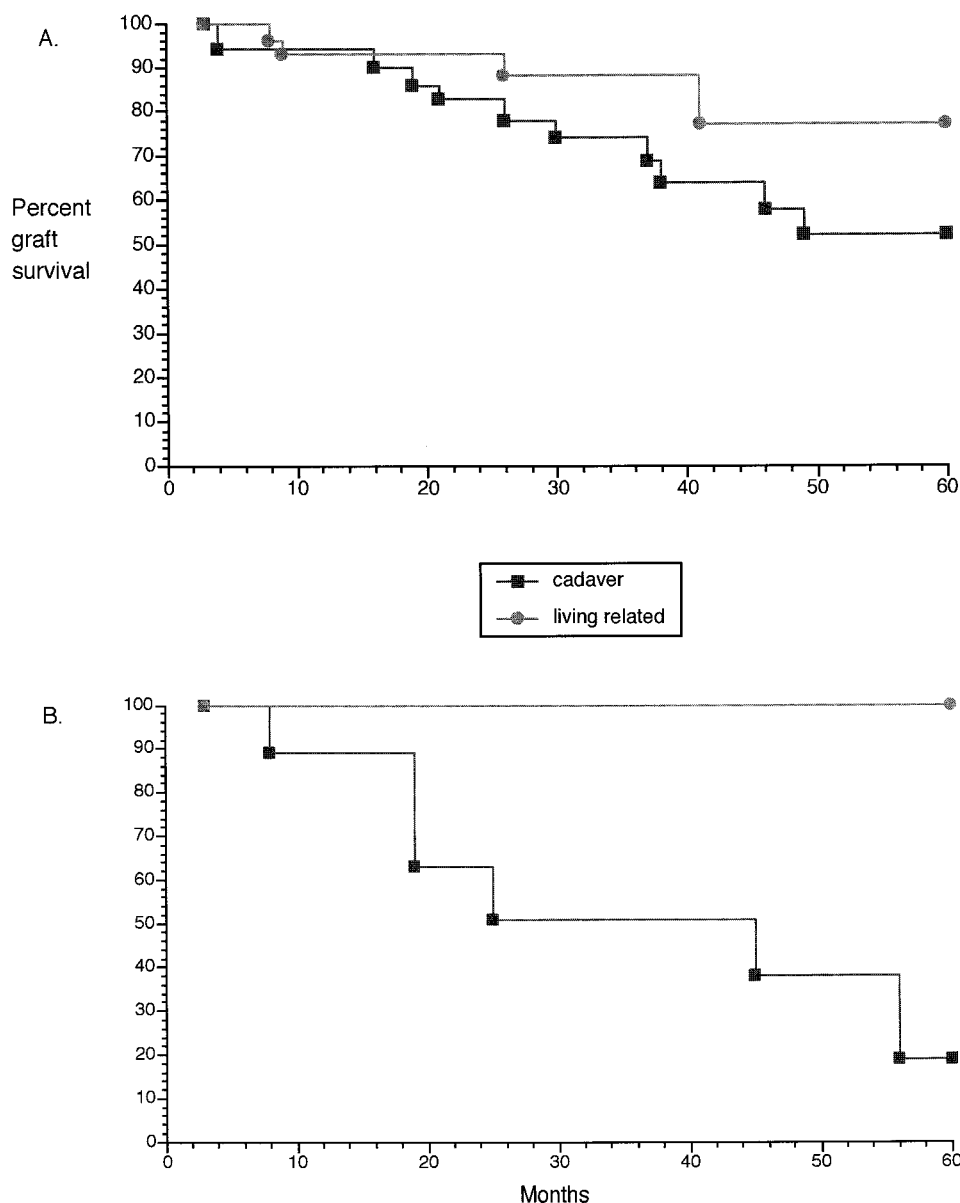
A.

Percent
graft
survival

FIGURE 5. Chronic rejection-free graft survival of acute rejection cohort stratified by recipient race. (A) non-African American recipients, (B) African American recipients.

B.

Months

hood of better histocompatibility matching; a more careful pretransplantation assessment of donor renal function; and the avoidance of prolonged cold ischemic preservation injury. Although there was no difference in the history of acute rejection between the living related versus the cadaveric groups, it is possible that better histocompatibility matching afforded by living related transplantation resulted in better graft survival in that cohort. One view of chronic rejection is that it is entirely an immunologic injury that results from ongoing subclinical rejection (2). Thus, the better matched living donor recipients may have been less susceptible to persistent immunologic injury after treatment of an acute rejection episode compared with the cadaveric cohort.

A second benefit of living donation is the opportunity to evaluate donor renal function in a more discriminating fashion than is possible with cadaveric donor selection, which relies on relatively scanty information collected over a brief period of time. Thus, the recipient of a living donor graft is

more likely to receive a kidney with good functional reserve. Furthermore, the living donor graft is procured in a hemodynamically stable environment with minimal warm ischemic injury, whereas cadaveric organs typically are procured from donors maintained on variable amounts of vasopressor agents. Recent data showed that, in the immediate preprocurement period, kidneys from cadaver donors exhibit increased expression of pro-inflammatory cytokines that may have an important detrimental effect on long-term function. Specifically, one study using a rodent brain-death model showed increased expression of VCAM-1 and ICAM-1 in the kidney and liver of brain-dead animals compared with controls. Tilney, using a similar model, showed increased mRNA expression of both lymphocyte- and macrophage-associated cytokines compared with controls (8, 9). These data suggest that cadaveric donor organs may be more susceptible to cytokine-mediated injury in the early posttransplantation period resulting from the preprocurement brain-death syndrome.
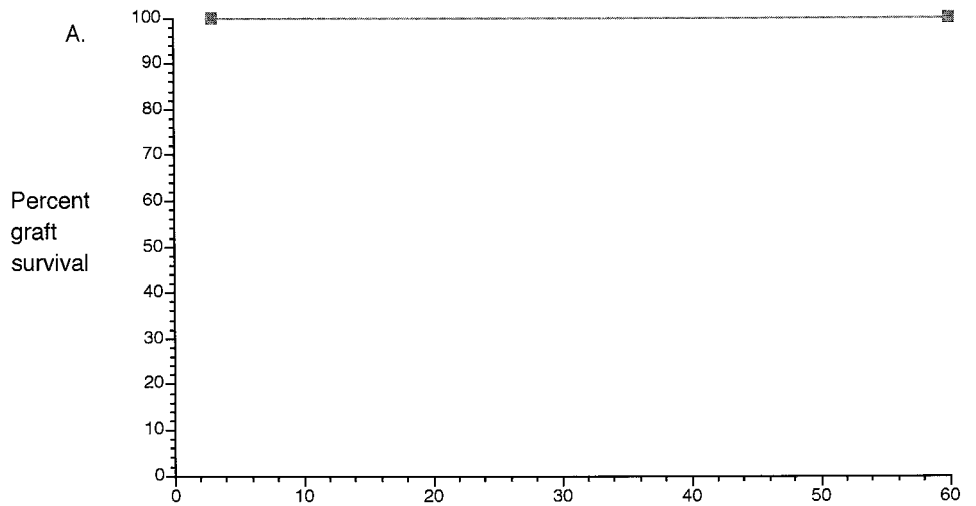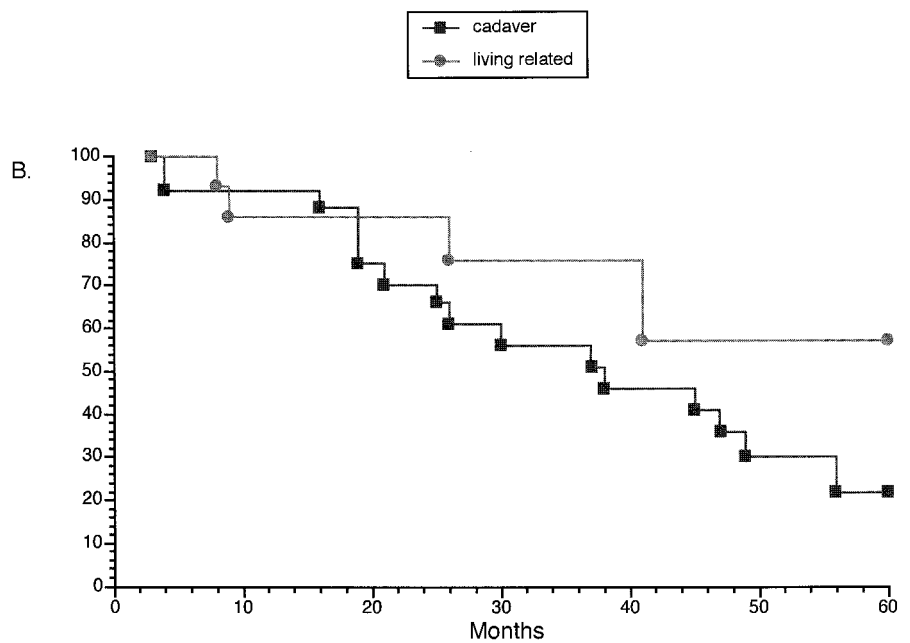
FIGURE 6. Chronic rejection-free graft survival of acute rejection cohort stratified by 3-month serum creatinine. (A) creatinine <2.0 mg/dl, (B) creatinine >2.0 mg/dl.

The third advantage of living donation is the avoidance of cold ischemic preservation injury. There is now a large body of evidence to support the view that preservation injury acts in concert with acute rejection to accelerate the progression to chronic rejection (6, 10, 11, 12). Halloran has termed this effect "accelerated senescence", suggesting that repeated injuries to the transplanted kidney in the early posttransplantation period may ultimately lead to inadequate repair mechanisms, resulting in replacement of functioning renal tissue by fibrosis (13).

A useful way to distinguish the importance of alloantigen-dependent and -independent factors is to analyze the long-term results of living nonrelated grafts. In this way, one can isolate the effect of cold ischemic preservation injury from histoincompatibility. Recent single and multicenter data indicate that the long-term survival of living nonrelated grafts is significantly better than cadaveric kidneys (5, 14, 15). Similarly, our data suggest that living nonrelated transplants have long-term survival equivalent to living related

donor transplants. In fact, among the eight recipients of living nonrelated grafts that suffered an early acute rejection, the probability of survival at 5 years was 100%. Unfortunately, the sample size was too small to confirm this effect using standard statistical methods.

Survival data in this study was analyzed using two statistical techniques. First, the overall difference between cadaveric and living related groups was calculated using the log-rank test; and second, the accumulated difference in survival at 5 years was compared using the z-test. The log-rank test is useful when comparing two groups with constant relative failure risks over time, but may underestimate survival differences when the difference between groups increases over time. In renal transplantation, long-term survival curves of cadaveric and living related grafts tend to diverge over time, thus the cumulative difference in survival was also calculated at 5 years using the z-test. The latter technique may be criticized because one chooses an arbitrary time point to compare survival. Nevertheless, the 5-year point is often

used to estimate long-term graft survival in solid organ transplantation. Furthermore, it is unlikely that survival curves of cadaveric and living related grafts would converge beyond 5 years after transplantation. For these reasons, we think that comparison of graft survival at 5 years using the z-test is a more useful tool than comparing overall differences using the log-rank test.

The important detrimental impacts of alloantigen-independent factors such as older donor age and African American recipient race shown by others was confirmed in this study (*16*, *17*, *18*, *19*). Among recipients who suffered an early rejection episode, both factors were found to be independent predictors of graft loss for both living related and cadaveric grafts. Older recipient age, however, had no impact on long-term graft loss in this cohort. Additionally, the need for antibody therapy to reverse an acute rejection did not increase the risk of graft loss. This finding may be explained by the fact that it is not the severity of the rejection, but the response to therapy as evidenced by the recovery of function that plays a more important role in improving long-term graft survival (*20*).

The importance of good early renal function was highlighted in this study by comparing graft survival based on 3-month serum creatinine level. Among recipients who suffered an acute rejection episode, with a creatinine less than 2 mg/dl at 3 months after transplantation, the estimated likelihood of chronic rejection-free survival at 5 years was 100%, irrespective of whether the graft was of living or cadaveric source. Using the Cox proportional hazards model, this parameter was the most discriminating in terms of long-term survival. This finding supports the view that long-term function is dependent on avoiding or controlling both immunogenic and nonimmunogenic insults within the early posttransplantation period. Thus, judicious selection of donor grafts, avoidance of preservation injury, careful use of nephrotoxic immunosuppressive agents, and prompt treatment of early rejections are all critical factors required to achieve good function within the early transplantation period.

In conclusion, these data suggest that the long-term benefit of living related transplantation results from the fact that a living related graft will progress from acute to chronic rejection at a slower rate than a cadaveric graft. Furthermore, for a cadaveric graft free of acute rejection at 3 months after transplantation, the likelihood of functioning at 5 years is equivalent to that of a living related graft. The small cohort of living nonrelated grafts that suffered an acute rejection episode showed excellent long-term survival, comparable to living related grafts. This information strengthens the view that alloantigen-independent factors such as donor quality and preservation injury play a critical role in accelerating the course of chronic rejection, but are less important in isolation.

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