Steroid Avoidance in Renal Transplant Patients Maintained on a Cyclosporine-based Protocol

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Objective: **The aim of this study was to analyze the effect of steroid avoidance, as compared with our pre-existing protocol that contained steroids, on renal allograft and patient survival. Secondary outcomes included body weight, diabetes, hyperlipidemia, and infection.**

Materials and Methods: **This retrospective chart review of the results of steroid avoidance was performed in 169 patients who had undergone renal transplant between January 2000 and March 2002 and had received an immunosuppression regimen of cyclosporine, mycophenolate mofetil, and prednisone; and 148 patients who had undergone transplant between November 2002 and November 2004 who had received induction immunosuppression with a steroid taper by postoperative day 4 and were maintained on cyclosporine and mycophenolate mofetil.**

Results: **One-year allograft survival rates, rejection-free graft survival rates, and patient survival rates were 88%, 76%, and 97%, respectively, in the steroid-maintenance group compared with 90%, 74%, and 96%, respectively, in the steroid-avoidance group (*P* = NS). No differences were detected in multiple secondary variables related to the metabolic effects of steroid therapy.**

Conclusions: **These data suggest that steroid avoidance can be performed safely and effectively in patients on a cyclosporine-based protocol of immunosuppression. Longer follow-ups are suggested to determine the effects of limited steroid exposure on the metabolic profiles of patients.**

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Improvements in immunosuppressive regimens have made renal transplant a viable alternative to dialysis. Antibody therapies, calcineurin inhibitors, and antimetabolites have improved 1-year graft survival rates following deceased-donor renal transplant to better than 90% and have decreased acute graft rejection rates to 10% to 30% (1). This improved survival and function of allografts has permitted transplant physicians to shift their emphasis toward minimizing the morbidity associated with immunosuppressive medications.

Long-term immunosuppression has the potential for toxicity. Hypertension, diabetes, and hyperlipidemia all can be exacerbated by corticosteroid use (2). Reducing steroid exposure could reduce toxicity while maintaining efficacy. Preliminary studies on steroid withdrawal or steroid avoidance have used widely varying immunosuppressive protocols and thus, have had inconsistent results. Although acute rejection rates increased, patient and allograft outcomes did not worsen (3, 4). Recent research has shown that steroid withdrawal can be safe when induction and antimetabolite therapies are used (5-9).

Our steroid avoidance protocol started in 2002, and most patients undergoing renal transplant have been enrolled. The aim of this study was to analyze the effect of steroid avoidance, as compared with our pre-existing protocol that contained steroids, on renal allograft and patient survival rates. Secondary outcomes included body weight, diabetes, hyperlipidemia, and infection.

Materials and Methods

Patients

The institutional review board approved the study protocol. Patients undergoing renal transplant at our institution between January 2000 and November 2004 were studied. The steroid-maintenance group

consisted of 169 patients who had undergone transplant between January 2000 and March 2002. Immunosuppression among these patients included a calcineurin inhibitor (usually cyclosporine), mycophenolate mofetil, and prednisone. The steroid-avoidance group consisted of 148 patients who had undergone transplant between November 2002 and November 2004. These patients had a rapid steroid taper after surgery, and were then maintained on cyclosporine and mycophenolate mofetil. Patients on pre-existing chronic steroid therapy, those with a panel reactive antibody titer greater than 30%, or persons with a history of rapid rejection were not candidates for steroid avoidance and were excluded from this analysis as were patients who had undergone heart, liver, pancreas, or simultaneous pancreas-kidney transplants.

Immunosuppressive Protocols

All patients in the steroid-avoidance group received induction therapy, as did a minority of patients in the steroid-maintenance group. Induction therapy consisted of basiliximab or antithymocyte globulin. Patients < 60 years old without coronary artery disease or diabetes received induction therapy with antithymocyte globulin (1.5 mg/kg) in 4 intravenous doses that were started intraoperatively; a total of 6 mg/kg was given during hospitalization. Elderly patients and those with coronary artery disease or diabetes received basiliximab (20 mg) intraoperatively and again on day 4. Steroid avoidance patients received 500 mg intravenous methylprednisolone during surgery, 250 mg the next day, and 125 mg on day 2. On days 3 and 4, patients received oral prednisone (60 mg and 30 mg).

Steroid-maintenance patients received 4 doses of perioperative methylprednisolone at 12-hour intervals: 2 doses of 1 mg/kg were followed by 2 doses of 0.5 mg/kg. Oral prednisone was begun at 20 mg/day and reduced over 6 months to a maintenance dosage of 7.5 to 10 mg/d.

Both groups received cyclosporine (10 mg/kg) preoperatively, followed by 5 mg/kg every 12 hours. Dosages were adjusted to achieve trough concentrations of 250 to 300 ng/mL in the early posttransplantation period and 150 to 200 ng/mL subsequently. Mycophenolate mofetil was started at 2 g/d and adjusted if adverse effects such as leukopenia and gastrointestinal disturbance occurred. Both groups received identical prophylaxis for secondary infections, with acyclovir or ganciclovir to prevent cytomegalovirus infection, depending on the immunity status of the donor and the recipient. All patients received trimethoprim/sulfamethoxazole as *Pneumocystis* pneumonia prophylaxis.

At discharge, steroid-maintenance patients were taking cyclosporine, mycophenolate mofetil, and prednisone; steroid-avoidance patients were receiving cyclosporine and mycophenolate mofetil only. Steroid therapy was permanently reinstated in any steroid-avoidance patient who experienced 2 episodes of acute allograft rejection as determined by clinical and/or histologic criteria. Acute rejection was diagnosed if serum creatinine levels rose more than 25% from their baseline levels in the absence of other identifiable factors, or if an allograft biopsy revealed typical rejection.

Methods

Retrospective analyses of the 2 groups were performed with an intention-to-treat methodology. Demographic, laboratory, and clinical data were obtained by chart review. Primary outcomes were patient and allograft survival and rejection-free survival. Secondary outcomes included body weight, blood glucose and cholesterol levels, and incidence of hospitalizations and infections.

Statistical Analyses

Continuous variables were compared using the *t* test; categorical data were compared using the chi-square test. Patient, graft, and rejection-free graft survival rates were compared using Kaplan-Meier life table analyses using a log rank test. *P* values < .05 were considered statistically significant.

Results

Aside from the immunosuppressive strategy, the 2 groups were well matched at baseline (Table 1). Induction therapy and chronic steroid use were different between the groups. Follow-up was longer for patients in the steroid-maintenance group than it was for patients in the steroid-avoidance group.

Survival analyses by log rank revealed no significant differences between the groups. Patient survival at 1 year was 97% in the steroid-maintenance group and 96% in the steroid-avoidance group (*P* = NS) (Figure 1). One-year allograft survival rates were 88% in the steroid-maintenance group and 90% in the steroid-avoidance group (*P* = NS) (Figure 2). Rejection-free graft survival rates at 1 year were 76% in the steroid-maintenance group vs 74% in steroid avoidance patients (*P* = NS) (Figure 3). Acute rejection occurred in 40 of 148 patients (27%) in the steroid-avoidance group versus 45 of 169 patients (27%) in the steroid-maintenance group (*P* = NS). Delayed

graft function (defined as a need for dialysis during the first week after surgery or failure of the serum creatinine level to decline by the third postoperative day) did not differ between groups (38% vs 36%; P = NS).

The metabolic outcomes of both groups are shown in Table 2. Patient weights and serum glucose levels did not differ at months 1, 6, 12, or 24 posttransplant. New-onset diabetes was diagnosed in 12 patients on steroids and in 7 patients in the steroid-avoidance group (P = NS). Systolic blood pressure was statistically significantly lower in the steroid-avoidance group at 1 month (143 ± 22 vs 136 ± 17 mm Hg; P = .01). A trend toward persistently lower systolic blood pressures in the steroid-avoidance group was not statistically significant. Serum cholesterol levels were usually lower in the steroid-avoidance group but reached statistical significance only at months 1 and 6 (P < .001). Serum creatinine levels were similar between the groups at 1, 6, 12, and 24 months. Postoperative infections

Table 1. Patient characteristics

	Maintenance	Avoidance	*P* value
Number	169	148	NS
Patients maintained on steroids	169 (100%)	14 (9.5%)	< .001
Patients receiving induction	49 (29%)	148 (100%)	< .001
Antithymocyte globulin	4 (2%)	58 (39%)	
Basiliximab	45 (27%)	90 (61%)	
Average age (y)	50±14	52±13	NS
Average body mass index	27±5	28±5	NS
Average follow-up (mo)	41±18	16±7	< .001
Race			
White	141	125	NS
African American	25	23	NS
Other	3	0	NS
Diagnosis			
Diabetes mellitus	46	33	NS
Glomerulonephritis	45	34	NS
Hypertension	15	15	NS
Polycystic kidney disease	15	15	NS
Vascular	3	3	NS
Other	0	0	NS
Patients on dialysis prior to transplant	144	133	NS
Patients with previous transplant	25	23	NS
Average panel reactive antibody titer (%)	7±18	3±7	.008
Average cold ischemia time (h)	21±11	23±10	NS
Average HLA mismatches	A:1 B:1 DR:1	A:1 B:1 DR:1	NS
Patients started on cyclosporine	169	148	NS
Patients switched to tacrolimus	4	1	NS

HLA, human leukocyte antigen

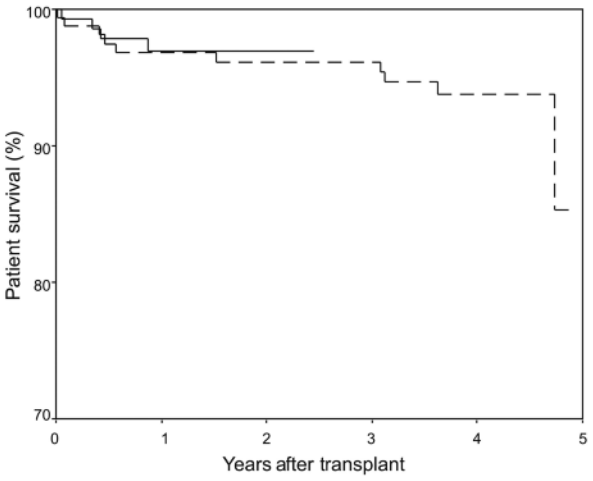

Figure 1. Kaplan-Meier estimate of patient survival. Similar outcomes for the steroid-avoidance group (solid line) and the steroid-maintenance group (dashed line) are shown (P = .75, log rank).

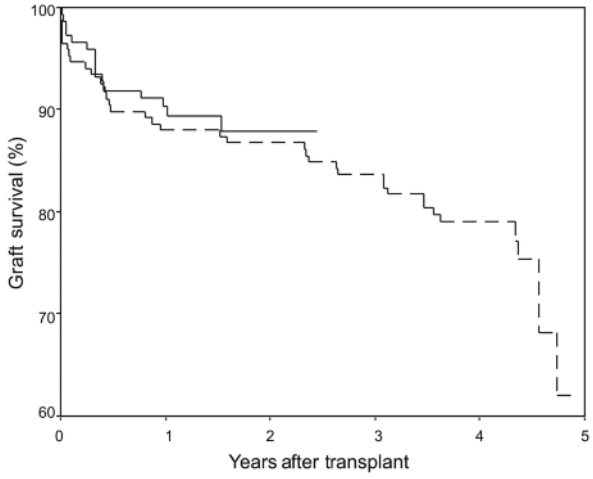

Figure 2. Kaplan-Meier estimate of allograft survival. Outcomes for the steroid-avoidance group (solid line) and the maintenance group (dashed line) are similar (P = .94, log rank).

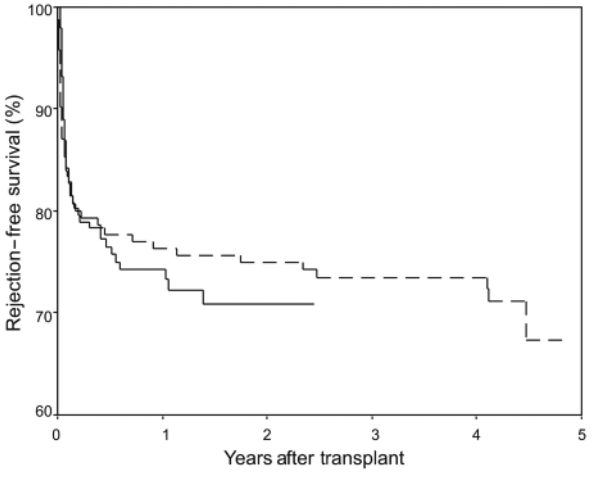

Figure 3. Kaplan-Meier estimate of rejection-free survival. The steroid-avoidance group (solid line) and the maintenance group (dashed line) showed similar experiences with regard to rejection-free survival at 1 and 2 years (P = .64, log rank).

Table 2. Metabolic outcomes of both groups

	Admission		1 Month		6 Months		12 months		24 months	
	SM (n=169)	SA (n=148)	SM (n=134)	SA (n=124)	SM (n=117)	SA (n=104)	SM (n=113)	SA (n=80)	SM (n=108)	SA (n=14)
Glucose (mmol/L)	6.6±4.0	6.9±3.5	6.9±3.2	6.6±3.1	7.1±3.3	6.6±2.6	7.1±3.7	6.6±2.6	6.8±3.4	6.8±2.3
T cholesterol (mmol/L)	5.15±1.19	5.07±1.16	5.84±1.29	5.17±1.11*	5.35±1.11	4.73±0.96*	5.07±0.98	4.86±1.24	4.78±1.03	4.50±1.0
WBC (× 10^9/L)	8±5	8±3	10±3	6±3*	8±3	6±3*	8±2	6±2*	7±2	6±2*
Weight (kg)	81±18	79±16	77±17	80±16	84±19	82±18	86±20	86±18	84±19	88±19
SBP (mm Hg)	143±22	144±19	143±22	136±17*	140±18	135±17	141±15	139±18	139±16	135±19

SA, steroid-avoidance group; SBP, systolic blood pressure; SM, steroid-maintenance group; T cholesterol, total cholesterol; WBC, white blood cells
Average values for various metabolic variables analyzed during the course of patient follow-up.
*P = .05 steroid-maintenance group versus steroid-avoidance group.

requiring hospitalization occurred infrequently, and their incidence did not statistically significantly differ between the groups.

Total leukocyte counts at the time of transplant were similar between the groups; at subsequent intervals, a significant difference emerged (Table 2). Steroid-avoidance patients had lower white blood cell counts at 1, 6, 12, and 24 months ($P < .001$). The leukocyte nadir was significantly different between the avoidance and maintenance groups (2.7 ± 1.6 vs 4.1 ± 1.9; $P < .001$).

A subgroup analysis was performed among subjects in the steroid-avoidance arm to compare basiliximab and antithymocyte globulin induction therapies. Of the 148 patients in the steroid-avoidance arm, 90 patients (61%) received basiliximab induction and 58 patients (39%) received antithymocyte globulin induction. Although we observed a trend toward increased 1-year allograft survival rates among patients receiving basiliximab induction when compared with patients receiving antithymocyte globulin, this result did not reach statistical significance (94% vs 87%, $P = .08$). Rejection-free survival at 1 year was 70% in the basiliximab group versus 76% in the antithymocyte globulin group ($P = .35$), and 1-year patient survival rates were 98% in the basiliximab group versus 96% in the antithymocyte globulin group ($P = .53$). Patients receiving antithymocyte globulin had lower white blood cell counts at 1, 3, 6, 12, and 18 months of follow-up ($P < .05$).

Discussion

This study showed safe implementation of a steroid-avoidance protocol in a renal transplant program using a cyclosporine-based immunosuppression. Patients treated with a perioperative induction immunosuppression protocol with an early steroid taper had allograft and patient survival rates similar to patients on a traditional immunosuppression protocol with steroids, as well as similar times to first rejection and incidences of rejection. We were unable to detect expected improvements in the metabolic profile of patients with limited steroid exposure.

Previous work has produced conflicting results concerning the safety and efficacy of steroid avoidance or withdrawal (1, 3). Differences in institutional protocols, timing of steroid withdrawal, and use of induction therapy may factor into the heterogeneity of results. The present study is strengthened by standardization of the induction and steroid-avoidance protocols. These data suggest that clinical outcomes in patients withdrawn from steroids are similar to historical controls, and show the safety of avoiding steroid maintenance, which is consistent with other studies using similar immunosuppressive protocols (5, 7, 8).

Long-term graft survival and avoiding adverse effects from medication are goals of transplant professionals. The metabolic benefits from steroid avoidance, while intuitive, are not supported by the literature. Some studies may have lacked the statistical power to show benefit, while others may have been hindered by short follow-ups (10). Despite extended follow-up, we failed to detect sustained improvements in hypertension, hyperlipidemia, or hyperglycemia. The relatively low doses of corticosteroids taken by patients in the steroid-maintenance arm of this study might have contributed to the similar outcomes between the groups. Sivaraman and associates reported benefits in patients when prednisone was tapered from 10 mg/day to 10 mg every 2 days, but found no benefit with further reduction (11). Other studies have reached different conclusions. Rogers and associates reported less weight gain among patients undergoing early steroid withdrawal (12), and Smak Gregoor and associates showed a reduction in mean arterial blood pressure values with steroid withdrawal (13). Rostaing and associates reported

safe steroid withdrawal in patients treated with daclizumab, tacrolimus, and mycophenolate mofetil, but noted a decrease in posttransplant diabetes, perhaps due to the additive effects of tacrolimus and steroids (14). Our use of cyclosporine may have predisposed patients in both groups to less posttransplant diabetes and lessened the distinction between the avoidance and maintenance groups. Finally, a longer follow-up might reveal more slowly evolving differences between the groups.

Our data showed consistently lower leukocyte counts in the avoidance group, especially among those who received antithymocyte globulin, but lower counts and a significantly lower leukocyte nadir in steroid-avoidance patients did not translate to increases in rates of infection or incidences of hospitalization. Antithymocyte globulin induction has been shown to reduce T-cell counts for as long as 2 years after liver transplant (15), findings that are consistent with our observations. Patients who receive antithymocyte globulin induction therapy followed by steroid withdrawal may warrant increased clinical surveillance for relative leukopenia. Antimetabolite and antiviral therapies could be confounding factors that further complicate the management of steroid-avoidance patients.

A subgroup analysis showed a trend toward improved allograft survival among steroid-avoidance patients who received induction therapy with the interleukin-2 receptor blocker (basiliximab) as compared with patients receiving a polyclonal antibody (antithymocyte globulin). This finding may indicate that the difference in leukocyte counts was affecting the dosing decisions for other immunosuppressive agents. Antithymocyte globulin patients had significantly lower white blood cell counts during follow-up, which may have prompted transplant physicians to reduce the dosage of mycophenolate mofetil, which promotes leukopenia. A systematic tendency to reduce leukopenia by reducing mycophenolate mofetil exposure might explain some of our findings. This study was not designed to collect data on mycophenolate mofetil doses; however, further studies to detect differences between the available antibody therapies may be warranted. Finally, the patients receiving basiliximab were older with more comorbidities and may have had less potential to generate harmful immunologic phenomena such as graft rejection.

A limitation of this study is its retrospective design, but the large number of patients receiving homogeneous regimens and the extended follow-up in this study suggest that these findings may be generalizable to large groups of transplant patients. Prospective randomized studies with longer follow-ups may provide further insight into optimal strategies for posttransplant immunosuppression.

Conclusions

Early steroid avoidance can be safely undertaken in renal transplant recipients who have received induction with basiliximab or antithymocyte globulin. Decreases in graft and patient survival rates were not observed. Leukocyte counts were lower, but significant improvements in metabolic profiles were not observed.

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