Successful rescue therapy with mycophenolate mofetil in kidney transplantation improves the long-term graft survival

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Key words: *kidney transplantation; graft survival; mycophenolate mofetil; azathioprine.*

Summary. *Objective. The aim of this study was to compare the graft survival after kidney transplantation in patients treated with azathioprine (AZA) or mycophenolate mofetil (MMF) and analyze the significance of different risk factors for graft survival.*

Material and methods. A total of 137 patients, transplanted between January 1996 and June 2001, were retrospectively divided into two groups: patients who received AZA together with cyclosporine A and methylprednisolone (AZA group, n=72) and patients who received MMF either immediately or were switched from AZA to MMF during 3 months (MMF group, n=65).

Results. According to Kaplan-Meier analysis, a 1-year graft survival was 79% in the AZA group and 85% in the MMF group; a 6-year graft survival was 51% and 67%, respectively (P=0.046). Multivariate Cox survival model demonstrated that MMF therapy reduced the risk of graft loss by 34% (P=0.028), while delayed graft function increased the risk of graft loss (risk ratio 2.26, P=0.009). A statistically significant difference in total cholesterol level (6.7 vs. 5.7 mmol/L, respectively; P=0.002), mean systolic blood pressure (145 vs. 134 mmHg, P=0.009), and cyclosporine A daily dose (238 vs. 203 mg, P=0.015) between the AZA and MMF groups at 1 year was revealed.

Conclusion. MMF rescue therapy improves the long-term graft survival compared to AZA despite high early rejection rate and avoids the negative impact of acute rejections on graft survival.

Introduction

Triple immunosuppression consisting of calcineurin inhibitor, antiproliferative agent, and steroids has been the mainstay of kidney transplantation programs during the last decades. Mycophenolate mofetil (MMF) has been shown to be more potent immunosuppressive drug than azathioprine (AZA), reducing the incidence of acute rejection episodes (1, 2). However, improvement of long-term graft survival with MMF has been difficult to determine with contradictory results in different studies. Tricontinental Mycophenolate Mofetil Renal Transplantation Study failed to show a statistically significant survival advantage of MMF over AZA at 3 years (3). Shah *et al.* reported no difference in patient or graft outcome between the MMF- and AZA-treated groups in a paired kidney analysis (4). In older renal transplant recipients, MMF-containing treatment may result in a poor outcome compared with the less potent combination with AZA (5), although other studies showed no difference in graft or patient survival (6). Some studies, however, have found the survival advantage with MMF therapy: a 3-year follow-up from the European MMF study indicated a modest beneficial effect of MMF on graft survival. (7), also U.S. renal transplant scientific registry data revealed significantly better 4-year graft survival in the MMF-treated group as opposed to the AZA-treated group (8).

MMF became available in Estonia 1996, but until year 2002, it was predominantly used as rescue therapy after severe acute rejection and in immunized patients. Since 2002, MMF has been included in the standard immunosuppression protocol in all kidney transplant patients. The aim of this study was to compare long-term results of cadaveric kidney transplantation in patients treated with AZA or MMF in the same era and analyze the impact of different risk factors on graft survival.

Material and methods

Data. This is a retrospective case-control single center analysis. Between January 1, 1996, and June

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30, 2001, 178 deceased donor kidney transplantations were performed in our center. Six of the transplants were never functioning and were excluded. One hundred seventy-two patients were followed up to 6 years. Patient data as donor age, recipient age and gender, human leukocyte antigen (HLA) mismatches, delayed graft function, dialysis time before transplantation, dialysis mode, previous transplants, cold ischemia time, early rejection episodes (first 3 months) were collected from the case histories and medical record database. Patients who were switched from AZA to MMF later than 3 months after transplantation (35 patients) were excluded, so the number of study subjects was 137. All patients received cyclosporine A (CsA) and glycocorticosteroid (CS) according to our standard protocol; rejections were treated with corticosteroid pulse therapy, steroid-resistant rejections with antithymocyte globulin infusion. Patients were divided into two groups: those who received AZA (AZA group, n=72) and those who were treated with MMF immediately (n=17) or switched from AZA to MMF (n=48) within 3 months (MMF group, n=65). Patients were switched to MMF in case of early severe rejection (according to Banff classification – Ib or more, n=35) or AZA intolerance (n=13). Parameters of maintenance therapy (CsA dose and C0 concentration, treatment with statins, antihypertensive treatment) and follow-up data (serum creatinine concentration, cholesterol level, systolic and diastolic blood pressures) were recorded at 1 year after transplantation. A graft was considered as failed when the patient returned to regular dialysis, when the graft was removed, or when the patient died with a functioning graft.

Statistical analysis. Differences in the characteristics of the patients treated with MMF *versus* AZA were tested with Student's *t* test for continuous variables; the nonparametric Mann-Whitney test was used where necessary. Fisher's exact test was employed for binary categorical variables. Graft survival was analyzed with the Kaplan-Meier method; group comparisons were performed with the log-rank test. Multivariate survival analysis, hazard ratios and their 95% confidence interval (95% CI) were performed with the Cox proportional hazard regression. A stepwise selection method was used to identify a model including the variables which were significantly associated with graft loss. All statistical tests were two-tailed, and a p value less than 0.05 was considered statistically significant. Statistical analyses were performed with the SAS version 8.1.

Results

The characteristics of two patients' groups are presented in Table 1. A statistically significant difference between the groups was revealed in the following characteristics: the mean recipient age in the MMF group was 8.5 years lower, and there were more retransplantations in the MMF group. The HLA mismatch was also numerically higher in the MMF group although not reaching statistical significance. There were no zero mismatches and 8.8% of six mismatches in our material. As the main indication of MMF treatment in this cohort was high immunological risk (retransplant) or early acute rejection, was the 3-month acute rejection rate significantly higher in the MMF group (67.7%) compared to the AZA group (31.9%), reflecting the baseline differences. More than three-quarters (79.5%) of the rejection episodes in the MMF group, however, occurred during AZA treatment before switching. Patients receiving MMF immediately after transplantation had a rejection rate of 41.2 % (7/17).

According to the Kaplan-Meier analysis, graft survival for the AZA and MMF groups was 79% and 85% at 1 year and 51% and 67%, respectively, at 6 years (P=0.046) (Fig.).

Considering better graft survival in the MMF group, we further assessed the independent effect of MMF. The univariate Cox proportional hazard analysis showed that donor age, dialysis mode, and therapy type (AZA or MMF) proved to be significant factors. The inclusion of the variables with P<0.25 in the multivariate model revealed that only onset of graft function and therapy group proved significant factors for graft survival (Table 2). The multivariate Cox survival model demonstrated that irrespective of recipient age, MMF therapy reduced the risk of transplant loss by 34% (P=0.028), while delayed graft function increased the risk 2.26 times (P=0.009). The other risk factors (recipient age, dialysis time, donor age, HLA mismatch) proved to be insignificant.

Comparison of the follow-up characteristics in both groups at year 1 shows that in the MMF group, the mean cholesterol level was 1.0 mmol/L (P=0.002) and mean systolic blood pressure was 11 mmHg lower as compared to the AZA group (P=0.009) (Table 1). Although the proportions of the patients who received statins and hypotensive medicines were somewhat smaller in the MMF group, this difference was not significant. In spite of significantly lower daily dose of CsA (P=0.015) in the MMF group, the mean serum creatinine concentration was similar in both groups.

Discussion

The primary goal of our study was to assess the efficacy of MMF treatment in patients at high immunological risk characterized by a significantly higher

Table 1. **Comparison of the baseline characteristics and the characteristics at the end of the first year**

	Characteristic	AZA group (n=72)	MMF group (n=65)	P value
Baseline characteristics	Donor age, mean (SD), years	38.5 (12.3)	35.9 (13.7)	0.261
	Recipient age, mean (SD), years	50.0 (11.1)	41.5 (13.3)	<0.0001
	Female gender, %	26.4	40.0	0.075
	HLA mismatch, mean (SD)	3.6 (1.4)	4.0 (1.2)	0.071
	Delayed graft function, %	16.7	20.0	0.522
	Dialysis time, months	10	12	0.070
	Repeat transplantations, %	2.8	16.9	0.004
	Cold ischemia time, mean (SD), hours	14.6 (5.6)	15.4 (5.1)	0.423
	Early rejection episodes, %	31.9	67.7	<0.0001
Characteristics at the end of the first year	Serum creatinine, mean (SD), mmol/L	132 (34)	129 (35)	0.765
	Cholesterol, mean (SD), mmol/L	6.7 (1.5)	5.7 (1.0)	0.002
	Users of statins, %	13.0	8.1	0.506
	Systolic BP, mean (SD), mmHg	145 (19)	134 (21)	0.009
	Diastolic BP, mean (SD), mmHg	86 (13)	84 (10)	0.439
	Users of hypotensive medicines, %	78.3	72.9	0.463
	CsA daily dose, mean (SD), mg	238 (66)	203 (61)	0.015
	CsA C0 level, mean (SD), ng/mL	140 (48)	127 (52)	0.263

BP – arterial blood pressure; CsA – cyclosporine A; AZA – azathioprine; MMF – mycophenolate mofetil; HLA – human leukocyte antigen; SD – standard deviation.

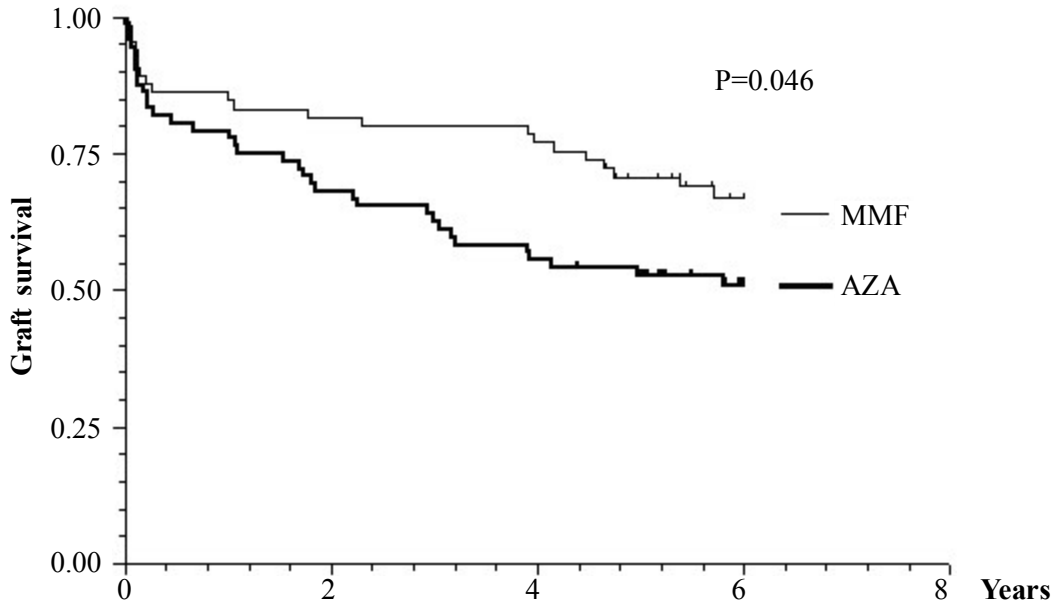

Fig. **Kaplan-Meier estimates of graft survival in mycophenolate mofetil (MMF) and azathioprine (AZA) groups**

Table 2. **Analysis of the risk factors for graft survival**

	Risk factor	Crude hazard ratio	95% CI	P value
Univariate analysis	Female donor	1.23	0.61–2.10	0.703
	Donor age (per 10 years)	1.21	0.99–1.48	0.072
	Female recipient	0.90	0.51–1.59	0.708
	Recipient age (per 10 years)	1.09	0.88–1.34	0.432
	HLA mismatch: >3	0.931	0.55–1.59	0.795
	Dialysis mode: hemodialysis	1.35	0.79–2.30	0.065
	Dialysis time (per year)	0.92	0.73–1.15	0.455
	Ischemia time (per hour)	0.99	0.94–1.04	0.570
	Delayed graft function	2.10	1.14–3.85	0.016
	Early acute rejection	1.08	0.64–1.84	0.763
	MMF treatment	0.57	0.34–0.99	0.046
Multivariate analysis	Delayed graft function	2.26	1.22–4.16	0.009
	MMF treatment	0.54	0.31–0.94	0.028

MMF – mycophenolate mofetil; HLA – human leukocyte antigen; CI – confidence interval.

retransplant number, low HLA matching, and early acute rejections (Table 1). The kidney transplant waiting list in our center is relatively small reflecting the size of our population (1.4 million), so one of the main problems is unsatisfactory HLA matching possibility. Large registry data have shown clear relationship between HLA matching and graft survival, which persists in a recent era of modern immunosuppressive therapy (9, 10). According to the data of Collaborative Transplant Study, the difference in 3-year graft survival in transplantation with 0 and 6 mismatches is 14% (10). The same decrease in the incidence of graft loss in the 0 mismatch group as opposed to the 6 mismatch group was seen when assessed separately in MMF- *versus* AZA-treated patients (11). Considering low HLA match in most of the patients, it is clear that these patients are at higher risk of acute and chronic rejection compared to other studies.

Our study demonstrates that MMF treatment improves graft survival as compared to AZA treatment. Better graft survival in the MMF group was observed despite the fact that this group is characterized by the larger number of retransplantations and early rejection episodes before changing from AZA to MMF. It has been shown earlier that the second grafts have lower survival than the first grafts, difference being approximately 10% at 1 to 5 years (12). So we could expect actually poorer graft survival in the MMF group. In a retrospective study, there is always possibility of biases in patient selection. The MMF group in our study consisted of higher-risk patients who needed immunosuppression intensification. Therefore, the bias in our study population was actually against possible beneficial survival effect on MMF treatment.

Acute rejections are still one of the main risk factors for chronic allograft injury. According to our results, switching from AZA to MMF as rescue therapy after acute rejection can avoid the negative impact of rejection on long-term graft survival. This is consistent with previous studies where MMF in addition to reducing the acute rejection rate also improved the prognostic significance of these rejection episodes (13). One of the possible mechanisms may be that MMF prevents development of chronic allograft nephropathy independent of acute rejections. Nankivell *et al.* have recently shown that MMF therapy is associated with reduced fibrosis in the glomerular, vascular, and interstitial compartments and a delayed expression of CsA nephrotoxicity over AZA treatment (14).

In univariate Cox proportional hazard analysis, only delayed graft function and therapy type (AZA or MMF) proved to be significant factors for graft survival. The same factors remained significant also in multivariate survival analysis. HLA mismatch, recipient and donor age, dialysis time and mode, cold ischemia time proved to be insignificant factors, which may be related to small patient number in the study.

One of the important aspects of our study is relatively long follow-up time as number of other studies concerning differences in survival between MMF- and AZA-treated patients have shorter (1–4 years) follow-up times (4–6, 11, 13). We were able to show that the

difference in graft survival between groups persisted significant to 6 years.

We also demonstrated that at one year after kidney transplantation, the mean systolic blood pressure, mean cholesterol level, and CsA daily dose were significantly lower in the MMF group compared with the AZA group although concomitant medication did not differ between groups. This supports the use of MMF in reducing the risk of cardiovascular mortality as the main cause of death after transplantation (15).

Conclusion

Our study shows that MMF treatment has a positive effect on graft survival after kidney transplantation compared to AZA in high-risk patients, and switching from AZA to MMF as rescue therapy after acute rejection avoids the negative prognostic implication of these episodes.

Sėkminga gelbėjimo terapija mikofenolato mofetiliu inkstų transplantacijoje prailgina transplantato išgyvenimo trukmę

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Raktažodžiai: inksto transplantacija, transplantato išgyvenimo trukmė, mikofenolato mofetilis, azatioprinas.

Santrauka. *Tyrimo tikslas*. Palyginti transplantato išgyvenimo trukmę po inksto persodinimo pacientams, gydytiems azatioprinu arba mikofenolato mofetiliu ir išanalizuoti skirtingų rizikos veiksnių, turinčių įtakos transplantato išgyvenimo trukmei, svarbą.

Tyrimo medžiaga ir metodai. Po inksto persodinimo 137 pacientai (1996 m. sausio – 2001 m. birželio mėn.) buvo retrospektyviai padalyti į dvi grupes: pacientus, kurie vartojo azatiopriną (AZA) kartu su ciklosporinu A ir metilprednizolonu (AZA grupė, n=72), ir pacientus, kurie vartojo mikofenolato mofetilį (MMF) iškart po inksto persodinimo arba AZA buvo pakeistas į MMF per tris mėnesius (MMF grupė, n=65).

Rezultatai. Remiantis Kaplan-Meier analize, vienerių metų transplantato išgyvenimo trukmė buvo 79 proc. AZA grupėje ir 85 proc. MMF grupėje, šešerių metų transplantato išgyvenimo trukmė buvo atitinkamai – 51 ir 67 proc. (p=0,046). Daugiavariantis Cox išgyvenimo trukmės modelis parodė, kad MMF terapija mažina transplantato netekimo riziką 34 proc. (p=0,028) ir priešingai – užsitęsęs transplantuoto inksto funkcijos atsikūrimas didina transplantato netekimo riziką (rizikos santykis – 2,26, p=0,009). Statistiškai reikšmingas skirtumas tarp AZA ir MMF grupių praėjus vieneriems metams po inksto persodinimo nustatytas, remiantis bendrojo cholesterolio kiekio (6,7 *vs.* 5,7 atitinkamai, p=0.002), vidutinio sistolinio kraujo spaudimo (145 *vs.* 134 mmHg, p=0,009) ir kasdienės ciklosporino A dozės (238 mg *vs.* 203 mg, p=0.015) duomenimis.

Išvados. Mikofenolato mofetilio veiksmingumas, palyginus su azatioprinu, prailgina transplantato išgyvenimo trukmę, nepaisant didelio ankstyvų atmetimo reakcijų dažnio, ir padeda išvengti negatyvaus ūminės atmetimo reakcijos poveikio, turinčio įtakos transplantato išgyvenimo trukmei.

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Received 15 May 2007, accepted 17 October 2007
Straipsnis gautas 2007 05 15, priimtas 2007 10 17