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Steroid withdrawal in living donor renal transplant recipients using tacrolimus and cyclosporine: a randomized prospective study*

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Summary

Steroids have been a mainstay of immunosuppressive regimens in renal transplantation despite their adverse effects. The introduction of new immunosuppressant has improved the survival rates and prompted trials of steroid withdrawal. We conducted a randomized prospective study to compare steroid withdrawal at 6 months post-transplant between tacrolimus + mycophenolate mofetil (MMF) (FK group) versus cyclosporine A + MMF (CsA group). Steroid was withdrawn at 6 months post-transplant under the condition of no rejection episode proven by biopsy and maintenance of serum creatinine level <2.0 mg/dl. Fourteen recipients were excluded because of acute rejection within 6 months or protocol violation. Steroid could be tapered off in 62 in FK group and 55 in CsA. Three cases in FK group and five in CsA had acute rejection within another 6 months after steroid withdrawal ($P > 0.05$). At 12 months, the incidence of post-transplant diabetes was 18.6% vs. 8.0% in FK and CsA group. And hypercholesterolemia was presented in 8.5% vs. 2.0%, hypertension in 47.5% vs. 56.0%, and serum creatinine level 1.18 ± 0.24 mg/dl vs. 1.18 ± 0.20 mg/dl, respectively ($P > 0.05$). Steroid withdrawal may be carried out successfully using both FK and CsA with MMF, but long-term follow-up is necessary.

Introduction

Despite their adverse effects, steroids have been a mainstay of immunosuppressive regimens in renal transplantation over the past several decades. The use of corticosteroids to control acute allograft rejection was a breakthrough that allowed renal transplantation to become a routine procedure. They are effective in reducing the incidence of acute rejection and reversing rejection episodes. However, chronic use of steroids increases cardiovascular risk such as hypertension, diabetes mellitus (DM) and hypercholesterolemia, and has deleterious effects on bone metabolism, infection, and neoplasia.

Since the emergence of cyclosporine A (CsA) as the primary immunosuppressant for organ transplantation, immunosuppressive regimens have been successful in achieving a high 1-year graft survival rates after renal allograft transplantation. Recently, the introduction of newer and more potent immunosuppressants such as tacrolimus (FK), mycophenolate mofetil (MMF), humanized anti-IL2R antibodies, and sirolimus has led to important declines in the incidence of acute rejection and could provide a more potent substrate with which to attempt safe steroid-sparing regimens that would decrease the morbidity associated with chronic steroid therapy.

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Many transplant centers have attempted steroids withdrawal from renal allograft recipients at various time interval after transplantation. Data from the Collaborative Transplant Study reported that a 5-year graft survival was significantly higher in patients that changed from triple drug therapy to steroid-free maintenance with CsA or CsA and azathioprine [1].

But in the study of Ratcliffe *et al.* [2], steroid withdrawal showed to be feasible in most patients with stable graft function maintained on CsA and azathioprine. Pittsburgh group demonstrated that steroids could be safely withdrawn in a majority of the patients with tacrolimus-based immunosuppression after the first 6 months post-transplantation with 5% acute rejection rate [3]. Moreover, Boots *et al.* [4] reported that steroid could be safely withdrawn after 7 days post-transplant in the patients maintained on tacrolimus. And many reports showed the benefits attributed to steroid withdrawal including improvement in hypertension, correction of post-transplant DM (PTDM), reduction in serum lipid levels without compromising graft survival [2,5–7].

We have attempted to withdraw steroids in the recipients under tacrolimus or CsA plus MMF. The primary purpose for performing this exploratory study was to determine whether steroid-free maintenance could be achieved without negative effect on graft or patient survival and which one of tacrolimus or CsA would be more effective and safe in patients with steroid withdrawal.

Patients and methods

Patient selection

Between September 2000 and August 2003, patients more than 15 years old who had undergone first living donor renal transplantation in Samsung Medical Center were included in this study. The exclusion criteria were congestive heart failure <35% EF, chronic liver disease, DM, systemic infection, multiple organ transplantation, and serologic evidence of human immunodeficiency virus. All 131 recipients were studied and randomly divided into FK group ($n = 68$) and CsA group ($n = 63$). The study protocol was described in detail to the patients before transplantation and informed consent to perform the study was obtained from all patients.

Immunosuppression protocol

Patients in FK group were treated with a triple immunosuppressive regimen consisting of tacrolimus (Prograf®; Fujisawa, Osaka, Japan), MMF (Cellcept®; Roche, Basle, Switzerland) and steroid, and patients in CsA group received triple regime with CsA microemulsion, MMF, and steroid. Initial tacrolimus dose was 0.15 mg/kg/day i.v. and CsA (Cipol inj.®; Chong Kun Dang, Seoul, Korea) was initially administrated at 4 mg/kg/day i.v. and CsA microemulsion (Cipol-N soft cap.®; Chong Kun Dang), the dosage of which was tripled, was administered orally on postoperative second day. The levels of tacrolimus and CsA were measured and adjusted in order to maintain target trough levels according to the protocol (Table 1). All the patients in both groups took MMF (1500 mg/day) unless side effect was noticed.

Table 1. Target trough levels of tacrolimus and cyclosporine (CsA) (ng/ml).

Time	Tacrolimus	CsA
1 week	12–15	300–350
2 weeks to 1 month	10–12	200–300
1–3 months	8–10	150–250
>3 months	6–8	100–200

Steroid withdrawal schedule

Post-transplant steroid was gradually tapered off and totally withdrawn at 6 months post-transplant.

Withdrawal conditions

When there was no acute rejection proven by biopsy and the level of serum creatinine was maintained at <2.0 mg/dl at 6 months post-transplant, steroid was completely withdrawn thereafter. If rejections occurred after steroid withdrawal, patients were treated with steroid pulse therapy and steroids were restarted.

Endpoint

The primary endpoint was acute rejection proven by biopsy within 1 year post-transplant. The prevalence of PTDM and hypercholesterolemia, the use of cholesterol-lowering agent or antihypertensive drug, the level of total cholesterol, and serum creatinine were also compared. Patients with hemoglobin A1C continuously over 6.5%, fasting plasma glucose over 126 mg/dl at least two occasional and repeated testing on a different day, or requiring oral hypoglycemic agent or insulin for glycemic control were diagnosed as PTDM. Hypercholesterolemia was defined by serum total cholesterol level ≥ 240 mg/dl.

Statistic analysis

Student's *t*-tests and chi-squared analysis were used accordingly, and a *P*-values of <0.05 was considered statistically significant.

Results

Among 131 recipients assigned before transplantation, 14 recipients were excluded either because of acute rejection proven by biopsy within 6 months or because of protocol violation (Fig. 1). Acute rejection episodes before steroid withdrawal occurred in nine recipients, which were assessed as mild or moderate according to Banff 97 classification. All of them were treated with steroid pulse therapy initially and all returned to normal graft function. However two of them had a second acute rejection episode, and were successfully treated with antithymothyte globulin with recovered graft function.

In 117 recipients (FK 62 vs. CsA 55), steroid could be tapered off and withdrawn at 6 months post-transplant. The baseline characteristics of recipients in FK and CsA group are shown in Table 2. Age, sex, cause of renal failure, panel-reactive antibody, and donor type were not significantly different between two groups.

After steroid withdrawal, acute rejection episodes confirmed by biopsy occurred within the next 6 months in three cases (4.8%) in FK group and five cases (9.0%) in the CsA group (Fig. 1 and Table 3). There were no significant differences in rejection rate between two groups($P > 0.05$). There was no graft failure or patient death during the follow-up period. The profile and clinical courses of the recipients with acute rejection within 6 months after steroid withdrawal are presented in Table 4. Most rejection episodes were mild or moderate on histologic review and were reversible with steroid pulse therapy. Following steroid pulse therapy, the patients were maintained under steroid medication. Two recipients in CsA group with an episode of acute rejection within 6 months after steroid withdrawal lost their graft function because of chronic rejection after end of study period. One recipient who returned to normal graft function with steroid pulse therapy for the initial rejection episode had chronic rejection at 27 months post-transplantation and ultimately lost his graft function. Other person poorly responded to ster-

Table 2. Baseline characteristics of recipients in FK and CsA group ($n = 117$).

	FK group ($n = 62$)	CsA group ($n = 55$)	*P*
Age	38.8 ± 9.15 (21–68)	38.5 ± 9.54 (21–57)	NS
Sex			NS
M	39 (62.9%)	26 (47.3%)	
F	23 (37.1%)	29 (52.3%)	
Cause of renal failure			NS
Glomerulonephritis	8 (12.9%)	10 (18.2%)	
Unknown	46 (74.2%)	39 (70.9%)	
Others	8 (12.9%)	6 (10.9%)	
HLA mismatches			NS
0	7 (11.3%)	10 (18.2%)	
1	5 (8.1%)	5 (9.1%)	
2	9 (14.5%)	12 (21.8%)	
3	22 (35.5%)	17 (30.9%)	
4	14 (22.6%)	8 (14.6%)	
5	2 (3.2 %)	1 (1.8%)	
6	3 (4.8%)	2 (3.6%)	
Panel-reactive antibody			NS
0%	59 (95.2%)	53 (96.4%)	
<50%	2 (3.2%)	2 (3.6%)	
>50%	1 (1.6%)	0 (0%)	
Donor			NS
Living related	36 (58.1%)	35 (63.6%)	
Living unrelated	26 (41.9%)	20 (36.4%)	
Age	37.7 ± 11.4 (19–65)	39.8 ± 10.1 (22–61)	
Sex			
M	36 (58.1%)	30 (54.5%)	
F	26 (41.9%)	25 (45.5%)	

NS = not significant.

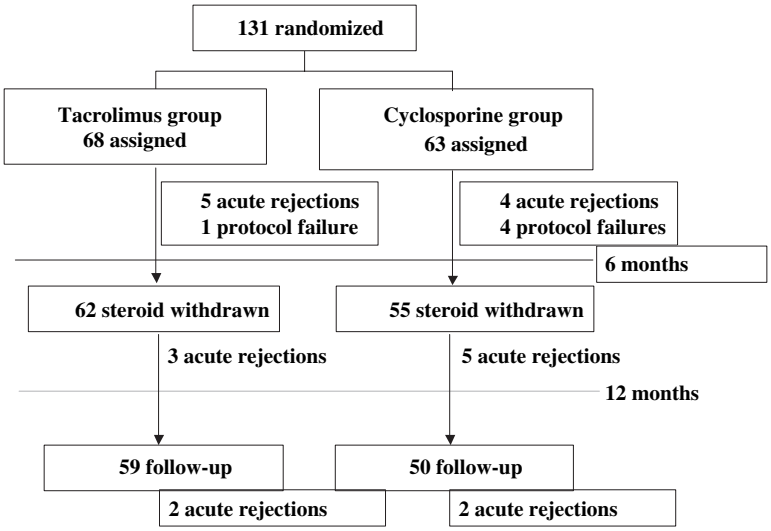

Figure 1 Follow-up after steroid withdrawal.

Table 3. Acute rejection, graft failure and death within post-transplant 1 year.

	FK group ($n = 62$) (%)	CsA group ($n = 55$) (%)	*P*
Rejection rate	3/62 (4.8)	5/55 (9.0)	NS
Graft failure	0 (0)	0 (0)	
Patient death	0 (0)	0 (0)	

NS = not significant.

oid pulse therapy and lost his graft function at 16 months post-transplant.

Other results were analyzed at 12 months post-transplant. The incidence of PTDM was 18.6% (11 cases) in FK group and 8.0% (four cases) in CsA group ($P > 0.05$). At 12 months post-transplant, one recipient (1.7%) in FK group required insulin more than 30 days for glycemic control. There were no statistically significant differences in the prevalence of hypercholesterolemia (8.5% vs. 2.0%) and hypertension (47.5% vs. 56.0%), and the level of serum creatinine (1.18 ± 0.24 mg/dl vs. 1.18 ± 0.20 mg/dl) between FK and CsA group ($P > 0.05$) (Table 5).

Table 5. Parameters.

	FK group ($n = 59$)	CsA group ($n = 50$)	*P*
Incidence of PTDM	11 (18.6%)	4 (8.0%)	NS
Use of cholesterol-lowering agent	4 (8.5%)	1 (2.0%)	NS
Use of antihypertensive	28 (47.5%)	28 (56.0%)	NS
Total cholesterol (mg/dl)	172.7 ± 32.49	175.0 ± 30.28	NS
Serum creatinine (mg/dl)	1.18 ± 0.24	1.18 ± 0.20	NS

NS = not significant.

Discussion

Steroid could be withdrawn successfully within an acceptable rate of acute rejection in the majority of renal transplant recipients who were maintained on tacrolimus or CsA with MMF, 4.8%, and 9.0%, respectively. Excellent graft function and graft survival could be achieved after steroid withdrawal in both groups. These results indicated that steroid withdrawal regimens do not detrimentally impact on short-term results as seen by acute rejection and graft survival.

Kasiske et al.'s meta-analysis of steroid withdrawal showed that patients on CsA with steroids withdrawn had a significantly higher incidence of acute rejection and the relative risk of graft failure was also high [8]. However, this analysis was performed from studies carried out before the advent of MMF. MMF-treated groups showed reduced incidence and severity of rejection, and improved outcome of graft function and survival [9,10]. And steroids could be safely and successfully withdrawn from renal allograft recipients receiving calcineurin inhibitors and MMF in the studies [11–13].

In this study, we compared and analyzed steroid withdrawal in both tacrolimus and CsA groups with the addition of MMF. Acute rejection rate in FK group was lower than in CsA group, but there were no significant differences. According to the study of Mayer *et al.* [14], the significant reduction in the incidence of episodes of allograft rejection observed with tacrolimus therapy may have important long-term implications given the prognostic influence of rejection on graft survival. Others showed that tacrolimus was significantly more effective than CsA microemulsion in preventing acute rejection and graft failure after renal transplantation without an increase in the incidence of adverse events associated with long-term immunosuppression [15–17]. But, there was no direct evidence to prove the efficacy of tacrolimus-based immunosuppression compared with CsA-based regimens in steroid withdrawal. Recently, the advent of new agents

Table 4. Profile and clinical courses of rejection patients proven by biopsy after steroid withdrawal.

Patient no.	Age/ sex	Time of Rx.	Donor type	Donor age/sex	HLA mismatches	Grade of Rx.	Tx. of Rx.	Response of Tx.	Follow-up	Graft status
FK group ($n = 3$)										
1	40/M	11 months	LR	39/M	2	IA	SPT	Full recovery	2 years and 4 months	Normal
2	20/F	8 months	LR	46/F	3	II A	SPT	Full recovery	2 years 2 months	Normal
3	28/M	11 months	LR	51/F	2	IA	SPT	Full recovery	l year and 9 months	Normal
CsA group ($n = 5$)										
1	30/F	11 months	LR	54/M	1	IA	SPT	Full recovery	4 years and 4 months	CR
2	36/F	9 months	LU	29/F	3	IA	SPT	2nd SPT	3 years and 4 months	CR
3	37/F	8 months	LU	39/M	3	II A	SPT	Full recovery	3 years and 3 months	Normal
4	47/F	9 months	LU	27/M	4	IA	SPT	Full recovery	3 years and 1 month	Normal
5	46/F	11 months	LR	25/M	1	IB	SPT	Full recovery	2 years and 4 months	Normal

Rx., rejection; Tx., treatment; LR, living related; LU, living unrelated; SPT, steroid pulse therapy; CR, chronic rejection.

during 1990s for induction such as basiliximab (Simulect®; Novartis, Basle, Switzerland) or daclizumab (Zenapax®; Roche) and maintenance such as rapamycin (Sirolimus®; Wyeth, Collegeville, PA, USA) boosted not only the concept of withdrawing, but also of avoidance of steroids [18,19]. Steroids avoidance, which can be another option, eliminates the potential side effects and dependency of the drug, and the need for steroid tapering with its inherent risk of outbreak of acute rejection.

In this study, the incidence of PTDM was 18.6% in FK group than 8.0% in CsA group and the 1-year prevalence was 1.7% in FK group and 0% in CsA group. The incidence of PTDM was reported with wide range according to definition of PTDM, immunosuppression regimens or race. Generally, the incidence of PTDM was known to be higher in tacrolimus-treated patients than in CsA-treated patients (9.8% vs. 2.7%) [20] and to be lower in the steroid withdrawal regimen than in steroid maintenance regimen (7% vs. 26%) [21]. Other studies defining PTDM as insulin use more than 30 days reported the incidence of PTDM in the steroid withdrawal regimens ranged between 3.2% and 6.6% [18,22].

There were no differences between two groups in the prevalence of hypercholesterolemia and hypertension, and the level of serum creatinine. Though the adverse effects of steroid appeared to be low in both groups, we could not come to any conclusion because of lack of control group. The benefits and risks of completely withdrawing steroids have not been fully evaluated. The potential benefits of steroid withdrawal must be balanced against an associated risk of precipitating acute rejection.

However, it is clear that the use of immunosuppressive regimens without steroids could improve long-term patient survival and quality of life.

In this study, steroid was totally withdrawn at 6 months post-transplant. Ratcliffe *et al.* [2] reported that late steroid withdrawal posed little short-term risk to the graft. Hricik *et al.* [23] reported that, compared with patients in whom prednisone was withdrawn more than 6 months after transplantation, those withdrawn from prednisone early after transplantation experienced more frequent and more severe rejection episodes that more often prompted a return to maintenance steroid therapy and concluded that the timing of steroids withdrawal was the most important clinical predictor of rejection associated with discontinuation of steroids. In the study of Grinyo *et al.* [24], there was no risk of acute rejection if steroids were withdrawn several months after transplantation in low-immunologic risk patients treated with MMF and CsA. But, recently studies assessing the regimens of steroid withdrawal in early days after transplantation have been attempted and are in progress [11,12]. In long-term results, Rama *et al.* [13] reported that whether steroids were withdrawn early or late (after 6 months post-transplant) did not influence outcome.

We selected patient who received kidney from living donor and had first transplantation. We excluded patients recognized to be at increased risk of rejection or graft loss, such as those with unsatisfactory renal function or with high immunologic risk. Diabetic patients were not enrolled in this exploratory study comparing between two regimens for the safety of recipients and the control of the various condition because diabetes was known to be one of the risk factors of elevated serum creatinine and decreased graft survival rate [25]. Patient selection was taken in the safety of steroid withdrawal. The adverse effects of steroid withdrawal on graft could be lessened by selection of appropriate patients. According to Hricik *et al.* [23], neither age, sex, HLA match, pretransplant PRA, source of the allograft (cadaver versus living related), acute tubular necrosis, nor the presence of diabetes was predictive of the outcome of steroid withdrawal. However, the serum creatinine level at the time of withdrawal was related to the risk of rejection [26]. Although criteria to define candidates of steroid withdrawal without increasing risk are not yet established, clinical studies should be strived to determine selection criteria of recipients from whom steroid would be withdrawn without risk.

In this study, the dose of MMF was identical in both groups, adjusted by adverse effects and not monitored by serum mycophenolic acid (MPA). But, recent studies have reported that CsA comedication in contrast with tacrolimus decreases MPA plasma concentration by interfering with enterohepatic circulation of MPA and proposed that therapeutic drug monitoring (TDM) of MPA was needed [27–29]. However, the value of TDM for MMF therapy has not been evaluated sufficiently, although current evidence, mostly derived from retrospective studies, indicated that measuring MPA plasma concentrations enhances patient management.

Acute rejection episode has been believed to be a major risk factor for long-term graft loss and chronic rejection [30]. Therefore, in order to evaluate the effectiveness of a new immunosuppressive regimen, the rate of acute rejection episodes has been analyzed and compared as the key of long-term graft condition. We evaluated the acute rejection episodes in this study, but the relation between acute rejection and long-term graft condition appears not to be simple. Ahsan *et al.* [31] reported an increase in acute rejection upon steroid withdrawal, but the majority of recipients with withdrawal remained free of acute rejection and chronic rejection. According to meta-analysis performed by Pascual *et al.* [32], steroid withdrawal on triple therapy with CsA or tacrolimus and MMF was associated with a higher incidence of acute rejection, but

did not affect graft survival at short- and medium-term follow-up.

In this study, eight of 117 recipients had acute rejection within 6 months after steroid withdrawal (range: 8–11 months) and the majority of the recipients were steroid-sensitive. Four recipients, two in each group, had an episode of acute rejection after the end of this study (Fig. 1). Late occurrence of rejection has been believed to be a worse prognosis for graft survival and refractory to rejection treatment [33]. However, all the recipients with steroid withdrawal and late onset rejections were reported to be steroid-sensitive and easily controlled with steroid therapy [4]. Although these patients need further follow-up, according to our preliminary data, all recipients with late acute rejection episode recovered graft function with steroid pulse therapy.

Although this study showed low acute rejection rate and excellent graft function and survival, there were limitations because of short-term results of only 1-year post-transplant follow-up and lack of control group. Additional long-term studies, of at least 5 years of follow-up, are required to assess the risk of chronic rejection in patients withdrawn from steroid therapy to assess this risk satisfactorily.

Conclusion

In summary, this study showed that it is safe to withdraw steroids in selected patient maintained on tacrolimus or CsA with MMF. There were no significant differences in steroid withdrawal between FK and CsA group upon steroid withdrawal. Long-term follow-up study should be performed to confirm our preliminary results.

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