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Mycophenolate mofetil in low-risk renal transplantation in patients receiving no cyclosporine: a single-centre experience

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Abstract

Background. We assess our long-term experience with regards the safety and efficacy of Mycophenolate Mofetil (MMF) in our low risk renal transplant population and compared it retrospectively to Azathioprine (AZA) immunosuppressive regimen.

Patients and methods. Between January 1999 and December 2005, 240 renal transplants received MMF as part of their immunosuppressive protocol (MMF group). AZA group of 135 renal transplants was included for comparative analysis (AZA group). Patients received Cyclosporine was excluded from this study.

Results. The incidence of biopsy proven 3-month acute rejections was 30 (12.5%) in MMF group and 22 (16%) in AZA group respectively (P = 0.307). Patient survival rates at 1 and 5 years for the MMF group were 97 and 94%, respectively, compared to 100% and 91% at 1 and 5 years respectively for the AZA group (P = 0.61). Graft survival rates at 1 and 5 years for the MMF group were 95 and 83%, respectively, compared to 97 and 84% at 1 and 5 years, respectively for the AZA group (P = 0.62).

Conclusion. There was no difference in acute rejection episodes between MMF and AZA based immunotherapy. Additionally, we observed no significant difference concerning graft survival in the MMF group when compared to AZA group.

Keywords: low risk; mycophenolate mofetil; renaltransplantation

Introduction

Mycophenolate mofetil (MMF) has replaced Azathioprine (AZA) in most transplant centres worldwide as part of their maintenance immunosuppression regimens. This is due to three studies produced in the 1990's [1–3]. These studies demonstrated a reduced occurrence of acute rejection rates in adult renal transplantation of 30–50% when compared with AZA or placebo [1–3]. However, a recent study has shown that reduction of acute rejection rates did not translate into improved graft survival [4].

When MMF was first introduced, it was used in what were considered high-risk renal transplantation patients. We assessed our experience with MMF in kidney transplantation with regard its safety and efficacy compared to AZA in patients with low risk for rejection episodes [i.e. first transplant and a low panel reactive antibody screen (PRA)].

Patients and methods

Between January 1999 and December 2005, a total of 375 patients were included in this study. The low risk inclusion criteria were patients >18 years old, PRA of ≤50% and undergoing a solitary first deceased renal transplant. Patients were divided into two groups based on their transplant era, i.e. patients who received renal transplants prior to 2002 were given AZA. The patients who received renal transplants after 2002 were given MMF. MMF group (240 patients) received MMF, combined with tacrolimus and predinsolone as maintenance immunotherapy (Group I). These patients consisted of 145 males and 95 females and mean age of 45.6 years (range 20–75). The second group, the AZA group (135 patients) received AZA, combined with tacrolimus and predinsolone as maintenance immunotherapy (Group II). The AZA group consisted of 80 males and 55 females and mean age of 44.5 years (range 20–71).

A retrospective comparative analysis was performed between both groups. Recipient/donor demographics are shown in Table 1. Cause of end-stage renal disease of both groups is illustrated in Table 2.

MMF (Cellcept®; Roche Laboratories, Nutley, NJ) dose was a 500 mg tablet form administered twice a day. MMF dosage was adjusted according to white blood cell count (WCC) and held if WCC was $<3.5 \times 10^3/\mu L$. AZA (Imuran®; GlaxoSmithKline, Feucht, Germany) dosage was 3 mg/kg given 4 h posttransplantation orally or intravenously (IV). Then, reduced to 2 mg/kg orally on the first postoperative day. Its dosage was also adjusted through daily monitoring of WCC during hospitalization. Tacrolimus (Prograf®; Astellas Pharma, Deerfield, IL) was given at a dose 0.15 mg twice daily 12 hourly for two doses only, then reduced to 0.1 mg/kg 12 hourly thereafter. The dose of tacrolimus was adjusted to maintain a trough level of 15 ng/mL in the first posttransplant month and a trough level of 10 ng/mL thereafter. Prednisolone was 500 mg IV infusion 12 h following transplantation. Then, this dose is tapered to 250 mg IV twice daily for 2 days until reduced to a daily morning dose of 250 mg IV for another 2 days. Following this, the patients were switched to a daily dose of 20 mg oral prednisolone, which is gradually tapered down to a

Table 1. Patient demographics of MMF and AZA groups

Variables	MMF group (no. = 240)	AZA group (no. = 135)	P-value
Mean age ± SD	45.6 ± 14.6	44.5 ± 15.0	0.476
Sex (male/female)	145/95	80/55	0.826
Mean donor age ± SD	38.5 ± 13.8	35.5 ± 15.7	0.099
Mean cold ischemia time (h) ± SD	17.6 ± 5.1	20.4 ± 5.5	0.027
Mean PRA (%) ± SD	4 ± 6.7	3.8 ± 6.5	0.879
Mean HLA mismatch ± SD	3.3 ± 1.3	2.9 ± 1.1	0.208
Renal replacement therapy			
HD	140	75	0.670
PD	84	48	
PE	16	12	
CMV donor/recipient status			
Negative/negative	43%	43%	0.503
Positive/negative	20%	26%	
Negative/positive	22%	17%	
Positive/positive	12%	10%	

HD, haemodialysis; HLA, human leukocytic antigen; PD, peritoneal dialysis; PE, preemptive; NA, not available.

Table 2. Cause of end-stage renal disease of MMF and AZA groups

MMF group	No. (%)	AZA group	No. (%)
Glomerulonephritis (GN)	76 (32%)	Glomerulonephritis (GN)	39 (29%)
Chronic pyelonephritis	45 (19%)	Chronic pyelonephritis	33 (25%)
Systemic disorders	44 (18%)	Systemic disorders	26 (19%)
Inherited renal disease	49 (20%)	Inherited renal disease	24 (18%)
Urological disorders	7 (0.3%)	Urological disorders	3 (0.2%)
Unknown	24 (1%)	Unknown	10 (0.7%)

daily maintenance dose of 5 mg of oral prednisolone by 2 months posttransplantation.

Antiviral agents used in our department for recipient cytomegalovirus (CMV) prophylaxis was valacyclovir (Valtrex®; GlaxoSmithKline). Prophylaxis is initiated shortly after renal transplant and continued for ~3 months. An oral dose of 2 g daily of valcyclovir was adjusted for renal function and WCC.

Assessment of acute rejection and chronic allograft nephropathy was based on clinical and biochemical features with or without a biopsy. Anti-rejection management consisted of 500 mg of IV of methylprednisolone/24 h for 3–5 days. Steroid resistant rejections were treated with rabbit antithymocyte globulin (Fresenius, Biotech, Germany) as 5 mg/kg IV for 4 h once every 24 h for 2 doses, followed by a dose of 2.5 mg/kg IV once every 24 h for 6–10 dose. There were two study end points, the occurrence of biopsy-proven acute rejection and graft failure.

Statistical methods

Patients were followed-up to the end of 2009 or were censored due to loss of follow-up. The latter had follow-up times up to date of last creatinine. Multifactorial analysis using Cox proportional hazards models was performed to determine independent significance from potentially confounding variables on the various end points. This included graft and patient survival and acute rejection incidence episodes (Table 3, I–III). Kaplan–Meier methods were used to construct survivor functions. Renal function comparisons from 1 to 5 years posttransplant were calculated using Wilcoxon rank-sum tests. Statistical analysis was conducted using Stata (version 10; College Station, TX).

Results

Patient survival

Actuarial patient survival rates at 1 and 5 years for the MMF group were 97 and 94%, respectively, compared to 100 and 91% at 1 and 5 years, respectively, for the AZA group (P = 0.61) (Figure 1). The causes of death were myocardial infarction in 6, haemorrhagic shock in 1, malignancy in 3, motor neuron disease in 1, sepsis in 4 and unknown in 10. Details of the causes of death in both groups are shown in Table 4.

Table 3. Cause of death in MMF and AZA groups

Cause of death (no. = 25)	MMF group (no. =12)	AZA group (no. = 13)
Myocardial infarction	3	3
Haemorrhagic shock	1	0
Malignancy	1	2
Motor neuron disease	0	1
Sepsis	2	2
Unknown	5	5

Graft survival

Actuarial graft survival rates at 1 and 5 years for the MMF group were 95 and 83%, respectively, compared to 97 and 84% at 1 and 5 years, respectively, for the AZA group (P = 0.62) (Figure 2). Thirty grafts failed in the MMF group (12.5%) and twenty-seven grafts failed in the AZA (20%) group, including death with functioning grafts. Details of the causes of the overall graft failure in both groups are shown in Table 5.

Renal function

There was no difference in renal function at any time point between 1 and 5 years post-renal transplantation (Table 6).

Acute rejection rate

Within the first 3 months posttransplant, the occurrence of biopsy-proven acute rejection was 30 (12.5%) in the MMF group and 22 (16%) in the AZA group (P = 0.307) (Figure 3).

Complications

Technical. No graft was lost secondary to a technical complication.

Infectious. Seventeen patients developed posttransplant viral infections in the MMF group, compared to seven in the AZA group. Eight patients developed CMV infections in the MMF group, compared to four patients in the AZA group (P = 1.000). There were nine biopsy-proven infections with polyoma virus in the MMF group, compared to three in the AZA group (P = 0.753). There were three lost grafts secondary to polyoma viral infection in the MMF group compared to one graft loss in the AZA group. None of the patients in either group developed posttransplant lymphoproliferative disorder.

Discussion

Current improvements in outcome in renal transplantation are mainly due to improvement in the surgical technique,

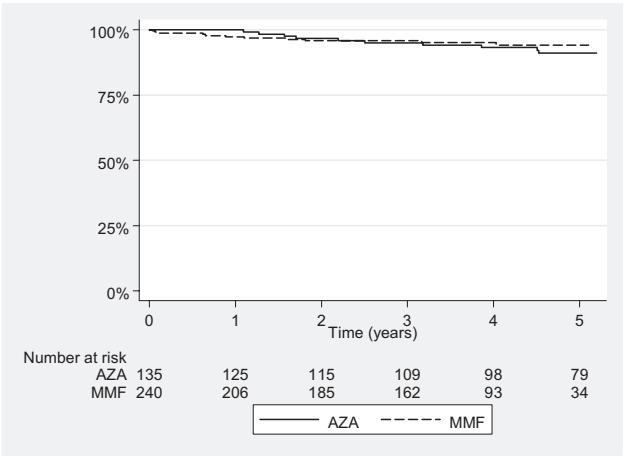

Fig. 1. Patient survival of MMF and AZA groups.

Table 4. Cause of overall graft failure in MMF and AZA groups

Cause of graft failure (no. = 57)	MMF group (no. = 30)	AZA group (no. = 27)
Chronic rejection	5	8
Recurrence of original renal disease	3	3
Polyoma viral infection	3	1
Death with functioning graft	11	10
Acute rejection	6	5
Miscellaneous	1	0
Not known	1	0

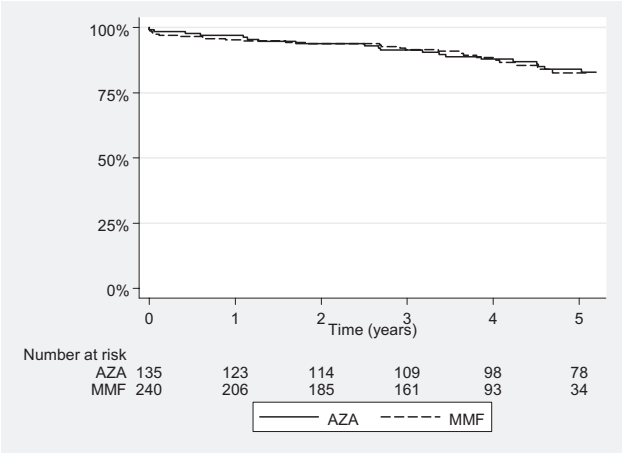

Fig. 2. Graft survival of MMF and AZA groups.

improved cross matching, more potent immunosuppressive protocols as well as provision of age-appropriate clinical care. Graft loss secondary to acute rejection continues to be a major problem in renal transplantation [5].

In this report, there was no difference in acute rejection episodes and immunological graft loss secondary to these rejection episodes between MMF- and AZA-based immunotherapy (P = 0.307). The incidence of acute rejection episodes in patients transplanted on MMF was 12.5% (30/240) compared to an acute rejection rate of 16% (22/135) in patients on AZA-based immunotherapy. More importantly, the use of low-risk renal transplant patients showed no significant difference concerning graft survival between the two groups studied (P = 0.62). In spite of the care used in patient selection, where the absence of bias was uppermost, the two groups were selected from slightly different time periods. This is a limitation in retrospective survival studies as discussed by Altman and Bland [6]. Problems associated with the above are minimized by patient inclusion criteria, at least 5-year follow-up of all patients and a reasonably tight time frame for selection purposes.

In a recent multi-institutional study from the USA, the MMF- and AZA-based immunosuppressive therapy of a total of 98 580 adult renal transplantations (MMF = 94 747 patients versus AZA = 3833 patients) were evaluated over 6 years. The overall graft survival of MMF and AZA groups were 76 and 74%, respectively, at 5 years posttransplantation. The therapeutic requirement for acute rejection was statistically significantly higher (P < 0.001) among AZA patients (13.1%) versus MMF patients (9.7%). The proportion of patients with indications of malignancies at 1 year was not statistically significantly different between MMF and AZA patients (0.9 versus 1.1%, respectively). The treatment of BK virus at 1 year was also not statistically significantly different (P = 0.38) between MMF (2.5%) and AZA (1.6%) patients. Overall, data of this large study show a relatively similar complication profile, renal function and graft loss rates among patients with AZA and MMF and suggesting that there are instances in which AZA can be utilized safely with current regimens [7].

In contrast, the beneficial effect of MMF on long-term graft survival was examined by Ojo *et al.* [8] on 66 774 renal transplant recipients from the USA renal transplant scientific registry. In this study, MMF-based immunotherapy decreased the risk for development of chronic allograft failure by 27% and ultimately improved graft survival at 4 years posttransplantation (85.61 versus 81.9% for MMF and AZA groups, respectively), however, independent of the outcome on acute rejection [8].

We experienced an increased risk of viral infections in the posttransplant period in the MMF study population compared to the AZA study population (7%, 17/240 and 5%, 7/135, respectively). In a recent report from the UK, the infectious complications following the introduction of MMF in a group of adult renal transplant patients, on a calcineurin inhibitor withdrawal protocol was assessed [9]. In this report, the incidence of infections increased from 26.7% (8/30) prior to the use of MMF to 66.6% (20/30) after its introduction in the study group-immunosuppressive protocol.

In the era of the decreased financial resourcing for the health and medical services worldwide, many national transplantation programmes are eagerly aiming to reduce the significant cost of their immunosuppressive regimens. Although MMF is significantly more expensive than AZA, its introduction and costs are rationalized on the basis that reduction of rejection episodes will improve graft survival and ultimately counterbalance the increased expenses [10].

Table 5. Renal function of MMF and AZA groups[a]

Groups	1 year posttransplant	2 years posttransplant	3 years posttransplant	4 years posttransplant	5 years posttransplant
AZA	123 (102–149)	121 (102–164)	117 (100–165)	117 (98–176)	124 (96–181)
MMF	121 (104–144)	127 (106–164)	118 (99–165)	121 (96–172)	134 (99–298)
P-value	0.653	0.636	0.762	0.924	0.408

[a]Data was represented as median and interquartile range in parenthesis. Note: Table 5 above incorporates graft loss with imputed creatinine of 600 mmol/L for graft loss. The reason for this is that the highest functioning graft creatinine is 553 mmol/L. Median creatinine levels are thus a bit higher than before. Potentially, a problem could arise if measuring graft function due to large accumulated graft losses. Eventually, median creatinine at estimated graft half-life would be 600 for both groups. In our study, however, graft loss was low and did not affect median and interquartile range values to a great extent. Due to very similar creatinine results for both groups, we did not consider much additional useful information would be derived by conducting additional multi-factorial models for graft function at the various time points posttransplant.

Table 6. (I, II and III): multi-factorial Cox proportional hazards models of patient and graft survival and acute rejection episodes

Variable	Hazard ratio	95% Confidence interval	P-value
Patient survival (I)			
MMF	0.52	0.22–1.24	0.138
No. HLA mismatch	1.12	0.78–1.59	0.541
Donor age (years)	1.03	0.99–1.06	0.145
Donor sex (male)	0.79	0.35–1.79	0.580
Age at transplant (years)	1.07	1.03–1.11	0.001
Sex (male)	0.27	0.11–0.67	0.005
Diabetic status	4.72	1.65–13.49	0.004
Delayed graft function	1.49	0.55–4.09	0.431
Cold ischaemia time (h)	0.99	0.90–1.10	0.932
Graft survival (II)			
MMF	0.97	0.79–1.23	0.901
No. HLA mismatch	1.03	0.57–1.83	0.940
Donor age (years)	1.02	0.99–1.04	0.104
Donor sex (male)	0.77	0.45–1.32	0.338
Age at transplant (years)	1.02	0.99–1.04	0.115
Sex (male)	0.55	0.32–0.97	0.038
Diabetic status	1.72	0.67–4.34	0.258
Delayed graft function	1.37	0.66–2.86	0.397
Cold ischaemia time (h)	1.02	0.97–1.08	0.436
Acute rejection episodes (III)			
MMF	1.13	0.91–1.43	0.272
No. HLA mismatch	0.68	0.38–1.21	0.189
Donor age (years)	1.01	0.99–1.04	0.234
Donor sex (male)	0.65	0.37–1.13	0.127
Age at transplant (years)	0.97	0.95–0.99	0.013
Sex (male)	2.01	1.08–3.73	0.027
Diabetic status	1.85	0.68–5.03	0.226
Delayed graft function	1.43	0.67–3.06	0.356
Cold ischaemia time (h)	1.02	0.95–1.08	0.617

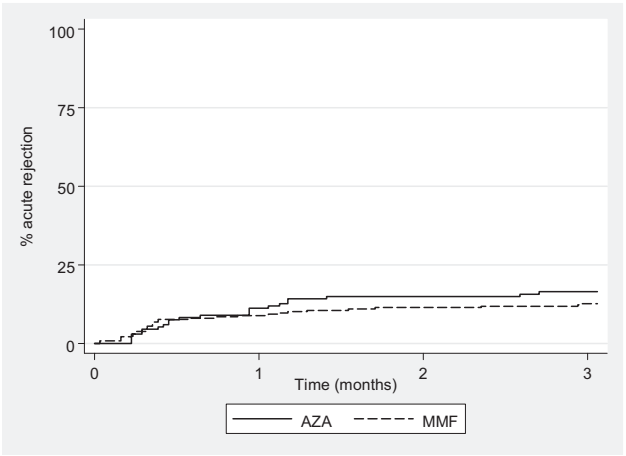

Fig. 3. Acute rejection episode of MMF and AZA groups.

This economic argument is well refuted by Remuzzi *et al.* [11]. In a socioeconomic study, these authors evaluated and published in a peer-reviewed journal a cost/benefit analysis for immunosuppresive treatment with MMF versus AZA [11]. Since the cost of MMF exceeds AZA by 15 times (€5416 versus €354 per patient), >€4000 per patient per year could be saved if AZA were used instead of MMF. In addition, a net annual saving of ~€75 million can be reached from switching to AZA in Europe alone. In Ireland, the annual cost of 500 mg twice daily dosage of MMF is €3624 per patient. With regard to reducing the incidence of the acute rejection episodes, graft losses and adverse effects, Remuzzi *et al.* [11] found that MMF does not have a greater risk/benefit profile than AZA. This study concluded that AZA should be included in the immunosuppressive regimens instead of MMF in view of its expensive cost and questionable benefits [11].

There are also some long-term concerns regarding the safety of MMF have recently been recognized in the literature as teratogenic in humans [12, 13]. *In utero* exposure to MMF can lead to phenotypic spectrum of MMF embryopathy such as cleft lip and palate, microtia with atresia of external auditory canal, micrognathia and hypertelorism. Ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations and diaphragmatic hernia have also been reported [13]. The patient information insert also advises both men and women to discontinue MMF if contemplating parenthood.

With respect to liver transplantation, Wiesner *et al.* [14] conducted a large randomized controlled trial comparing AZA and MMF after liver transplantation and reported particularly patient/graft survival and acute rejection episodes. Similar to our findings, Wisener *et al.* [14] found that rejection rates were 25% lower in MMF than in AZA-treated patients (38.5 and 47.7%, respectively). However, this failed to improve patient or graft survival in the MMF-treated

group compared to AZA-treated group (88 and 87.1; 85.3 and 85.4, respectively). In a multivariate observational study conducted by Samonakis *et al.* [15], AZA-treated patients were associated with reduced severity of hepatitis C viral recurrence and had a survival advantage.

In a recent retrospective study of renal transplants by Opelz *et al.* [16]. The 5-year graft survival in renal transplant recipients was equivalent in patients receiving MMF and in non-MMF groups. However, a published meta-analysis by Knight *et al.* [17] has shown a reduced risk of acute rejection when MMF was used ($P < 0.00001$). In Knight's analysis, there was no significant difference in patient survival or renal transplant function between the MMF and non-MMF groups. It however concluded that MMF usage does indeed confer a clinical benefit over AZA by reducing the risk of acute rejection and also possibly reducing graft loss [17].

In summary, although MMF had some beneficial effects in terms of acute rejection episodes, this has not translated into statistically significant improved graft survival when compared to AZA. In addition to adding significantly to the cost of transplantation, potential teratogenic side effects in patients who will spend long time on immunosupression are an unanswered question. We conclude from this small single-centre experience that the addition of MMF to the current immunosuppressive regimen is of questionable benefit. The answer will only be found in a large randomized study where the end points are patient and graft survival not rejection episodes and/or cost.

Conflict of interest statement. None declared.

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