Clinical Significance of Mycophenolate Mofetil Withdrawal in Kidney Transplant Recipients

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ABSTRACT

Introduction. The most effective immunosuppressant protocol in kidney transplantation (KT) is the combination of a calcineurin inhibitor, steroid, and mycophenolate mofetil (MMF) until now. However, MMF withdrawal (MW) is performed for many reasons, and the clinical course of the KT recipients after MW is not clearly known. The purpose of this study was to investigate the clinical outcomes of KT after MW.

Materials and Methods. We retrospectively analyzed the medical records of 626 KT recipients between 2000 and 2016. We evaluated the incidence of biopsy-proven acute rejection (BPAR), graft and patient survival rates, and risk factors related with graft failure.

Results. The proportion of MW was 33.2% (208 of 626 patients). The median time between KT and MW was 6.4 months (range, 3.2–32.1 months). The common causes of MW were infection (70.7%), hematologic abnormalities (9.1%), and gastrointestinal trouble (7.7%). The incidence of BPAR was significantly higher in the MW group compared with the MMF continuation group (27.4% vs 8.9%, respectively, $P < .001$). Death-censored graft survival and patient survival rates were significantly lower in the MW group compared with the MMF continuation group ($P < .001$; $P < .001$, respectively). In the multivariate analysis, BPAR after MW was an independent risk factor for graft failure (hazard ratio 6.058, 95% confidence interval, 3.172–11.569, $P < .001$).

Conclusions. The incidence of rejection, graft failure, and patient mortality in KT were high after MW. Therefore, MW should be considered carefully.

THE MOST effective immunosuppressant protocol in kidney transplantation (KT) has been the combination of a calcineurin inhibitor (CNI), steroid, and mycophenolate mofetil (MMF) until now [1,2]. MMF is a very important immunosuppressant and inhibits B- and T-cell proliferation by controlling DNA synthesis [3,4]. A CNI alone or the combination of a CNI and steroid with MMF withdrawal (MW) is used for many reasons [2], but the clinical course of the kidney transplant recipients (KTRs) after MW is not clearly known. The purpose of this study was to investigate the clinical outcome of KT after MW.

MATERIALS AND METHODS

Study Design

We retrospectively analyzed the medical records of 626 KTRs between 2000 and 2016. We divided them into 2 groups, the MMF continuation (MC) group and MW group, according to the MW. We evaluated causes of MW, the incidence of biopsy-proven acute rejection (BPAR), allograft and patient survival rates between the MC and MW groups, and risk factors related with acute rejection and graft failure according to the MW.

The Institutional Review Board of Keimyung University Dongsan Medical Center approved this study (2018–12–032).

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Table 1. Causes of MMF Withdrawal in Kidney Transplantation

Variables	
Infection	147 (70.7)
CMV infection	89 (60.5)
BKV infection	27 (18.4)
Bacterial infection	18 (12.2)
Other viral infection	3 (2.0)
Fungal infection	3 (2.0)
Others	7 (4.8)
Hematologic abnormalities	19 (9.1)
GI trouble	16 (7.7)
Malignancy	9 (4.3)
Pregnancy	11 (5.3)
Toxic hepatitis	3 (1.4)
Poor compliance	1 (0.5)

Values are expressed as No. (%).
Abbreviations: BKV, BK virus; CMV, cytomegalovirus; GI, gastrointestinal; MMF, mycophenolate mofetil.

Immunosuppression Protocols

We intravenously administered basiliximab (20.0 mg at days 0 and 4, respectively; Simulect, Novartis, Basel, Switzerland) or antithymocyte globulin (Thymoglobulin, Genzyme, Cambridge, MA, United States; 1.5 mg/kg at day 0 and 1.0 mg/kg between day 1 and day 3) as the induction immunosuppressant in KTRs according to their immunologic-sensitized status. We administered tacrolimus (Prograf, Astellas Pharma Inc, Toyama, Japan), prednisolone, and MMF (Cellcept, Hoffmann-La Roche Inc, Nutley, United States) as the maintenance immunosuppressant.

We maintained the trough level of tacrolimus at 5.0 to 10.0 ng/mL within 1 month after KT and at 3.0 to 8.0 ng/mL after 1 month of KT. We also administered prednisolone (15.0 mg, twice a day) for 2 weeks and reduced the dosage according to the immunologic status. We maintained MMF at fixed doses (1.0–1.5 g/d) according to the body weight of the candidate before KT.

Table 2. Comparison of Clinical Parameters Between MMF Withdrawal and MMF Continuation in Kidney Transplantation

Variables	MMF Withdrawal (n = 208)	MMF Continuation (n = 418)	*P* Value
Donor age at KT, y	42.4 ± 13.2	41.0 ± 13.3	.231
Donor sex, male	119 (57.2)	243 (58.1)	.864
Donor type			.022
Living donor	92 (44.2)	227 (54.3)	
Deceased donor	116 (55.8)	191 (45.7)	
Recipient age at KT, y	44.8 ± 12.1	43.7 ± 11.3	.253
Recipient sex, male	88 (42.3)	274 (65.6)	< .001
KT number			.361
First	183 (88.0)	355 (84.9)	
Second	25 (12.0)	59 (14.1)	
Third	0	4 (1.0)	
Dialysis type before KT			.629
Hemodialysis	155 (74.5)	306 (73.2)	
Peritoneal dialysis	37 (17.8)	70 (16.7)	
None	16 (7.7)	42 (10.0)	
Cause of end-stage renal disease			.926
Glomerulonephritis	164 (78.8)	372 (78.2)	
Diabetes mellitus	25 (12.0)	58 (13.9)	
Hypertension	11 (5.3)	18 (4.3)	
ADPKD	7 (3.4)	12 (2.9)	
Others	1 (0.5)	3 (0.7)	
HLA mismatch number	3.3 ± 1.6	3.3 ± 1.7	.750
Induction immunosuppressant			
Basiliximab	126 (61.2)	300 (71.4)	.011
Antithymocyte globulin	5 (2.4)	56 (13.3)	< .001

Values are expressed as means ± standard deviations or No. (%).
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; KT, kidney transplantation; MMF, mycophenolate mofetil.

Table 3. Comparison of Clinical Outcomes Between MMF Withdrawal and MMF Continuation in Kidney Transplantation

Variables	MMF Withdrawal (n = 208)	MMF Continuation (n = 418)	*P* Value
Delayed graft function	28 (14.3)	2 (10.0)	1.000
Biopsy-proven acute rejection	57 (27.4)	37 (8.9)	< .001
CMV infection	35 (17.0)	54 (12.9)	.181
BK virus infection	5 (2.4)	4 (1.0)	.164

Values are expressed as No. (%).
Abbreviations: CMV, cytomegalovirus; MMF, mycophenolate mofetil.

Demographic and Clinical Data

We analyzed the age at KT and sex of donor and recipient, donor type, the number of KTs, dialysis type before KT, causes of end-stage renal disease, the number of HLA mismatches, immunosuppressant for induction and maintenance treatments, proportions of delayed graft function, and BPAR. We investigated the causes of MW and clinical outcome of KTRs according to the MW.

Statistical Analyses

Student *t* test was performed in continuous variables with a normal distribution, and the variables were expressed as the means ± standard deviations. A χ^2 or Fisher's exact test were performed in categorical variables, and the variables were expressed as the numbers and percentages. Death-censored graft survival and patient survival rates according to the MW was analyzed by the Kaplan-Meier analysis with the log-rank test. Risk factors for graft rejection and failure were analyzed by Cox regression analysis. *P* values < .05 were statistically significant. Statistical analysis was done by SPSS (version 18.0, SPSS Inc, Chicago, IL, United States) statistical software package.

RESULTS

Baseline Characteristics of the KTRs

Mean follow-up duration was 87.0 ± 59.6 months. A total of 626 patients who received KTs during the study period were enrolled. The mean age of KTRs was 44.1 ± 11.6 years, and the proportion of men was 57.8%. The median time between KT and MW was 6.4 months (range, 3.2–32.1 months). The proportion of MW was 33.2% (208 of 626 patients).

Causes of MW in KT

Common causes of discontinuation of MMF were infection (70.7%), hematologic abnormalities (9.1%), and gastrointestinal trouble (7.7%). The rate of cytomegalovirus (CMV) infection (60.5%) was the highest among all infections, followed by BK virus infection (18.4%) (Table 1).

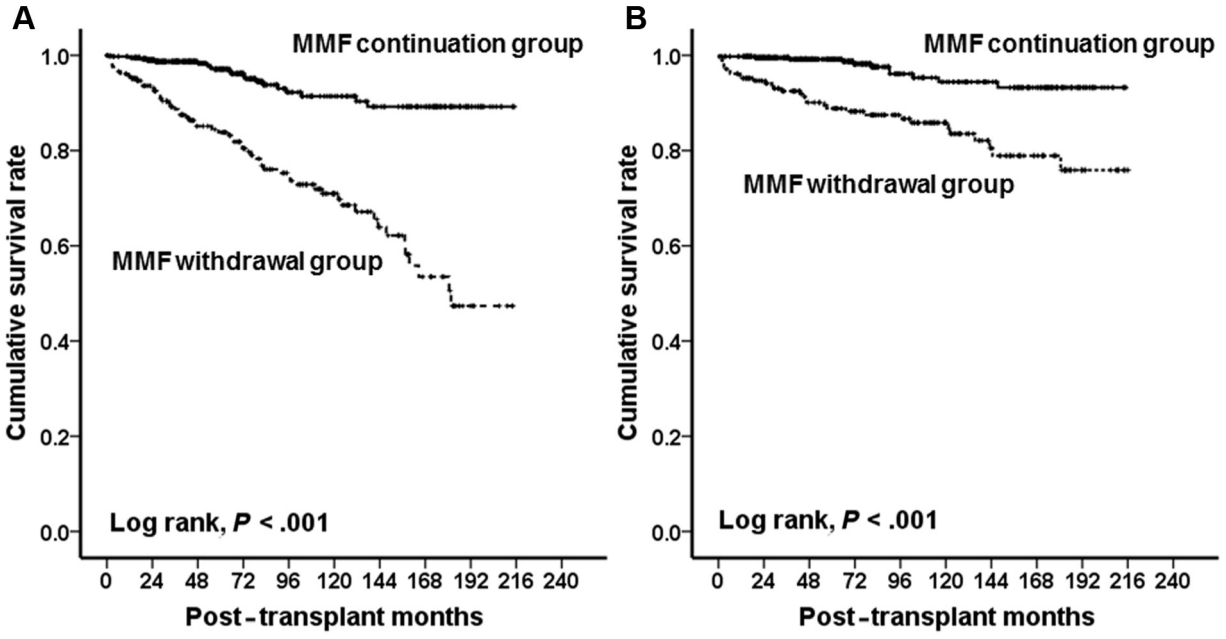

Fig 1. Death-censored graft survival **(A)** and patient survival **(B)** rates were significantly lower in the MMF withdrawal group compared with the MMF continuation group in kidney transplantation. MMF, mycophenolate mofetil.

Comparison of Clinical Parameters and Outcomes Between MW and MC Groups in KT

The proportions of women and deceased donor kidney transplantation were significantly higher in the MW group in comparison with the MC group (57.7% vs 34.4%, $P < .001$; 55.8% vs 45.7%, $P < .001$, respectively). However, the proportion of induction immunosuppressants, such as basiliximab or antithymocyte globulin, was significantly higher in the MC group in comparison with MW group (70.6% vs 63.0% and 10.3% vs 8.7%, respectively, $P = .035$). There were no significant differences in the donor and recipient ages at KT, donor sex, frequency of KTs, dialysis type before KT, causes of end-stage renal disease, number of HLA mismatches, and maintenance immunosuppressants (Table 2).

The proportion of BPAR were significantly higher in the MW group compared with the MC group (27.4% vs 8.9%, respectively, $P < .001$). However, there were no significant differences in the incidences of delayed graft function, CMV infection, and BK virus infection between the 2 groups (Table 3).

Comparison of Death-Censored Graft and Patient Survivals Between MW and MC Groups in KT

Death-censored graft survival and patient survival rates were significantly lower in the MW group compared with the MC group (Fig 1A, B). In multivariate analysis, MW was an independent risk factor for graft failure after adjustment for recipient age, sex, infection, and deceased donor KT (hazard ratio 6.058, 95% CI, 3.172–11.569, $P < .001$) (Table 4).

DISCUSSION

There were many reasons for MW, and infection was the most common reason in our study. Among several infections, CMV infection was the most common cause of MW. Because MMF can cause proliferation of bacteria,

Table 4. Risk Factors Associated With Graft Failure in Kidney Transplantation

	Univariate			Multivariate		
Variables	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Recipient sex, male	1.390	0.839–2.301	.201			
HLA mismatch number	1.120	0.952–1.319	.172			
ATG induction	1.525	0.429–5.422	.514			
Infection	2.128	1.300–3.483	.003	0.580	0.317–1.062	.077
Recipient age at KT	0.976	0.955–0.997	.028	0.969	0.948–0.991	.006
Deceased donor kidney transplantation	1.794	1.094–2.943	.021	1.871	1.122–3.122	.016
MMF withdrawal	4.272	2.499–7.304	< .001	6.058	3.172–11.569	< .001

Abbreviations: ATG, antithymocyte globulin; CI, confidence interval; HR, hazard ratio; KT, kidney transplantation; MMF, mycophenolate mofetil.

viruses, and fungi [5], MC can make CMV infections worse. Therefore, in most KTRs with CMV infection, MMF is removed to obtain adequate clinical and viral responses [6]. This is true for BK virus infection and bacterial infection as well [7]. Because hematologic abnormalities, such as leukopenia or thrombocytopenia, can occur with MMF, which is possible with any myelosuppressive therapies, along with antithymocyte globulin and ganciclovir for the treatment of CMV and viral infection, dose reductions or modifications of MMF should be performed first [6]. The proportions of CMV infection and BK virus infection tended to be higher in the MW group in comparison with the MC group in our study, but there was no significant difference. This suggests that the incidence of CMV or BK virus infection was very low in both of the 2 groups. After the MW, there was no change in the target value of the CNI trough level. However, when MMF was discontinued, CNI was discontinued in 13 (6.3%) KTRs. The main causes of MMF and CNI withdrawals were severe infection such as septic shock (63.2%), lymphoma (15.4%), and graft failure (15.4%). Two KTRs with lymphoma replaced the CNI with a mammalian target of rapamycin inhibitor.

However, the incidence of BPAR was significantly higher in the MW group in comparison with MC group. This suggests that when MMF was stopped after a CMV or BK virus infection, the incidence of BPAR increased accordingly [8]. In the Cox regression analysis, risk factors associated with allograft rejection in KT were recipient age, HLA mismatch number, and MW, and because an independent risk factor for allograft failure was BPAR, MC could be very important to maintain the function of the allograft kidney [4].

In our study, the patient survival rate was significantly lower in the MW group in comparison with the MC group. This suggests that the incidence of BPAR increased after MW, and uncontrolled infection status, such as *pneumocystis jirovecii* pneumonia, CMV pneumonitis, and bacterial pneumonia, after strong immunosuppressive treatment against BPAR is considered to be a cause of low patient survival rate. This suggests that since uncontrolled infections were fatal in KTRs, it is important to minimize the use of a strong immunosuppressant for a short duration, which may cause BPAR to occur because of the indiscriminate interruption of MMF.

In conclusion, the incidence of BPAR, allograft failure, and patient mortality were significantly higher in the MW group in comparison with MC group. Therefore, MW should be considered carefully.

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