

SHOULD LIVING-UNRELATED RENAL TRANSPLANT RECIPIENTS RECEIVE ANTIBODY INDUCTION? RESULTS OF A CLINICAL EXPERIENCE TRIAL

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Background. Living-donor kidney transplant recipients generally do not receive antibody induction. Induction avoidance may not be appropriate, particularly for living-unrelated renal transplant (LURT) recipients, in whom matching may not be optimal. We compared the incidence of acute rejection and graft outcome of LURT recipients who were administered no induction and cadaveric renal transplant (CRT) recipients who were administered anti-CD25 antibody. These groups both had immediate graft function and similar maintenance immunosuppression.

Methods. This retrospective analysis included patients who received kidney transplants between 1999 and 2000. CRT recipients received basiliximab, corticosteroids, mycophenolate mofetil (MMF), and delayed tacrolimus (serum creatinine <3 mg/dL). LURT recipients received tacrolimus (initiated pretransplantation), MMF, and corticosteroids.

Results. The analysis included 136 LURT recipients and 126 CRT recipients. CRT recipients included more African Americans (52.4% vs. 30.9%, $P < 0.01$). LURT recipients included more patients with at least one human leukocyte antigen mismatch (97.8% vs. 85.7%, $P < 0.01$). A higher acute rejection rate was observed in LURT recipients at both 6 months (LURT recipients 19.1% vs. CRT recipients 3.2%, $P < 0.01$) and 1 year (21.3% vs. 4.0%, $P < 0.0004$); a higher rate also was observed in African American LURT recipients compared with African American CRT recipients (35.7% vs. 4.5%, $P < 0.0015$) at 1 year. LURT recipients demonstrated a threefold greater rejection risk than CRT recipients who were administered basiliximab (relative risk: 3.6, $P < 0.002$). Graft survival was similar at 1 year.

Conclusion. The higher rejection rates in LURT recipients (no induction) compared with CRT recipients (basiliximab induction), despite similar chronic immunosuppression (tacrolimus, MMF, and steroids) and immediate graft function, indicate the potential advantage of anti-CD25 induction in LURT protocols to reduce the risk of acute rejection.

During recent years, substantial reductions in acute rejection and increases in graft survival rates have been reported for both cadaveric- and living-donor renal transplant recipients (1, 2). However, donor shortage remains a serious concern, and living donors represent a means for expanding the limited donor pool. Whereas the number of cadaveric-donor kidney transplantations performed in the United States has remained essentially stable during recent years, the number of patients undergoing living-donor kidney transplantation has increased (3). Although related donors continue to be the dominant source of living renal transplants, there has been a steady increase in the number of unrelated living donors in kidney transplantation. Unrelated donors now account for more than 20% of all kidney transplant donors (3).

Living-donor kidney transplant recipients are perceived to be at particularly low risk for developing rejection (4). They usually have a low incidence of delayed graft function and therefore typically receive immunosuppression with calcineurin inhibitors early posttransplantation. For kidney transplant recipients at low risk of rejection, antilymphocyte induction therapy is generally avoided because of concerns about complications and cost. The avoidance of induction therapy may not be appropriate for all living-donor transplant recipients, particularly living-unrelated renal transplant (LURT) recipients. Recent data have shown that an increasing percentage of living-donor transplant recipients have one or more human leukocyte antigen (HLA) mismatch (4). Because LURT recipients typically do not share the same HLA type with their donors, it is unlikely that they will benefit from the same absolute risk reduction for acute rejection as those patients who receive a kidney transplant from a living-related donor. Induction in these transplant recipients may be warranted. In fact, a recent study has also demonstrated that therapy with the anti-CD25 antibody basiliximab reduced the incidence of rejection in living-donor transplant recipients (4). As an alternative to induction with polyclonal antibodies, induction with anti-CD25 monoclonal antibodies may be considered in living-donor transplant recipients.

Anti-CD25 monoclonal antibodies selectively bind to the interleukin (IL)-2 receptor of activated T cells, thus inhibiting T-cell growth and proliferation. Basiliximab (chimeric) and daclizumab (humanized) are potent and effective in the prevention of acute rejection (5). Anti-CD25 antibodies have been shown to reduce the incidence of rejection in cadaveric renal transplant (CRT) recipients (4, 6). In this retrospective study, we compared the rejection rates and graft survival of a cohort of patients who received a LURT and no induction therapy with the rejection rates and graft survival of a cohort

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of patients who received a CRT and induction therapy with the anti-CD25 antibody basiliximab.

MATERIALS AND METHODS

An analysis was conducted in renal transplant recipients who received organs between 1999 and 2000. Patients were divided into two study groups based on whether they were LURT or CRT recipients. Patients with delayed graft function were excluded from the analysis to provide comparability of immediate graft function for each group. Delayed graft function was defined as the need for hemodialysis in the immediate postoperative period.

CRT recipients received two 20-mg doses of basiliximab, one before transplantation and one on postoperative day 4. LURT recipients did not receive induction therapy. The maintenance immunosuppressive regimen for both study groups consisted of tacrolimus (and rarely cyclosporine), mycophenolate mofetil (MMF), and corticosteroids. Tacrolimus was initiated in CRT recipients when serum creatinine levels decreased to less than 3 mg/dL. Tacrolimus was initiated in LURT recipients 3 days before transplantation; preoperative tacrolimus therapy was started at 0.05 mg/kg twice daily and dosed to achieve target 12-hr trough levels of 12 to 15 ng/mL at the time of transplant. For patients in both study groups, MMF was initiated in the immediate postoperative period at a dosage of 1 g twice daily. All patients received intravenous methylprednisolone at the time of the transplantation, followed by an oral prednisone taper to approximately 10 mg/day by day 30.

All continuous variables were expressed as mean \pm standard error. All categorical variables were expressed as N and percentage of total. The outcomes evaluated in this study included acute rejection and graft survival. Kaplan-Meier curves were used to demonstrate the difference in the incidence of acute rejection and graft failure between the two study groups. Cox proportional hazard models were used to estimate the adjusted risk for acute rejection in each study group. All analyses were performed as intention to treat.

RESULTS

A total of 262 renal transplant recipients were included in the study population (136 LURT recipients and 126 CRT recipients). Patient demographics are shown in Table 1. Patients in both study groups were similar with regard to age and gender. Both LURT and CRT study groups included a higher percentage of men, 64% and 65.9%, respectively. There were significant differences between the two study groups with regard to race ($P < 0.01$), number of patients with at least one HLA mismatch ($P < 0.01$), and mean cold ischemia time ($P < 0.01$). The percentage of African American patients was significantly higher in the CRT group than in the LURT group (52.4% vs. 30.9%, $P < 0.01$). The number of

patients with at least one HLA mismatch was significantly greater in the LURT recipient study group than in the CRT recipient study group (97.8% vs. 85.7%, $P < 0.01$). The mean cold ischemia time was significantly longer in the CRT group with a mean of 25.69 ± 10.90 hr compared with 1.70 ± 0.69 hr in the LURT group. Mean nadir serum creatinine levels were similar in both study groups. The mean length of follow-up was significantly longer for LURT recipients (35.2 ± 2.1 months) compared with CRT recipients (13.2 ± 1.1 months).

Mean doses of tacrolimus were similar between groups at all time points from months 3 to 24 posttransplantation. Although mean trough levels of tacrolimus were generally higher in the living-unrelated donor group, the differences between groups were not significant except at month 3 (11.5 ng/mL LURT vs. 9.4 ng/mL CRT, $P = 0.009$). During the first 3 months posttransplantation, 13 patients in the LURT group were converted from therapy with tacrolimus to cyclosporine because of intolerance of tacrolimus, 11 patients were converted at various times later in the study, and 1 patient was converted from therapy with cyclosporine to tacrolimus. In the CRT group, six patients were converted at various times in the study from therapy with tacrolimus to cyclosporine. Mean doses of MMF were comparable between groups at all time points in the study with the exception of month 18 (LURT 1,385 mg vs. CRT 1,654 mg, $P = 0.047$). Therapy with MMF was switched to sirolimus in five patients in the CRT group; seven patients in the LURT group were administered sirolimus in lieu of MMF.

The overall incidence of acute rejection was significantly higher in LURT recipients who did not receive induction therapy compared with CRT recipients who received induction therapy with basiliximab (20% vs. 6.2%, $P < 0.001$). The rejection rate remained significantly lower when excluding the zero-mismatch transplants (24.6% LURT vs. 6.1% CRT, $P < 0.001$). At 6 months posttransplantation, the incidence of acute rejection was significantly higher in LURT recipients (no basiliximab) compared with CRT recipients (basiliximab) (19.1% vs. 3.2%, $P < 0.01$), and at 1-year posttransplantation, the incidence of acute rejection continued to be significantly higher in LURT recipients compared with CRT recipients (21.3% vs. 4.0%, $P < 0.0004$, Fig. 1). The adjusted risk of acute rejection for those patients who received a LURT and no induction therapy was 3.6 times greater than for CRT recipients treated with basiliximab ($P < 0.002$).

At 1-year posttransplantation, graft survival rates were similar in both study groups. The graft survival rates in LURT and CRT recipients were 95.24% and 94.12%, respectively.

Because African American transplant recipients may experience higher rejection rates than non-African American recipients, patients were also stratified by race. Acute rejection rates at 1 year posttransplantation were significantly higher in African American LURT recipients who did not receive induction therapy compared with African American CRT recipients who were treated with basiliximab (35.7% vs. 4.5%, $P < 0.0015$). At both 6 months and 1 year posttransplantation, the length of time to an acute rejection episode tended to be shorter in African American patients compared with non-African American patients, although this difference did not reach significance. At 1 year posttransplantation, African American and non-African American patients demonstrated

TABLE 1. Patient demographics

	LURT (n=136)	CRT (n=126)	P value
Age	47.08 \pm 1.19	49.29 \pm 1.4	0.18
Sex: Female	49 (36.0%)	43 (34.1%)	0.75
Male	87 (64.0%)	83 (65.9%)	
Race: African American	42 (30.9%)	66 (52.4%)	0.00
Other	94 (69.1%)	60 (47.6%)	
0 mismatch: No	133 (97.8%)	108 (85.7%)	0.00
Yes	3 (2.2%)	18 (14.3%)	
Mean cold ischemia time (hr)	1.70 \pm 0.69	25.69 \pm 10.90	0.00
Nadir creatinine	1.14 \pm 0.08	1.16 \pm 0.03	0.57
Follow-up (mo)	35.21 \pm 2.1	13.2 \pm 1.1	0.00

LURT, living-unrelated renal transplant; CRT, cadaveric renal transplant.

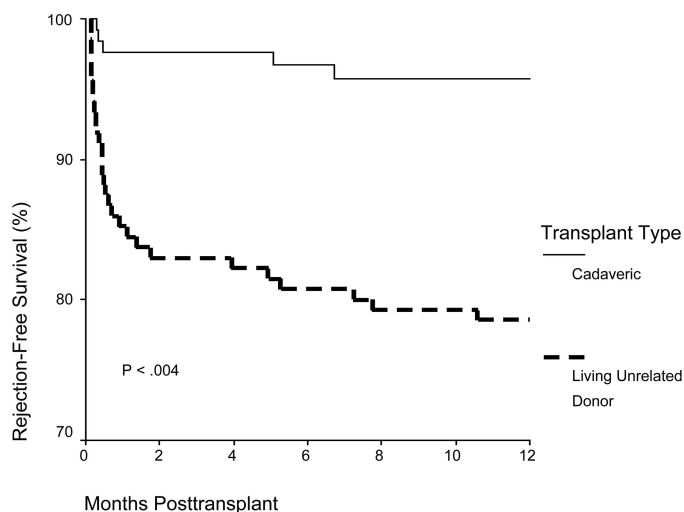


FIGURE 1. Rejection-free survival (Kaplan-Meier estimates) for cadaveric-donor kidney transplant recipients who received basiliximab and living-unrelated donor transplant recipients who received no antibody induction therapy.

similar graft survival rates (95.4% vs. 94.2%, P =not significant).

Multivariate regression analysis showed that age, gender, zero HLA mismatch status, and length of follow-up did not affect the incidence of acute rejection in transplant recipients (Table 2). Race and nadir serum creatinine level were determined to have a significant impact on the incidence of acute rejection, with a relative risk of 2.26 in African American patients ($P=0.03$) and 1.26 in patients with elevated serum creatinine levels ($P=0.02$).

At study entry, mean nadir serum creatinine levels were similar in both LURT recipients (1.65 ± 0.07 mg/dL) and CRT recipients (1.64 ± 0.08 mg/dL). At 6 months posttransplantation, mean serum creatinine levels remained similar across study groups. LURT and CRT recipients had mean serum creatinine levels of 1.65 ± 0.07 mg/dL and 1.64 ± 0.08 mg/dL, respectively.

DISCUSSION

The present study was conducted to assess the incidence of acute rejection in LURT recipients who have not had the benefit of induction therapy compared with CRT recipients who have received induction therapy. We believed that by

TABLE 2. Relative risk for acute rejection (living-unrelated renal transplant recipients vs. cadaveric renal transplant recipients)

	RR	CI	P value
Age	1.002	0.97–1.03	0.88
Sex: Female	1.00	—	—
Male	0.99	0.44–2.23	0.99
Race: Other	1.00	—	—
African American	2.26	1.06–4.81	0.03
0 mismatch: No	1.00	—	—
Yes	0.003	0.001–0.0005	0.97
Nadir creatinine	1.26	1.03–1.54	0.02
Follow-up (mo)	1.002	0.99–1.001	0.63

RR, relative risk; CI, confidence interval.

comparing rejection rates we could evaluate the opportunity for further reducing rejection rates in our LURT recipients. In our study, LURT recipients who were not administered basiliximab demonstrated a significantly higher incidence of acute rejection during the first posttransplant year compared with CRT recipients who were treated with basiliximab. The higher rejection rates in the LURT recipients occurred despite initiation of tacrolimus before transplantation, which should have put this group at an advantage in regard to prevention of rejection. The CRT recipients received delayed tacrolimus administration. Studies have shown that acute rejection is a significant risk factor for graft survival in both living- and cadaveric-donor transplant recipients (7, 8). Patients who do not experience acute rejection less frequently develop chronic rejection, and they have improved graft survival at 10 years posttransplantation. Prevention of acute rejection episodes may decrease the immunogenicity of the graft and preserve nephron mass, thereby resulting in improved graft survival. It is also possible that by preventing early activation of lymphocytes and subsequent rejection, basiliximab may be important in controlling the immunologic factors that chronically injure renal allografts.

A recent study demonstrated that the incidence of rejection may be reduced in living-donor and cadaveric-donor kidney transplant recipients treated with basiliximab (4). Living-donor transplant recipients who received basiliximab demonstrated a significantly lower incidence of death, graft loss, and acute rejection at 6 months posttransplantation compared with those living-donor transplant recipients who did not receive induction (29.6% vs. 49%, $P=0.038$). The use of basiliximab and a cyclosporine-based immunosuppressive regimen also resulted in a 27% lower incidence of rejection in similarly treated cadaveric-donor transplant recipients. Of living-donor transplant recipients who did experience an acute rejection episode, significantly fewer basiliximab-treated patients required augmented immunosuppression other than steroids compared with transplant recipients who did not receive induction (23.2% vs. 41.3%, $P=0.046$).

An increased therapeutic effect is observed in clinical trials when anti-CD25 antibodies and calcineurin inhibitors (cyclosporine and tacrolimus) are used in combination, probably because the two agents have complementary mechanisms of action. Both cyclosporine and tacrolimus inhibit IL-2 receptor gene transcription, whereas anti-CD25 antibodies selectively block the IL-2 receptor on T cells (6, 9, 10). Clinical studies have shown that tacrolimus is an effective immunosuppressive agent (11, 12) and that basiliximab may also be used safely and effectively with tacrolimus-based regimens (13). A recent study by Philosophe et al. (14) compared basiliximab with OKT3 in patients receiving tacrolimus-based triple-therapy. At 1 year posttransplant, basiliximab-treated patients demonstrated a substantial reduction in the incidence of rejection compared with OKT3-treated patients (15% vs. 31%). Clinical studies have also demonstrated the effectiveness of basiliximab in cyclosporine-based regimens for both cadaveric- and living-donor kidney transplant recipients. The addition of basiliximab to a dual-therapy, cyclosporine-based immunosuppressive regimen has been shown to reduce the incidence of acute rejection in renal transplant recipients (6). More substantial reductions in the incidence of acute rejection have been achieved when basiliximab is used

with cyclosporine-based triple therapy, including azathioprine or MMF (15–17).

Basiliximab was well tolerated by patients in the present study. This is similar to what has been observed in other studies with both cyclosporine- and tacrolimus-based regimens (18, 19). Compared with patients treated with polyclonal antibodies, patients treated with basiliximab do not seem to experience any increase in adverse events (19, 20).

Preliminary studies have shown that certain subpopulations of patients may also benefit from the inclusion of anti-CD25 antibody in combination with chronic immunosuppressive therapy. A recent study in pediatric renal transplant recipients demonstrated that the effectiveness of a tacrolimus-based regimen is increased with the addition of basiliximab (21). A recent study in African American transplant recipients demonstrated that patients who received basiliximab demonstrated a reduced incidence of acute rejection and significant improvement in 6-month graft survival compared with patients who did not receive induction (6). In our study, the significant reductions in acute rejection observed in CRT recipients who were treated with basiliximab, compared with LURT recipients who did not receive the benefit of induction therapy, also were observed in African Americans. Although African American LURT recipients who did not receive induction therapy experienced an increased incidence of acute rejection compared with non-African American LURT recipients, this was not unexpected. Historically, acute rejection rates have been higher in African American patients than in non-African American patients (22, 23). However, the rates of acute rejection that we observed in African American CRT recipients who received induction therapy with basiliximab compared favorably with the rates observed in the non-African American CRT recipients.

The results of our study show that living-unrelated transplant recipients who did not receive the benefit of induction therapy experienced a significantly higher incidence of acute rejection than CRT recipients treated with basiliximab. The inclusion of basiliximab in current immunosuppressive regimens also could potentially improve outcomes in living-related donor transplant recipients. This study was not designed to specifically look at antibody induction in LURT recipients. Although our experience is retrospective, the comparison of rejection rates between these two groups, despite tacrolimus, MMF, and prednisone immunosuppression, allows us to speculate that basiliximab induction therapy should provide an advantage in LURT recipients that remains to be tested in future prospective clinical trials. A multicenter registry was created to assess the safety, efficacy, and cost-effectiveness of basiliximab in living-related and unrelated donor transplantation to test this hypothesis. This new registry may represent a valuable means for evaluating new strategies to optimize immunosuppression in all types of living-donor renal transplantation (24).

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