

Retrospective Study

Tacrolimus confers lower acute rejection rates and better renal allograft survival compared to cyclosporine

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Abstract**AIM**

To compare the impact of tacrolimus (FK) and cyclosporine (CYA) on acute rejection and graft survival and to assess the predominant causes of graft loss between patients receiving these two calcineurin inhibitors (CNIs).

METHODS

Retrospective review of 1835 patients who received a kidney transplant (KTX) between 1999-2012. Patients were grouped based on initial CNI utilized: 1195 in FK group, 640 in CYA group. Data on baseline characteristics, clinical outcomes, and causes of graft loss in both groups were analyzed.

RESULTS

Cumulative acute rejection rates were 14% in the FK vs 24% in the CYA group. Despite more marginal donor characteristics in the FK group, these patients had better graft survival rates compared to the CYA group. Three and five year graft survival rates were 88% and 84% respectively in the FK group compared to 79% and 70% respectively in the CYA group ($P < 0.001$). After multivariate analysis, which controlled for confounders, FK use was a strong predictor for lower acute rejection

rates [odds ratio (OR) 0.60, 95%CI: 0.45-0.79] and better renal allograft survival (OR 0.740, 95%CI: 0.58-0.94). Death with a functioning graft was the most common cause of graft loss in both groups. Common causes of death included cardiovascular disease, infections, and malignancies. Chronic allograft nephropathy was also found to be an important cause of graft loss, being more prevalent in the CYA group.

CONCLUSION

The use of FK-based maintenance immunosuppression therapy is associated with a significantly lower rate of acute rejection and better graft survival compared to CYA-based regimen. Individualizing immunosuppression through risk-stratified CNI choice may lead to improved outcomes across all spectra of KTX patients.

Key words: Tacrolimus; Cyclosporine; Renal allograft survival

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Core tip: Tacrolimus (FK) has surpassed cyclosporine (CYA) as the calcineurin inhibitor (CNI) of choice for the vast majority of kidney transplant (KTX) programs. Yet, CYA continues to be an important alternative for patients intolerant to FK. FK is associated with significantly lower rate of acute rejection and better graft survival compared to CYA. Individualizing immunosuppression through risk-stratified CNI choice may lead to improved outcomes across all spectra of KTX patients.

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INTRODUCTION

Calcineurin inhibitors (CNIs) are the main immunosuppressive agents utilized in kidney transplantation^[1]. Cyclosporine (CYA) and tacrolimus (FK) are currently the most widely used maintenance immunosuppressants for prevention of acute rejection in kidney transplant recipients. CYA-based regimen was more common in the era of 1990 until 2002, after which FK-based regimen became more commonly used in most transplant programs. In our transplant center, FK became the primary CNI of choice in 2005. FK and CYA show variable side effect profiles. Hypertension, hyperlipidemia, gum hypertrophy, and hirsutism occur more frequently with CYA use. On the other hand, a higher incidence of post-transplant diabetes mellitus is observed with FK therapy. Prolonged use of CNI may result in nephrotoxicity.

FK use is associated with less acute rejection

compared to CYA, as documented in different studies^[2,3]. Mayer *et al*^[2] found that among 448 renal transplant recipients who were on triple therapy (FK or CYA + Azathioprine + Prednisone), patients who were in the FK group had a significant reduction in the frequency of acute rejection at 12 mo (FK 25.9% vs CYA 45.7%; $P < 0.001$). Ekberg *et al*^[3] also found that at 12 mo post-transplant, the use of FK-based regimen is associated with less biopsy-proven acute rejection compared to CYA use (12.3% vs 25.8%, $P < 0.01$).

FK is frequently preferred in patients with high immunologic risk (highly sensitized, ABO-incompatible organ recipients), delayed graft function, and African American race. Data regarding graft survival based on the use of FK vs CYA is controversial with most studies showing similar graft survival rates with the use of either agent^[4]. Vincenti *et al*^[5] showed comparable patient (79.1% vs 81.4%; $P = 0.472$) and graft (64.3% vs 61.6%; $P = 0.558$) survival between treatment arms at 5 years of follow-up among FK and CYA-treated patients. However, after accounting for patients initially on CYA who crossed over to FK, the authors found significantly reduced graft failure in the FK group^[5]. Gonwa *et al*^[6] showed that among 223 kidney transplant recipients who experienced delayed graft function, patients who used FK-based therapy had a better 3-year graft survival compared to CYA use (84.1% vs 49.9%, $P = 0.02$). Given these conflicting findings, this study aims to compare rates of acute rejection and graft loss among patients who receive FK and CYA.

MATERIALS AND METHODS

Patients

This was a retrospective cohort study of 1835 patients who received a KTX between 1999-2012 at a single center. Patients were grouped based on the type of CNI they were prescribed: 1195 patients utilized FK-based immunosuppression whereas 640 patients were on a CYA-based regimen. All patients received an antimetabolite and prednisone in combination with CNI. The initial CYA dose was 4-5 mg/kg PO BID. Target CYA levels were 350-400 ng/mL for weeks 1-4, 250-350 ng/mL for weeks 5-12, 200-300 ng/mL within the first year post-transplant, and 100-200 ng/mL thereafter. Initial FK doses were given at 0.025-0.05 mg/kg PO BID. Target FK levels were kept between 8-12 ng/mL within the first four weeks post-transplant, then 6-10 ng/mL within the first year post-transplant, and 4-6 ng/mL subsequently. Characteristics of recipients (age, race, sex, BMI, etiology of kidney disease, history of heart disease, diabetes, hypertension, years on dialysis, panel reactive antibody, preemptive transplant, living donor transplant), and donors [age, race, kidney donor risk index (KDRI)] were compared between groups. Characteristics of the kidney transplant (cold ischemia time, induction agent) as well as clinical outcomes (cumulative acute rejection rate, delayed graft function, three, and five year graft survival) were also analyzed. The Banff '97 criteria were used to define the

Table 1 Characteristics of patients in tacrolimus and cyclosporine group *n* (%)

Parameter	Cyclosporine <i>n</i> = 640	Tacrolimus <i>n</i> = 1195	<i>P</i> -value
Mean recipient age (yr)	49 ± 12	50 ± 13	0.059
Race			0.96
Non-African American	281 (44)	526 (44)	
African-American	359 (56)	669 (56)	
Sex			0.78
Male	371 (58)	693 (58)	
Female	269 (42)	502 (42)	
BMI	26 ± 7	28 ± 5	0.462
Etiology of kidney disease			
DM	172 (26.9)	375 (31.4)	0.044
HTN	317 (49.5)	559 (46.8)	0.26
FSGS	36 (5.6)	78 (7.3)	0.177
IgA nephropathy	24 (3.8)	34 (2.8)	0.291
Polycystic kidney	63 (9.8)	89 (7.4)	0.076
History of DM	186 (29)	394 (33)	0.092
History of HTN	595 (93)	1135 (95)	0.122
History of heart disease	134 (21)	227 (19)	0.38
Years on dialysis	3 ± 2.4	3 ± 2.9	0.01
PRA	5%	17%	< 0.010
Preemptive transplant	122 (19)	239 (20)	0.49
Living donor transplant	122 (19)	179 (15)	0.27
CIT (h)	13 ± 9	16 ± 9	0.621
Mean donor age (yr)	31 ± 18	36 ± 16	< 0.010
KDRI	0.9 ± 0.6	1.3 ± 0.4	< 0.010
African-American donor	122 (19)	203 (17)	0.27
Induction therapy			< 0.010
Cytolytic agents	70 (11)	550 (46)	
IL-2 receptor antagonist	570 (89)	645 (54)	

DM: Diabetes mellitus; HTN: Hypertension; FSGS: Focal segmental glomerulosclerosis; PRA: Panel reactive antibody; CIT: Cold ischemia time; KDRI: Kidney donor risk index.

different grades of rejection. Based on center protocol, Banff 1A and 1B rejection episodes were treated with Methylprednisolone IV. Rejection episodes with Banff 2A grade or higher were treated with anti-thymocyte globulin. Subset analysis was conducted on subjects who had graft loss to retrospectively investigate the factors leading to graft loss. For patients who died, causes of death were presented as overall prevalence of infections (encompassing sepsis, bacterial, fungal, CMV, and other viral infections), malignancies (encompassing solid organ tumors, hematologic malignancies, and post-transplant lymphoproliferative disorder), and cardiovascular diseases (encompassing acute myocardial infarction and cerebrovascular accident). Cause of death classified under "other" includes accidents, unknown, or undocumented. Non-adherence was defined as documentation in the medical record by a provider that a patient was not taking their immunosuppressive regimen as prescribed. Under immunosuppression was defined as evidence of kidney transplant injury related to rejection that led or contributed to graft loss.

Statistical analysis

The statistical review was performed by a clinician with advanced biostatistical training and experience.

Two-sided independent student's *t*-test was used to compare continuous data while the χ^2 test was used to compare categorical data. A two-sided *P*-value of less

than 0.05 was considered statistically significant.

Multivariate survival analysis, using both logistic and Cox regression, was used to assess the association between CNI choice and acute rejection (logistic), graft survival (Cox), and patient mortality (Cox), while controlling for additional transplant variables known to influence outcomes or those that differed across CNI choice. In a subset analysis of patients who had graft loss, causes of graft loss, and causes of death were compared between the two groups using standard univariate comparative statistics. All analyses were conducted using SPSS version 21.0 (IBM Corp, Armonk, NY).

RESULTS

Patient characteristics

Table 1 displays demographic characteristics of the two groups. Mean recipient age, race, BMI, etiology of kidney disease, comorbidities, and dialysis vintage, were similar between the two groups. Patients on FK had higher PRA compared to patients on CYA group (17% vs 5%, *P* < 0.01). Rates of living donor transplants were similar between the two groups. Among patients who received a deceased donor transplant, KDRI was higher in those who received FK. More patients in the FK group received induction agent with depleting antibodies (46% vs 11%, *P* < 0.01).

Table 2 Clinical outcomes

Parameter	Tacrolimus <i>n</i> = 1195	Cyclosporine <i>n</i> = 640	<i>P</i> -value
Mean glomerular filtration rate	56 ± 19	46 ± 17	0.09
Delayed graft function <i>n</i> (%)	179 (15)	115 (18)	0.049
Acute rejection (biopsy proven) <i>n</i> (%)	167 (14)	154 (24)	< 0.010
Three years graft survival	88%	79%	< 0.010
Five years graft survival	84%	70%	< 0.010

Table 3 Multivariate analysis of factors associated with acute rejection

Variable	Hazard ratio	95%CI	<i>P</i> -value
CNI tacrolimus	0.6	0.45-0.79	< 0.001
Retransplant	1.43	0.91-2.24	0.123
PRA	1	0.99-1.00	0.529
Cytolytic induction	0.5	0.36-0.69	< 0.001

CNI: Calcineurin inhibitor; PRA: Panel reactive antibody.

Table 4 Multivariate analysis of factors associated with graft loss

Variable	Hazard ratio	95%CI	<i>P</i> -value
CNI tacrolimus	0.74	0.58-0.94	0.012
History of DM	1.41	1.13-1.76	0.002
History of HTN	0.56	0.34-0.94	0.029
Delayed graft function	2.1	1.66-2.66	< 0.001
Acute rejection	1.59	1.26-2.01	< 0.001

CNI: Calcineurin inhibitor; DM: Diabetes mellitus; HTN: Hypertension.

Clinical outcomes

Patients in the FK group had better clinical outcomes in terms of delayed graft function (DGF) rate (15% vs 18%, $P = 0.049$), cumulative biopsy proven acute rejection rates for Banff 1A and higher, as well as antibody-mediated rejection (14% vs 24%, $P < 0.01$), three year graft survival (88% vs 79%, $P < 0.010$), and five year graft survival (84% vs 70%, $P < 0.01$) (Table 2). FK was a strong predictor of lower acute rejection rates. After multivariate analysis, which accounted for recipient immunologic risks (age, gender, re-transplant, PRA, HLA mismatches, cold ischemic time, induction), donor characteristics (deceased status, ECD, age, race) and delayed graft function, FK continued to be strongly associated with lower acute rejection rates, as compared to CYA (OR = 0.60, 95%CI: 0.45-0.79; $P < 0.001$) (Table 3). Further analysis showed that even after controlling for all other variables, including delayed graft function and acute rejection, FK remained a strong and statistically significant predictor of graft survival (OR = 0.740, 95%CI: 0.58-0.94; $P = 0.012$) (Table 4) (Figure 1).

Graft loss

During the study period, there were 106 patients in the FK group and 123 in the CYA group who had graft loss. Death with a functioning graft was the cause of graft loss

in the majority of these patients. The leading causes of death among the patients include cardiovascular disease, infections, and malignancies (Table 5). The contribution of non-adherence and underimmunosuppression in patients who had graft loss was not significantly different between the FK and CYA groups.

DISCUSSION

The utilization of potent immunosuppressive medications such as CYA and FK has led to progressive improvement in renal allograft survival. Two large studies on kidney transplant recipients showed that the incidence of acute rejection is much lower with FK-based immunosuppression compared to CYA-based regimen^[2,3]. Our study demonstrated similar findings of lower acute rejection rates in patients using FK compared to those on CYA. Acute rejection rate was significantly lower in the FK group despite the relatively higher degree of sensitization, as evidenced by higher PRA, in this group. Multivariate analysis showed that FK was a strong predictor for lower acute rejection rates while controlling for recipient, donor, and transplant characteristics.

The shortage of deceased donor kidneys and the growing number of patients on the waiting list has driven the increased utilization of organs with relatively marginal donor characteristics. Donor factors affect initial graft function and survival^[7]. Donor factors that may influence graft survival include age, gender, hypertension, and cardiovascular disease^[8]. The KDRI is a comprehensive metric that was recently developed to assess the relative risk of graft failure associated with various combinations of donor characteristics. Kidneys with the highest KDRI quintile are associated with lower graft survival^[9]. Although many trials have shown similar graft survival outcomes with FK when compared with CYA-based regimen^[4], some studies showed better survival and outcomes with FK-based immunosuppression^[6]. Our

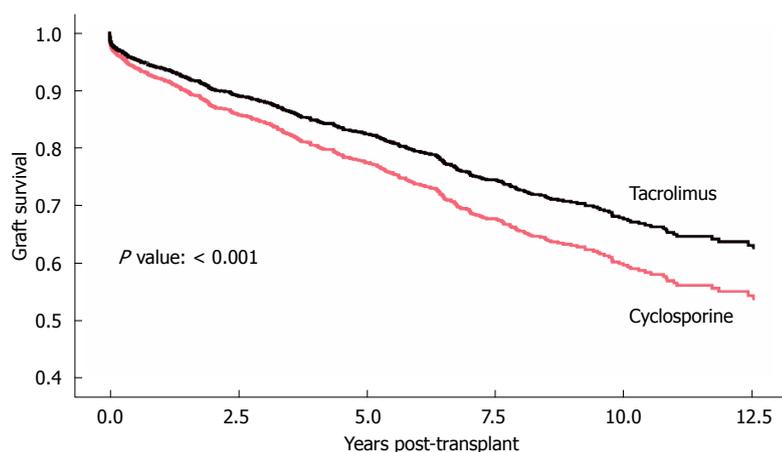


Figure 1 Kaplan Meier curve showing effect of tacrolimus vs cyclosporine on graft survival.

Table 5 Graft loss *n* (%)

Parameter	Tacrolimus <i>n</i> = 106	Cyclosporine <i>n</i> = 123	<i>P</i> -value
Death with functioning graft	61 (58)	66 (54)	0.55
Cause of death			0.85
Cardiovascular disease	19 (18)	19 (15)	
Infections	10 (9)	9 (7)	
Malignancy	10 (9)	9 (7)	
Others	33 (31)	41 (33)	
Causes of graft loss			0.44
Chronic allograft nephropathy	18 (17)	29 (24)	
Acute rejection	14 (13)	11 (9)	
Acute on chronic rejection	8 (8)	13 (11)	
Recurrent disease	1 (1)	1 (1)	
Death	63 (59)	68 (55)	
Component of non-adherence	15 (14)	20 (16)	0.65
Component of underimmunosuppression	21 (20)	25 (20)	0.92

study showed that although patients in the FK group received kidneys from more marginal donors (higher KDRI), the three year and five year graft survival was still more superior in this group compared to the CYA group (Figure 1).

The risk of infections after kidney transplant depends on the net state of immunosuppression. As FK was shown to be associated with less acute rejection compared to CYA^[10], it may concurrently cause more intense immunosuppressive effects compared to CYA. Thus, risk of infections after kidney transplant may be higher with FK compared to CYA. This may be exemplified by the higher incidence of polyomavirus (BK) viremia in patients on FK-based regimen compared to CYA^[11]. Progression of BK viremia may lead to BK nephropathy, which can then eventually cause premature renal allograft failure^[11]. However, in our subjects who had graft loss, we did not observe a significant difference in the prevalence of infections (including BK) in the FK and CYA groups.

The use of maintenance immunosuppressive medications among transplant recipients increases the long-term risk of malignancy, compared with that of the general population. The overall level of immunosuppression appears to be the principal factor that increases the risk of post-transplant malignancy. Both FK and CYA are associated

with an increased risk of malignancy following kidney transplant^[12,13]. No direct comparison between these two agents has been reported regarding the incidence of malignancy following kidney transplant. However, FK was found to have higher incidence of *de novo* malignancy after liver transplant compared to CYA^[14]. In our study, we did not find a significant difference in the prevalence of malignancies between the two groups.

Cardiovascular disease is a leading cause of mortality among kidney transplant recipients. Death from cardiovascular disease is the most common cause of renal allograft loss^[15]. CNIs potentially contribute to increased risk of cardiovascular events indirectly by the development of new-onset diabetes mellitus, hypertension, and hyperlipidemia. Clinical trials have shown a higher incidence of post-transplant diabetes mellitus with FK. However, the risk of hypertension and hyperlipidemia is slightly higher with CYA than FK. No direct comparison has been done between FK and CYA regarding the incidence of cardiovascular disease. In our study, we found that FK was associated with a slightly higher prevalence of cardiovascular disease compared to CYA, although the difference was not statistically significant.

In conclusion, FK is associated with lower prevalence of acute rejection compared to CYA. It confers better three and five year graft survival even with the use of

organs with marginal deceased donor characteristics. An individualized approach to the choice of CNI needs to be employed in order to achieve the best possible outcome while minimizing adverse effects. The use of either FK or CYA should be individualized according to the patient's comorbid conditions and immunological risk.

COMMENTS

Background

Calcineurin inhibitors (CNIs) [cyclosporine (CYA) and tacrolimus (FK)] are currently the most widely used maintenance immunosuppressants for prevention of acute rejection following kidney transplantation. However, data on the impact of these CNIs on acute rejection rate and graft survival have remained equivocal.

Research frontiers

The choice of immunosuppressive regimen that will achieve the best renal allograft outcomes remains an important focus in the care of kidney transplant recipients.

Innovations and breakthroughs

The data showed lower acute rejection rates and better graft survival in patients on FK compared to those on CYA.

Applications

The use of either FK or CYA should be individualized based on patient's comorbidities and immunological risk.

Terminology

FK: Tacrolimus; CYA: Cyclosporine; CNI: Calcineurin inhibitor; DGF: Delayed graft function; DM: Diabetes mellitus; HTN: Hypertension; FSGS: Focal segmental glomerulosclerosis; PRA: Panel reactive antibody; CIT: Cold ischemia time; KDRI: Kidney donor risk index; GFR: Glomerular filtration rate.

Peer-review

The authors are presenting their experience in the use of CNIs in the immunosuppression post renal transplantation.

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