

Mycophenolate Mofetil *versus* Azathioprine for Prevention of Chronic Allograft Dysfunction in Renal Transplantation: The MYSS Follow-Up Randomized, Controlled Clinical Trial

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The Mycophenolate Steroids Sparing (MYSS) study found that in renal transplant recipients who were on immunosuppressive therapy with the cyclosporine microemulsion Neoral, mycophenolate mofetil (MMF) was not better than azathioprine in preventing acute rejection at 21 mo after transplantation and was 15 times more expensive. The MYSS Follow-up Study, an extension of MYSS, was aimed at comparing long-term outcome of 248 MYSS patients according to their original randomization to MMF (1 g twice daily) or azathioprine (75 to 100 mg/d). Primary outcome was estimated GFR at 5 yr after transplantation. Mean 5-yr GFR difference between azathioprine and mycophenolate was 4.67 ml/min per 1.73 m² (95% confidence interval [CI] -0.43 to 9.77 ml/min per 1.73 m²; *P* = 0.07). GFR from month 6 (mean ± SEM: 54.3 ± 1.6 *versus* 53.9 ± 1.5 ml/min per 1.73 m²; *P* = 0.83) to month 72 after transplantation (49.5 ± 2.2 *versus* 47.3 ± 2.4 ml/min per 1.73 m²; *P* = 0.50); GFR slopes (mean ± SEM: -1.10 ± 0.56 *versus* -1.23 ± 0.31 ml/min per 1.73 m² per year; *P* = 0.83); and 72-mo patient mortality (4.0 *versus* 4.0% [*P* = 0.95]; HR 0.96; 95% CI 0.28 to 3.31; *P* = 0.95), graft loss (6.8 *versus* 6.1% [*P* = 0.82]; HR 0.89; 95% CI 0.32 to 2.46; *P* = 0.83), incidence of persistent proteinuria (25.0 *versus* 27.4%; *P* = 0.72), late (>6 mo after transplantation) rejections (25.3 *versus* 21.2%; *P* = 0.53), and adverse events were similar on azathioprine (*n* = 124) and MMF (*n* = 124), respectively. Outcomes in the two groups were comparable also among patients with or without steroid therapy, considered separately. In kidney transplantation, the long-term risk/benefit profile of MMF and azathioprine therapy in combination with cyclosporine Neoral is similar. In view of the cost, standard immunosuppression regimens for kidney transplantation should perhaps include azathioprine rather than MMF.

J Am Soc Nephrol 18: 1973–1985, 2007. doi: 10.1681/ASN.2006101153

Mycophenolate mofetil (MMF), an ester prodrug of mycophenolic acid, was introduced in clinical practice in 1997 as a novel antirejection drug (1). It suppresses proliferation of T and B lymphocytes by inhibiting inosine monophosphate dehydrogenase, a crucial enzyme in the *de novo* pathway of purine synthesis in the S phase of the cell cycle (2). In other

eukaryotic cells, however, inosine monophosphate dehydrogenase inhibition has little effect on cell division because purines can also be generated from nucleotide breakdown products. Because lymphocytes lack this "salvage pathway," MMF specifically inhibits their proliferation, thereby limiting cell-mediated immunity, but has little impact on other tissues with high proliferative activity, such as skin, intestine, and bone marrow (2). This property has been presented as a major advantage over other, less selective antiproliferative agents such as azathioprine (3).

Three groundbreaking, prospective, randomized, double-blind clinical trials in a total of 1593 patients who received an immunosuppressive regimen that included cyclosporine Sandimmune (Novartis, Basel, Switzerland) and steroids (4–6)

Received October 26, 2006. Accepted March 16, 2007.

Published online ahead of print. Publication date available at www.jasn.org.

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found a significantly lower proportion of patients with a first rejection episode on MMF 2 g/d (33.2%) or 3 g/d (35.0%) than on azathioprine or placebo (50.3%). A pooled analysis of the three trials found that this trend was still consistent at 1 yr (7). On the basis of these findings, European regulatory agencies and the US Food and Drug Administration approved MMF for the prevention of rejection in renal transplantation. In the subsequent years, MMF progressively replaced azathioprine as a part of standard treatment for preventing rejection in solid organ and bone marrow transplantation in most centers worldwide (8).

In 1997, however, at the same time MMF was introduced in clinical practice, a microemulsion preparation of cyclosporine, Neoral (Novartis), became available. The microemulsion was developed to provide greater and more consistent exposure to cyclosporine than the older, oil-based Sandimmune formulation (9). This facilitated the individual tailoring and monitoring of cyclosporine therapy, which translated into a reduced incidence of acute rejection episodes and an improved graft survival, without increasing adverse effects related to cyclosporine toxicity, not only in kidney transplantation (10,11) but also in other clinical settings such as heart (12) and liver (13) transplantation. As a result of the better risk/benefit profile, Neoral soon became the preferred form of cyclosporine in many centers (9,11,14).

The Mycophenolate Steroids Sparing (MYSS) study published in 2004 (15) was designed to test formally whether MMF retains its better antirejection activity even in immunosuppressive regimens that use the cyclosporine microemulsion formulation Neoral as opposed to Sandimmune. The MYSS trial was a fully independent, academic study and was not funded by pharmaceutical companies. It compared the incidence of acute rejections in 336 patients who were randomly assigned to MMF or azathioprine in the context of a Neoral-based immunosuppressive regimen. Data showed that MMF was not more effective than azathioprine in preventing acute rejection at 21 mo after transplantation, had a similar tolerability profile, but was 15 times more expensive. Because of the relatively limited follow-up, however, this study could not assess the effects of MMF and azathioprine on the onset and progression of chronic allograft dysfunction (16), a syndrome of proteinuria and worsening renal function with progressive nephron loss and scarring of the graft (chronic allograft nephropathy). This is a key issue because, after recipient death, chronic allograft dysfunction represents the major cause of graft loss in the long term (17). Moreover, results from registry analyses showed that continued treatment with MMF *versus* azathioprine was associated with a protective effect against renal function deterioration beyond 1 yr after transplantation (18) and superior graft survival at 4 yr (19). Despite the limitations of the retrospective design of these analyses, these data further limited the possibility to use results of the MYSS trial to change the practice of most transplant centers to regard MMF as a key component of immunosuppressive drug regimens that are based on cyclosporine microemulsion.

To address this issue, we designed the MYSS Follow-up study. This was an extension of the MYSS study and prospec-

tively compared long-term outcomes of the two cohorts of MYSS patients in the setting of a similar immunosuppressive regimen based on the microemulsion Neoral, according to their original randomization to MMF or azathioprine. The results of this MYSS Follow-up study formed the basis of this report.

Materials and Methods

Patients and Study Design

The MYSS study was a multicenter, prospective, randomized, parallel-group trial that compared the incidence of acute rejection in recipients of a first kidney transplant from deceased donors who were randomly assigned on a 1:1 basis within each center to receive treatment with 1 g of MMF twice daily or azathioprine once daily (100 mg if body weight <75 kg, 150 mg if \geq 75 kg) in combination with maintenance immunosuppressive therapy with the cyclosporine microemulsion Neoral and steroids (see Remuzzi *et al.* [15] for further details). From October 1997 to May 2001, 336 patients were included. However, two patients (one per group) did not receive the transplant for technical reasons. Thus, 334 patients (167 per group) received the study drugs (Figure 1). The randomization was centralized at the Laboratory of Biostatistics of the Clinical Research Centre for Rare Diseases of the Mario Negri Institute for Pharmacologic Research. At completion of the first 6-mo treatment period (phase A), steroid dosage was progressively tapered and discontinued in patients with (1) no more than two acute rejection episodes, (2) no steroid-resistant rejections, and (3) serum creatinine concentrations of \leq 177 μ mol/L (Figure 1). When an acute rejection episode was diagnosed, oral steroid was renewed at the dosage before the last reduction or at 6 mg every other day if the patient had already discontinued the medication. Patients were then followed up to 21 mo after transplantation (phase B).

Fifty-three patients (28 on azathioprine, 25 on MMF) who were included in the MYSS core trial and referred to the Centers of Genoa, Antwerp, and Montpellier were not included because of fund restrictions that did not allow covering the costs for active patient follow-up and data monitoring and recording. Of the remaining 281 patients who were included in the MYSS trial and referred to the Bergamo, Padua, Brescia, Turin, Varese, Florence, Palermo, and Naples transplant centers, 248 patients entered the MYSS Follow-up study, whereas 33 did not. Reasons for exclusion were death ($n = 2$, both on azathioprine), dialysis ($n = 2$ in each group), and withdrawal of consent ($n = 27$, 11 in the azathioprine, 16 in the MMF group). Donor and baseline characteristics, immunosuppressive therapy, and concomitant medications of patients who were or were not included in the follow-up study, as well as of patients who did or did not complete the study, were similar (data not shown).

Patients were prospectively followed up to October 2004 by visits every 6 mo (\pm 15 d). Clinical and laboratory parameters were recorded in dedicated forms and were doubly entered. Finally, MYSS and MYSS Follow-up databases were merged in a unique database that served for final analyses. All of these activities were coordinated and monitored by the Clinical Research Centre of the Mario Negri Institute without the involvement of pharmaceutical industry sponsorship.

All patients provided written informed consent to enter the MYSS study and a subsequent oral consent to have their follow-up extended for at least 2 yr. Outcome data were recorded without interfering with patient routine clinical management and were handled according to standard regulations for data registration, use, and preservation of patient anonymity and privacy.

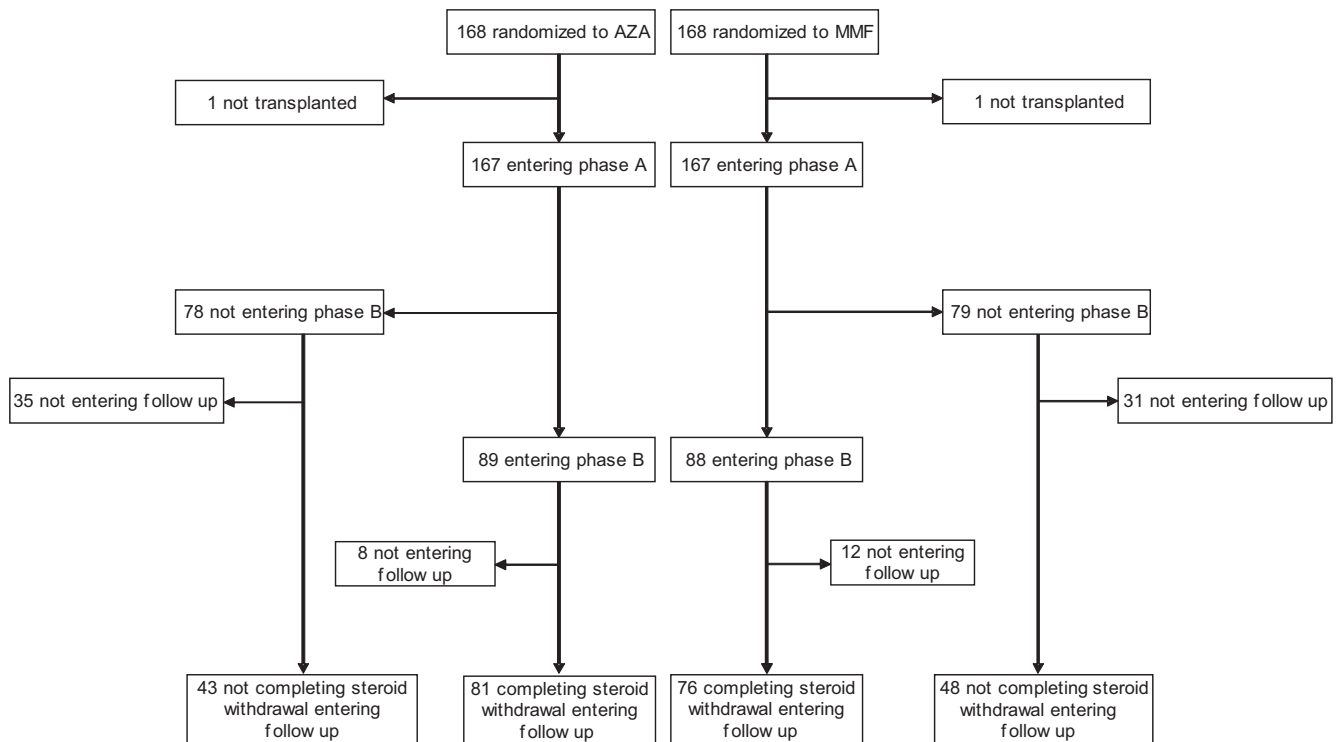


Figure 1. Trial profile.

Outcomes

Primary outcome variable was estimated GFR (eGFR). Secondary outcome variables were the rate of GFR decline over time (GFR slope), the incidence of new-onset persistent proteinuria (urinary protein excretion >0.5 g/24 h in two consecutive visits in patients without residual proteinuria since transplantation), patient and graft survival, acute rejections, and adverse events.

BP, serum creatinine concentration, proteinuria and other relevant laboratory parameters, treatments, and adverse events including acute rejections were recorded every 6 mo up to study end. The GFR was estimated on the basis of the Walsler equation (men: $GFR = 7.57 \times (\text{serum creatinine} \times 0.0884)^{-1} - 0.103 \times \text{age} + 0.096 \times \text{weight} - 6.66$; women: $GFR = 6.06 \times (\text{serum creatinine} \times 0.0884)^{-1} - 0.080 \times \text{age} + 0.080 \times \text{weight} - 4.81$), the equation that in renal transplantation generates the GFR estimates that better predict true GFR as measured by the iohexol plasma clearance (20). Complementary analyses used GFR data as estimated by the Modification of Diet in Renal Disease (MDRD) and Nankivell equations (21,22). The GFR slope was estimated in patients who had at least two GFR measurements from month 6 after transplantation (taken as baseline) to study end. The diagnosis of acute rejection episodes was made on the basis of clinical criteria as in the MYSS study (15). Kidney biopsy samples were taken whenever appropriate to confirm the diagnosis and for all steroid-resistant rejection episodes.

Statistical Analyses

All analyses were performed according to the original randomization in the MYSS trial. An additional “on treatment” analysis was performed in patients who assumed only the study drug as per protocol. Analyses first considered the study population as a whole, and then patients who completed steroid withdrawal while in the MYSS study separately from those who did not. For avoiding the confounding effect of different follow-up periods, main outcomes were also described in

three subcohorts of patients who were actively followed for at least 24, 48, and 72 mo, respectively.

Baseline recipient and donor characteristics were compared according to treatment groups by means of *t* test, χ^2 , or Fisher exact test as appropriate. Kaplan-Meier analysis was used to investigate whether survival functions differed between treatment groups. The difference between the survival curves was assessed by log-rank test. Cox proportional hazards models, with adjustment for main demographic and clinical covariates (site, donor and recipient gender, donor and recipient age, donor and recipient weight, and donor serum creatinine) were used to detect the effect of treatment on time-dependent end points. Proportional hazards assumptions were checked by means of Schoenfeld residuals. General linear mixed models were used to compare GFR levels at various time points (*e.g.*, every 6 mo since transplantation, between regimen treatments). Statistical analyses were accomplished with SAS software (version 9.1.3; SAS Institute, Cary, NC). The statistical level of significance was $P < 0.05$. All statistical analyses were performed by two-tailed tests. The study was not initially powered to detect a difference in graft survival or function between treatment groups, and the recruitment was finalized to have all MYSS patients on active follow-up for at least 2 yr in the setting of the MYSS Follow-up study.

Results

Patients

Main donor and recipient characteristics at time of transplantation were similar in the two treatment groups—except for a significantly higher percentage of female patients in the azathioprine arm—in the study population as a whole as well as in the two cohorts of patients who did or did not complete the steroid withdrawal protocol (Table 1). Cold ischemia time was similar between the two treatment arms in the study group as

Table 1. Baseline characteristics of recipients and donors^a

| Characteristic | Overall | | | Patient Who Completed Steroid Withdrawal | | | Patients Who Did Not Complete Steroid Withdrawal | | |
|----------------------------|------------------------|---------------|------|--|--------------|------|--|--------------|------|
| | Azathioprine (n = 124) | MMF (n = 124) | P | Azathioprine (n = 81) | MMF (n = 76) | P | Azathioprine (n = 43) | MMF (n = 48) | P |
| Recipients | | | | | | | | | |
| men | 73 (58.9%) | 91 (73.4%) | 0.02 | 49 (61%) | 52 (68%) | 0.30 | 24 (56%) | 39 (81%) | 0.01 |
| age (yr) | 44.7 (11.6) | 41.8 (12.3) | 0.06 | 45.3 (11.5) | 40.3 (11.9) | 0.01 | 43.5 (11.7) | 44.2 (12.6) | 0.79 |
| weight (kg) | 65.8 (11.4) | 69.5 (13.3) | 0.06 | 66.0 (12.2) | 68.9 (13.9) | 0.26 | 65.6 (10.2) | 70.6 (12.4) | 0.09 |
| serum creatinine (mg/dl) | 8.46 (3.24) | 8.50 (2.87) | 0.93 | 8.6 (3.3) | 8.4 (2.7) | 0.81 | 8.3 (3.2) | 8.6 (3.1) | 0.66 |
| SBP (mmHg) | 136.2 (21.1) | 143.2 (23.5) | 0.06 | 138.3 (22.0) | 146.2 (20.3) | 0.09 | 133.0 (19.5) | 138.5 (27.6) | 0.38 |
| DBP (mmHg) | 82.6 (12.8) | 85.3 (14.6) | 0.24 | 83.1 (13.3) | 86.3 (2.7) | 0.27 | 81.8 (12.4) | 83.7 (16.9) | 0.63 |
| Donors | | | | | | | | | |
| men | 69 (55.7%) | 74 (59.7%) | 0.52 | 50 (62%) | 47 (62%) | 0.99 | 19 (44%) | 27 (56%) | 0.25 |
| age (yr) | 42.4 (16.0) | 42.5 (15.7) | 0.95 | 41.3 (15.7) | 40.2 (16.4) | 0.68 | 44.4 (16.5) | 46.1 (13.9) | 0.61 |
| weight (kg) | 69.4 (10.3) | 70.3 (11.8) | 0.52 | 70.5 (10.9) | 68.9 (12.2) | 0.39 | 67.3 (9.0) | 72.6 (11.0) | 0.02 |
| HLA A, B, or DR mismatches | | | 0.58 | | | 0.25 | | | 0.68 |
| 0 | 5 (4%) | 3 (2%) | | 4 (5%) | 1 (1%) | | 1 (3%) | 2 (4%) | |
| 1 | 28 (23%) | 38 (31%) | | 16 (20%) | 24 (32%) | | 12 (30%) | 14 (29%) | |
| 2 | 62 (50%) | 53 (43%) | | 45 (55%) | 39 (51%) | | 17 (39%) | 14 (29%) | |
| 3 | 23 (18%) | 25 (20%) | | 16 (20%) | 12 (16%) | | 7 (16%) | 13 (27%) | |
| missing | 6 (5%) | 5 (4%) | | 0 | 0 | | 6 (14%) | 5 (11%) | |

^aData are n (%) or mean (SD). DBP, diastolic BP; MMF, mycophenolate mofetil; SBP, systolic BP.

whole (azathioprine 16.6 ± 7.2 h; MMF 16.0 ± 6.5 h), as well as in the two subgroups that did (azathioprine 15.6 ± 6.7 h, MMF 15.7 ± 6.1 h) or did not complete (azathioprine 19.2 ± 7.9 h; MMF 16.7 ± 7.1 h) steroid withdrawal. Patients were followed for a median (interquartile range) of 65.5 mo (52.7 to 73.6) in the azathioprine group and of 64.1 mo (53.8 to 73.6) in the MMF group. The flowchart of the study is shown in Figure 1. At last follow-up, 18.5% of patients who were randomly assigned to azathioprine and 8.1% of those who were randomly assigned to MMF were on reduced dosages of the study drugs compared with the dosages at 6 mo after transplantation (*i.e.*, before steroid reduction or withdrawal).

Primary Efficacy Outcome

GFR. All 248 patients had at least one GFR evaluated during the follow-up. Throughout the whole study period, eGFR was similar in the two treatment groups at each 6-mo visit (Figure 2). Mean GFR difference between azathioprine and MMF at 60 mo from transplantation was 4.67 ml/min per 1.73 m² (95% confidence interval [CI] -0.43 to 9.77 ml/min per 1.73 m²; $P = 0.07$; Table 2). At month 72 after randomization, mean (\pm SE) GFR was 49.5 ± 2.2 ml/min per 1.73 m² in the azathioprine group and 47.3 ± 2.4 ml/min per 1.73 m² in the MMF group ($P = 0.50$). eGFR values at various time points after transplantation were similar in the two treatment groups even within cohorts of patients with the same follow-up duration (Figure 3). Consistent results were obtained by “on treatment” analyses (data not shown). Among patients who completed

steroid withdrawal considered as a whole, the GFR progressively declined over time with a similar trend in both treatment groups (Figure 4, top). At variance, among patients who did not complete steroid withdrawal, those who were on azathioprine had a GFR with a slight progressive increase during the whole follow-up, whereas those who were on MMF had a slowly declining GFR (Figure 4, bottom). This different trend resulted in a numerically higher GFR at 72 mo after randomization in patients who were on azathioprine (51.2 ± 4.8 ml/min per 1.73 m²) than in those who were on MMF (36.2 ± 4.2 ml/min per 1.73 m²; $P = 0.07$).

Secondary Efficacy Outcomes

Patient and Graft Outcome. The 72-mo patient (azathioprine 4.0%; MMF 4.0%; $P = 0.95$) and graft loss (azathioprine 6.8%; MMF 6.1%; $P = 0.83$) were virtually identical in the two treatment groups (Figure 5). Patient mortality was also similar in the two cohorts of patients who did (azathioprine 2.5%; MMF 2.6%; $P = 0.96$) or did not complete (azathioprine 7.0%; MMF 6.2%; $P = 0.80$) steroid withdrawal considered separately, as well as graft loss (completing steroid withdrawal: azathioprine 3.8%; MMF 2.8%; $P = 0.71$; not completing steroid withdrawal: azathioprine 11.9%; MMF 11.1%; $P = 0.94$). Cox model did not show any difference between treatment groups even when adjusted for demographic and clinical covariates, cold ischemia time, steroid withdrawal, and azathioprine or MMF dosage reduction (at last follow up *versus* month 6 after transplantation; data not shown).

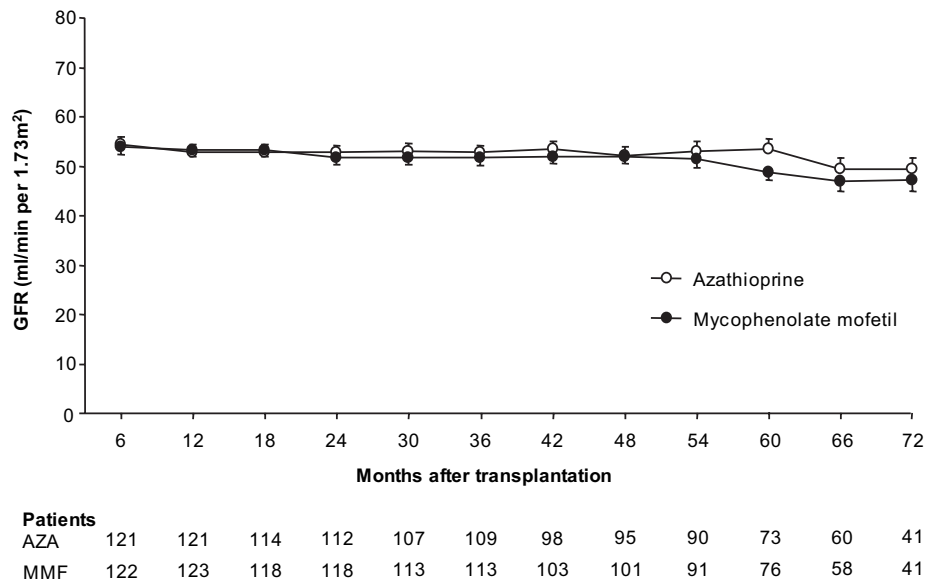


Figure 2. Estimated GFR (eGFR) values at various time points from transplantation in the two treatment groups according to the original patient randomization in the Mycophenolate Steroids Sparing (MYSS) study. Error bars indicate SE. **P* < 0.05 versus mycophenolate mofetil (MMF).

Table 2. Mean (95% CI) GFR difference between the two treatment groups at various time points during the study period^a

| Months | Mean Difference in GFR ^b | 95% CI | <i>n</i> | <i>P</i> |
|--------|-------------------------------------|-----------------|----------|----------|
| 6 | 0.45 | (−3.73 to 4.63) | 243 | 0.83 |
| 12 | −0.38 | (−4.27 to 3.52) | 244 | 0.85 |
| 18 | −0.26 | (−3.95 to 3.43) | 232 | 0.89 |
| 24 | 1.05 | (−2.88 to 4.98) | 230 | 0.60 |
| 30 | 1.41 | (−2.68 to 5.50) | 220 | 0.50 |
| 36 | 1.11 | (−2.98 to 5.20) | 222 | 0.59 |
| 42 | 1.41 | (−2.96 to 5.78) | 201 | 0.53 |
| 48 | 0.27 | (−4.04 to 4.59) | 196 | 0.90 |
| 54 | 1.68 | (−3.36 to 6.71) | 181 | 0.51 |
| 60 | 4.67 | (−0.43 to 9.77) | 149 | 0.07 |
| 66 | 2.40 | (−3.88 to 8.68) | 118 | 0.45 |
| 72 | 2.19 | (−4.26 to 8.64) | 82 | 0.50 |

^aCI, confidence interval.

^bNegative differences favor MMF; positive differences favor azathioprine.

GFR Slopes. Data for slope analyses were available for 121 patients who were on azathioprine and 124 who were on MMF. GFR slopes were similar in the two treatment arms (azathioprine -1.10 ± 0.56 ml/min per 1.73 m^2 per year; MMF -1.23 ± 0.31 ml/min per 1.73 m^2 per year; *P* = 0.83) in the study group as a whole, as well as in the subgroups that did (azathioprine -1.73 ± 0.39 ml/min per 1.73 m^2 per year; MMF -1.24 ± 0.38 ml/min per 1.73 m^2 per year; *P* = 0.36) or did not complete (azathioprine 0.19 ± 1.49 ml/min per 1.73 m^2 per year; MMF

-1.23 ± 0.55 ml/min per 1.73 m^2 per year; *P* = 0.35) steroid withdrawal.

Proteinuria. During the whole follow-up period, 31 (25.0%) patients in the azathioprine group and 34 (27.4%) patients in the MMF group developed persistent clinical proteinuria (*P* = 0.67). The number of patients who developed persistent proteinuria was similar in the two treatment groups even among patients who did (azathioprine *n* = 21 [25.9%]; MMF *n* = 20 [26.3%]) or did not complete (azathioprine *n* = 10 [23.3%]; MMF *n* = 14 [29.2%]) steroid withdrawal.

Adverse Events

Sixty-five (52.4%) patients in the azathioprine arm and 57 (46.0%) in the MMF arm experienced at least one acute rejection episode throughout the whole study period (*P* = 0.31; Figure 6). The number of patients who had late occurrence of rejection (>6 mo after transplantation) and were on azathioprine (*n* = 20, 25.3%) and on MMF (*n* = 18, 21.2%) was virtually identical as well (*P* = 0.53). Among patients who completed steroid withdrawal, the numbers of patients with acute rejections were similar in the two study groups (azathioprine *n* = 40 [49.4%]; MMF *n* = 31 [40.8%]; *P* = 0.28). The trend was similar in those who did not complete steroid withdrawal (azathioprine *n* = 25 [58.1%]; MMF *n* = 26 (54.2%); *P* = 0.70).

The total number of infections was similar in the two study groups, with no significant differences in the incidence of cytomegalovirus reactivations (Table 3). The number of cardiovascular events during the whole follow-up period was similar in the two treatment arms, whereas there was a NS trend to more neoplasms in those who were on azathioprine (Table 3). The overall incidence of adverse events was similar in the two treatment groups and also in the two cohorts of patients who did or did not complete steroid withdrawal considered separately (Table 3).

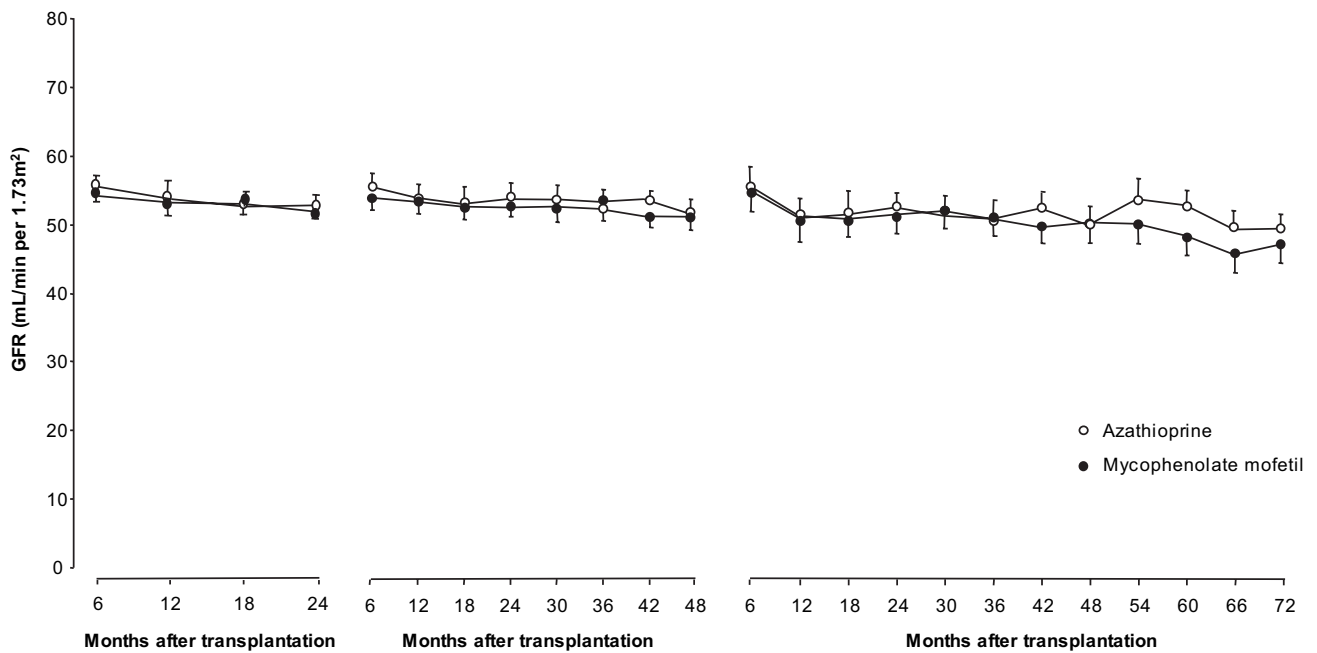


Figure 3. eGFR values at various time points from transplantation in cohorts with at least 24 (left; azathioprine $n = 111$, MMF $n = 116$), 48 (middle; azathioprine $n = 94$, MMF $n = 99$), and 72 (right; azathioprine $n = 40$, MMF $n = 41$) months of follow-up. Error bars indicate SE.

Immunosuppressive Therapy and Concomitant Medications

Cyclosporine trough levels throughout the whole study period were similar in the two treatment groups in both cohorts of patients who did or did not complete steroid withdrawal (Figure 7). The average dosages of azathioprine (ranging from 69 to 94 mg/d) and MMF (1533 to 1804 mg/d) at each time point of the follow-up were similar between cohorts of patients who did or did not complete steroid withdrawal. Among patients who did not complete steroid withdrawal, the average dosages of steroid (4 to 6 mg/d) were similar in the two treatment groups. Throughout the study period, the proportions of patients who received at least once an angiotensin-converting enzyme inhibitor (35.5 versus 36.3%), angiotensin II receptor antagonist (2.4 versus 4.0%), statin (38.7 versus 29.8%), or aspirin (43.6 versus 50.0%) therapy in the azathioprine and MMF groups, respectively, were similar.

Discussion

The MYSS Follow-up study was the longest prospective, randomized clinical trial ever attempted in kidney transplantation to compare formally the effects of various immunosuppressive drug regimens on patient and graft outcomes. *Post hoc* analyses of previous registration trials of MMF in kidney transplantation extended the observation period to a maximum of 3 yr after randomization. In the MYSS Follow-up study, outcome data were recorded over a median of 5.5 yr after patient allocation to MMF or azathioprine treatment. Analyses that were performed according to the original randomization in MYSS or to the actual treatment assumed on follow-up consistently showed that MMF was no better than azathioprine in preventing chronic allograft dysfunction in deceased-donor renal trans-

plant recipients who were on a cyclosporine Neoral-based immunosuppressive therapy. eGFR was similar in the two groups at 60 mo after transplantation—the primary outcome of the trial—as well as at each study visit. Consistently, GFR slopes; patient and graft survival; and the incidence of acute allograft rejections, new-onset proteinuria, and adverse events were similar in both groups throughout the whole study period. The outcome was similar in the two treatment arms even within the two subgroups that did or did not complete steroid withdrawal.

MMF and azathioprine were also equally well tolerated. Altogether, data of the MYSS Follow-up study suggest that MMF does not have a long-term better risk-benefit profile than azathioprine, even in the setting of a dual immunosuppressive regimen that does not include oral steroids. These findings are in harmony with data from the registration trials that showed a similar 3-yr mortality and graft loss in patients who were on azathioprine (23,24) or placebo (25) compared with those who were on MMF. Of note, however, regardless of treatment randomization, patient or graft loss was remarkably higher in previous trials (on average, 19.9% at 3 yr) than in our study (10.4% over 5.5 yr). Worse long-term outcome was also associated with a higher incidence of acute rejections at 6 mo (on average, 42.5%) than in our study (34.5%). This was not explained by differences in the study treatments, because the daily dosages of azathioprine (100 or 150 mg if body weight < or ≥ 75 kg, respectively) and MMF (2 g) were similar. Therefore, concomitant treatment most likely had a role. All patients who were included in the registration trials were on long-term steroid therapy, whereas a substantial proportion of patients who

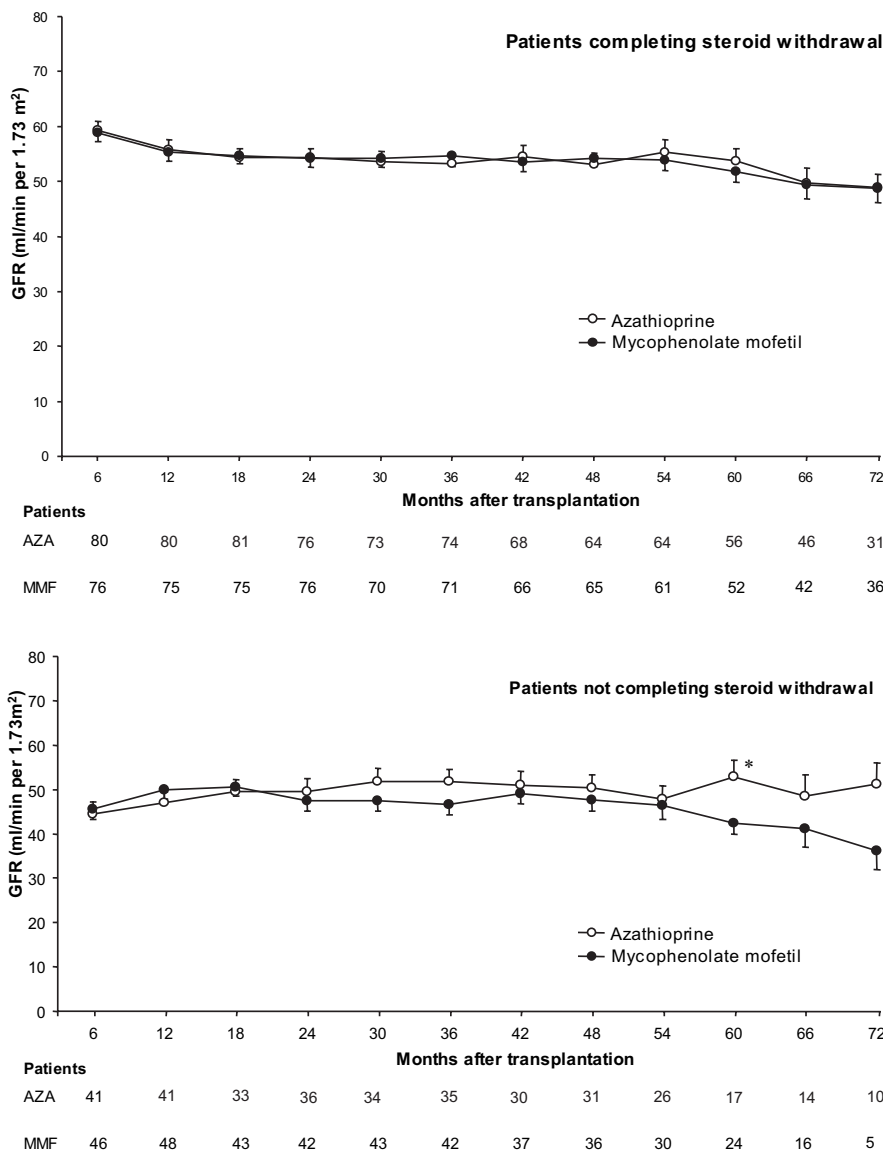


Figure 4. eGFR values at various time points from transplantation according to treatment groups in patients who did (top) or did not complete (bottom) steroid withdrawal. Error bars indicate SE. * $P < 0.05$ versus MMF.

were included in the MYSS Follow-up study withdrew steroids starting from month 6 after transplantation. Therefore, despite the seemingly less intensive concomitant immunosuppressive regimen, acute rejections were less frequent and long-term patient and graft survival were higher in the MYSS Follow-up study than in the registration trials. This may be the consequence of time-dependent factors that resulted in better patient care in more recent studies. However, another plausible—even if not exclusive—explanation may be the introduction of the cyclosporine microemulsion Neoral that was used in all patients who were included in the MYSS Follow-up study, but that was not available when the registration trials were performed. Similar confounders may explain why previous retrospective registry analyses (18,19) found a worse long-term patient and graft survival in patients who were on azathioprine, who in the large majority of cases received a kidney transplant before 1997 (*i.e.*, before Neoral became available), than in those

who were on MMF and received a graft in the following years and, therefore, in the large majority of cases were on concomitant treatment with Neoral. Consistent with this interpretation are data from two studies that were not biased by the confounding effect of time or concomitant medications: A pooled analysis of the three pivotal registration trials showing no differences in 3-yr graft function and survival on MMF as compared with azathioprine or placebo (26), and a paired kidney analysis showing similar graft function and survival in 476 renal transplant recipients who were on continued MMF or azathioprine therapy during a mean follow-up of 3.3 yr (27). Altogether, these data combined with MYSS Follow-up study findings, challenge the common belief that MMF has a specific protective effect against the development of chronic allograft nephropathy (CAN). This possibility was suggested by experimental data that MMF, in addition to inhibiting lymphocyte proliferation, has an antiproliferative effect on mesangial and

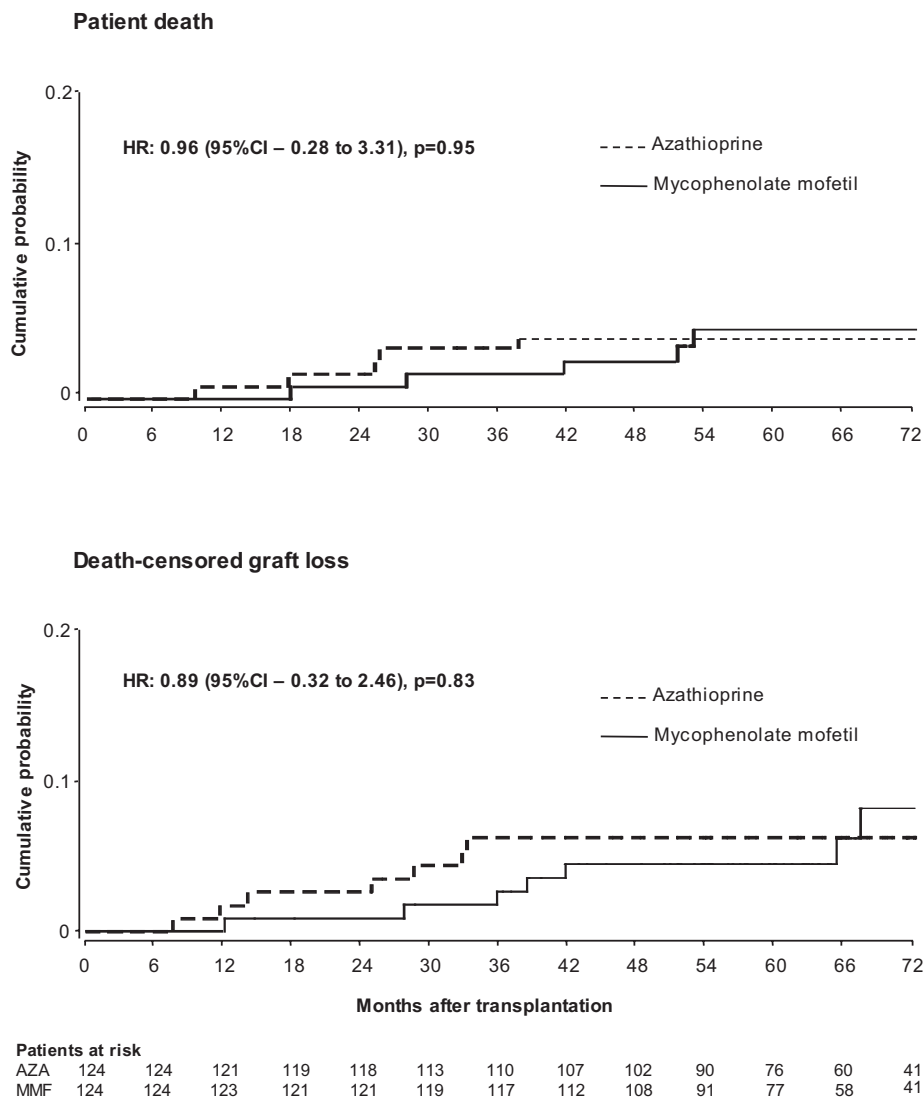
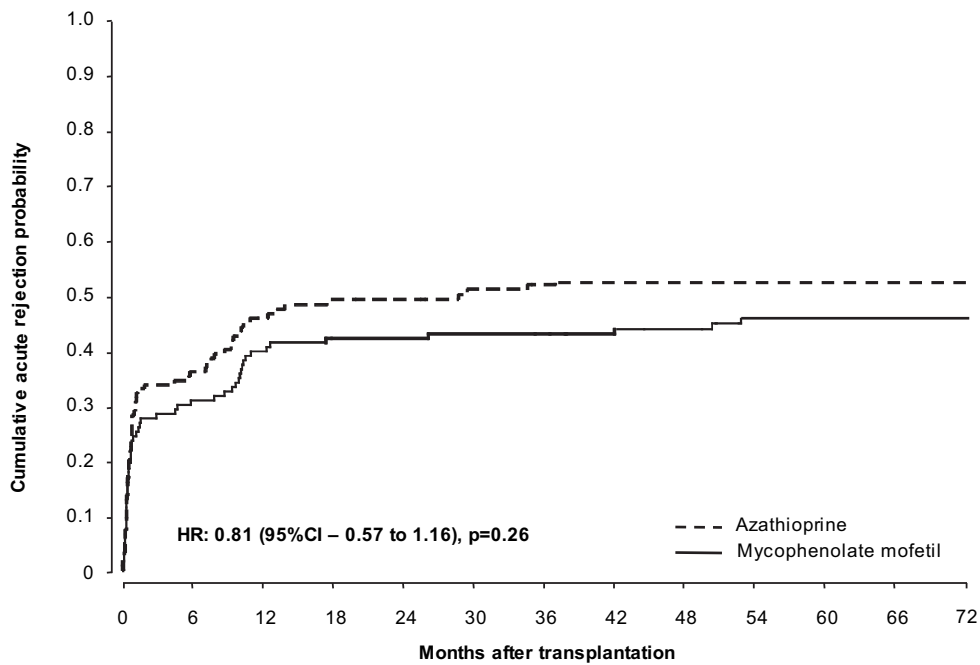


Figure 5. Cumulative patient mortality (top) and graft loss (bottom) probability in the two treatment groups according to the original patient randomization.

vascular smooth muscle cells, monocytes, and fibroblasts that might in theory prevent or limit the underlying scarring processes of CAN. Other potentially beneficial effects of MMF include inhibition of adhesion molecule expression on endothelial cells—which may retard tissue infiltration by inflammatory cells—increased apoptosis of monocytes, and reduced antibody production from B cells (reviewed in reference [28]). That these effects may translate into a clinically relevant benefit in humans, however, is unproved. Data in support of this possibility are generated by sequential studies showing improvements in graft structure and function after replacement of calcineurin inhibitors with MMF (29,30). These findings, however, may reflect a spontaneous recovery from the nephrotoxic effects of previous cyclosporine or tacrolimus treatment, rather than a specific protective effect of MMF against CAN. Observational studies showing a lower incidence of chronic interstitial fibrosis with MMF than with azathioprine therapy were likely affected by the confounding effect of time, because outcome data were

not analyzed in the setting of a randomized, prospective design (31). Only one randomized clinical trial prospectively compared the effects of MMF and azathioprine on the incidence of biopsy-proven CAN (32). On the basis of the analysis of the Banff score, MMF as compared with azathioprine therapy was associated with a lower incidence of nephropathy at 1 yr after transplantation. However, closer examination of the data (33) revealed that allograft glomerulopathy, mesangial matrix increase, vascular changes, interstitial fibrosis, and tubular atrophy, as well as renal function, were similar in the two treatment groups. These findings did not allow the conclusion that MMF is superior to azathioprine in preventing CAN (33). Actually, in the long term, the opposite might be true, as suggested by a recent observational study of 1511 renal transplant patients that showed that at 8.5 yr after transplantation, those who were on MMF had significantly lower GFR than those who were on azathioprine (34).

Altogether, the MYSS and MYSS Follow-up studies consis-



| Patients at risk | | | | | | | | | | | | | |
|------------------|-----|----|----|----|----|----|----|----|----|----|----|----|----|
| AZA | 124 | 79 | 65 | 59 | 58 | 53 | 51 | 49 | 49 | 44 | 38 | 29 | 17 |
| MMF | 124 | 85 | 74 | 70 | 70 | 69 | 68 | 65 | 62 | 51 | 42 | 27 | 20 |

Figure 6. Cumulative probability of acute rejection episodes in the two treatment groups according to the original patient randomization.

Table 3. Patients with adverse events^a

| Parameter | Overall | | | Patients Who Completed Steroid Withdrawal | | | Patients Who Did Not Complete Steroid Withdrawal | | |
|-------------------------------------|------------------------|---------------|------|---|--------------|------|--|--------------|------|
| | Azathioprine (n = 124) | MMF (n = 124) | P | Azathioprine (n = 81) | MMF (n = 76) | P | Azathioprine (n = 43) | MMF (n = 48) | P |
| Cardio/cerebrovascular ^b | 18 (15) | 22 (18) | 0.49 | 12 (15) | 11 (14) | 0.95 | 6 (14) | 11 (23) | 0.27 |
| arrhythmic | 3 (2) | 2 (2) | 0.99 | 2 (2) | 0 (0) | 0.50 | 1 (2) | 2 (4) | 0.99 |
| ischemic | 9 (7) | 6 (5) | 0.42 | 5 (6) | 5 (7) | 0.99 | 4 (9) | 1 (2) | 0.18 |
| other causes | 11 (9) | 16 (13) | 0.31 | 8 (10) | 7 (9) | 0.89 | 3 (7) | 9 (19) | 0.13 |
| Infections ^b | 89 (72) | 79 (64) | 0.17 | 55 (68) | 46 (61) | 0.34 | 34 (79) | 33 (69) | 0.26 |
| CMV | 45 (37) | 39 (32) | 0.42 | 28 (35) | 22 (29) | 0.45 | 17 (40) | 17 (35) | 0.69 |
| urinary tract infection | 39 (32) | 43 (35) | 0.59 | 26 (32) | 27 (36) | 0.65 | 13 (30) | 16 (33) | 0.75 |
| other causes | 58 (47) | 51 (41) | 0.37 | 32 (40) | 26 (34) | 0.49 | 26 (60) | 25 (52) | 0.42 |
| Cancers ^b | 13 (10) | 8 (6) | 0.25 | 11 (14) | 3 (4) | 0.05 | 2 (5) | 5 (10) | 0.30 |
| Kaposi | 3 (2) | 2 (2) | 0.99 | 2 (2) | 1 (1) | 0.99 | 1 (2) | 1 (2) | 0.99 |
| lymphoproliferative | 4 (3) | 2 (2) | 0.68 | 4 (5) | 0 (0) | 0.12 | 0 (0) | 2 (4) | 0.50 |
| cutaneous | 3 (2) | 2 (2) | 0.99 | 2 (2) | 2 (2) | 0.99 | 1 (2) | 0 (0) | 0.47 |
| other | 4 (3) | 3 (2) | 0.99 | 4 (5) | 0 (0) | 0.12 | 0 (2) | 3 (6) | 0.24 |

^aData are n (%). ^bSome patients have recorded >1 event.

tently show that MMF and azathioprine are equally effective in preventing both acute rejection and CAN (an equivalent of chronic rejection) in kidney transplantation. Studies suggest that MMF may be no better than azathioprine also in other areas of organ transplantation. A randomized clinical trial recently found that MMF and azathioprine were equally effective

in preventing acute rejection and obliterative bronchiolitis (the pathologic entity that represents “chronic rejection” in pulmonary allografts) in lung transplant recipients who were on immunosuppressive treatment with cyclosporine Neoral and corticosteroids (35).

Articles that were published after the registration studies

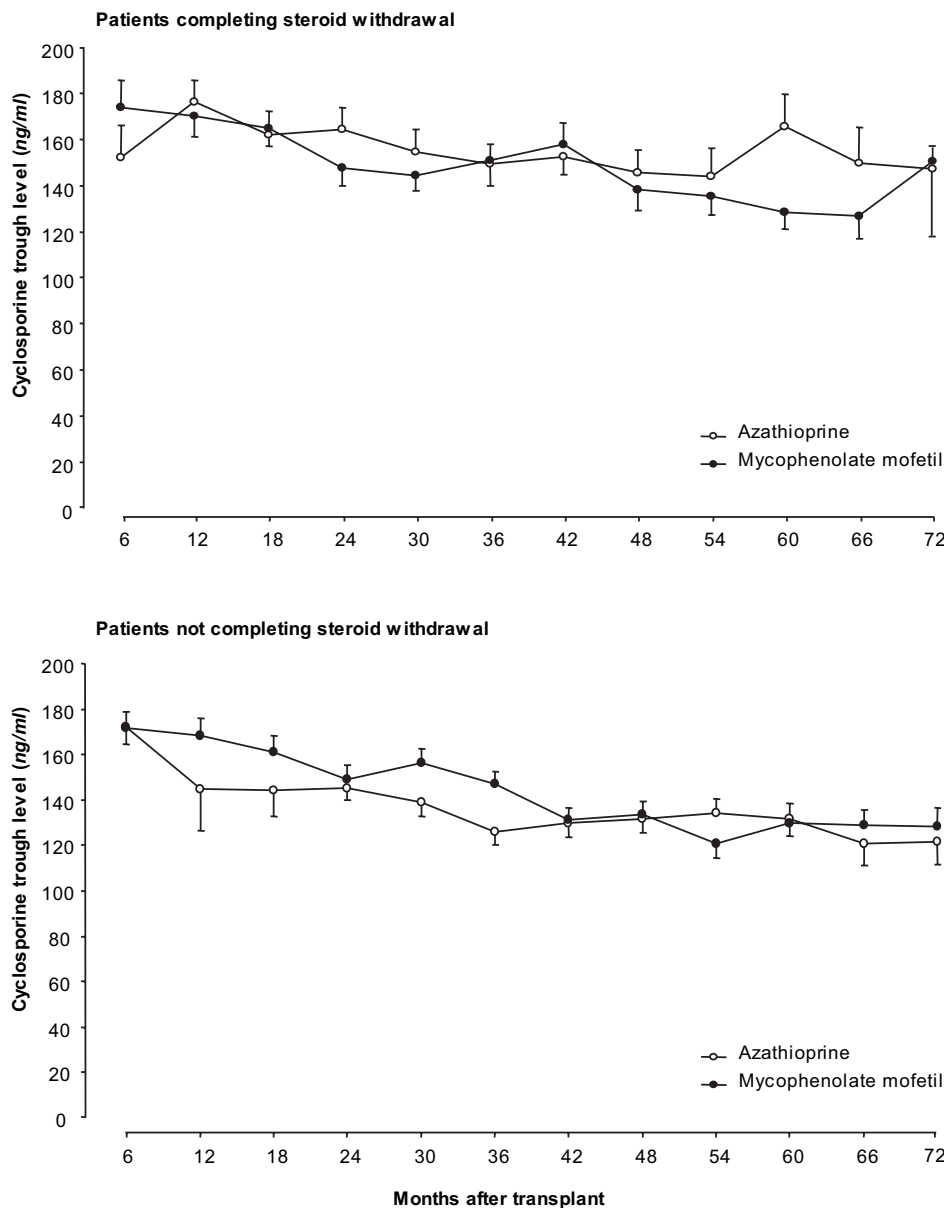


Figure 7. Cyclosporine trough levels at various time points from transplantation in the two treatment groups in patients who did (top) or did not complete (bottom) steroid withdrawal. Error bars indicate SE.

arose also some concern about the safety profile of MMF compared with azathioprine. A meta-analysis of 6387 renal transplant patients who were included in 20 randomized clinical trials of MMF *versus* azathioprine (36) found a significantly higher incidence of diarrhea, leucopenia, and cytomegalovirus disease in those who were on MMF. The Transplant European Survey on Anemia Management (37), a 5-yr survey of 4263 renal transplant recipients, showed significantly lower hemoglobin in patients who were on any immunosuppressive drug combination that included MMF, a finding that was at least in part explained by lower GFR. Recent reports showed also an increased risk for tuberculosis in renal transplant patients who received an immunosuppressive regimen that included MMF rather than azathioprine (38). However, in our study, we found a NS trend to more neoplasms on azathioprine than on MMF.

Although the study was not powered to assess the impact of treatment on these outcomes and a random effect could not be definitely ruled out, these findings are in harmony with results of previous retrospective analyses that showed a higher incidence of skin and nondermatologic malignancies with azathioprine than with MMF therapy (39).

The MYSS Follow-up study has some limitations. Long-term outcome was remarkably good regardless of treatment randomization, a finding that may reflect the effectiveness of both immunosuppressive regimens under evaluation but also the inclusion of relatively low-risk patients, such as relatively young white patients who were at their first kidney transplant and who seldom had diabetes as a primary cause of ESRD. Data from registration trials (23–26) and observational studies (27), however, suggest that azathioprine and MMF

may have a similar long-term risk/benefit profile also in second transplant recipients and in patients who are at higher immunologic risk and are on concomitant treatment with cyclosporine (or tacrolimus) and steroid, regardless of Thymoglobulin induction therapy. Whether MMF and azathioprine are equally effective also in renal transplant patients who are on tacrolimus-based immunosuppressive regimens remains to be addressed. Also, a relatively small number of patients were available for comparative analyses after >5 yr of follow-up, and, as in previous registration trials (23–25), the sample size was not estimated *a priori* on the basis of an expected effect on long-term efficacy variables. A confounding effect of a survival bias on GFR analyses was unlikely because patient and kidney survival were similar in the two treatment groups, and GFR and event analyses were consistent in showing similar long-term outcomes on MMF or azathioprine. Moreover, similar GFR outcomes were observed also when the analyses were performed in subgroups of patients with homogeneous follow-up. Finally, failure to detect a long-term benefit of MMF over azathioprine was not explained by a confounding effect of a reduction in the MMF dosage aimed to limit the risk of thrombocytopenia or leukopenia after steroid withdrawal. Indeed, at last follow-up, the proportion of patients who were on reduced dosages of MMF was consistently less than the proportion of patients who were on reduced dosages of azathioprine, and, at multivariate analyses, patient and graft outcomes were similar in the two treatment groups even after adjustment for dosage reduction.

Conclusion

Data from our study, consistent with *post hoc* analyses of previous registration trials (23–26) and recent observational studies (27), suggest that the long-term risk/benefit profile of MMF and azathioprine therapy in kidney transplantation are similar, even in the setting of a cyclosporine-based immunosuppressive regimen that does not include steroids. Because the costs for standard treatment with MMF remarkably exceed those of azathioprine (15), standard immunosuppression regimens for kidney transplantation should perhaps include azathioprine rather than MMF.

Acknowledgments

Marco Costantini is a recipient of a fellowship from Associazione Ricerca Trapianti, Milan, Italy.

Organization of the MYSS Follow-up Study Group: Principal investigator, Giuseppe Remuzzi, Azienda Ospedaliera, Ospedali Riuniti, Bergamo, Istituto di Ricerche Farmacologiche Mario Negri; study coordinator, Piero Ruggenti, Azienda Ospedaliera, Ospedali Riuniti, Bergamo, Istituto di Ricerche Farmacologiche Mario Negri. Ethical Committee: Livio Robba, Francesco Vaccari, Ottavio Roberto, Luigi Minetti, Valentina Paris, Eugenio Battaglia; Steering Committee: Giuseppe Remuzzi, Norberto Perico, Piero Ruggenti, Silvio Sandrini, Giuseppe Segoloni. Investigators and Institutions (the number of included patients is in parentheses): Azienda Ospedaliera, Ospedali Riuniti, Bergamo ($n = 89$): Principal Investigator, Eliana Gotti; Co-Investigator, Giuseppe Locatelli, Piero Ruggenti, Giovanni Rota; Ospedale Regionale di Circolo e Fondazione Macchi,

Varese ($n = 47$): Principal Investigator, Luigi Gastaldi; Co-Investigator, Donato Donati; Azienda Ospedaliera Careggi Monna Tessa, Firenze ($n = 44$): Principal Investigator, Maurizio Salvadori; Co-Investigator, Rosa Piperno, Elisabetta Bertoni; Azienda Ospedaliera Spedali Civili, Brescia ($n = 42$): Principal Investigator, Rosario Maiorca; Co-Investigator, Silvio Sandrini, Gisella Setti; Azienda Ospedaliera S.G. Battista, Torino ($n = 27$): Principal Investigator, Giuseppe Segoloni; Co-Investigator, Giuseppe Piccoli; Università Federico II, Napoli ($n = 12$): Principal Investigator, Stefano Federico; Ospedale Giustiniano, Padova ($n = 12$): Principal Investigator, Paolo Rigotti; Co-Investigator, Ermanno Ancona, Nicola Baldan; Ospedale Civico, Palermo ($n = 10$): Principal Investigator, Vito Sparacino; Co-Investigator, Sergio Calabrese. Laboratory measurements: F. Gaspari, D. Cattaneo, R. Caruso, S. Merlini, S. Baldelli, S. Ferrari, N. Stucchi, E. Centemeri, S. Zenoni, F. Carrara, M. Pellegrino (Istituto di Ricerche Farmacologiche Mario Negri); study monitoring: M. Lesti, G. Gherardi (Istituto di Ricerche Farmacologiche Mario Negri); statistical analysis: M. Costantini, M. Ganeva, A. Perna (Istituto di Ricerche Farmacologiche Mario Negri); data management: B. Ene-Iordache (Istituto di Ricerche Farmacologiche Mario Negri).

We are grateful to Manuela Vergani, Franca Gamba, Emilia Camoni, and all of the nurses of the participating centers for precious help in patient care and follow-up. Annalisa Perna helped to prepare the study protocol and to perform the analyses; Manuela Passera helped to prepare the manuscript.

Disclosures

None.

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