Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial

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See Comment page 481

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Summary

Background **Mycophenolate mofetil has replaced azathioprine in immunosuppression regimens worldwide to prevent graft rejection. However, evidence that its antirejection activity is better than that of azathioprine has been provided only by registration trials with an old formulation of ciclosporin and steroid. We aimed to compare the antirejection activity of these two drugs with a new formulation of ciclosporin.**

Methods **The mycophenolate steroids sparing multicentre, prospective, randomised, parallel-group trial compared acute rejections and adverse events in recipients of cadaver-kidney transplants over 6-month treatment with mycophenolate mofetil or azathioprine along with ciclosporin microemulsion (Neoral) and steroids (phase A), and over 15 more months without steroids (phase B). The primary endpoint was occurrence of acute rejection episodes. Analysis was by intention to treat.**

Findings **168 patients per group entered phase A. 56 (34%) assigned mycophenolate mofetil and 58 (35%) assigned azathioprine had clinical rejections (risk reduction [RR] on mycophenolate mofetil compared with azathioprine 13·7% [95% CI –25·7% to 40·7%], p=0·44). 88 patients in the mycophenolate mofetil group and 89 in the azathioprine group entered phase B. 14 (16%) taking mycophenolate mofetil and 11 (12%) taking azathioprine had clinical rejections (RR –16·2%, [–157·5% to 47·5%], p=0·71). Average per-patient costs of mycophenolate mofetil treatment greatly exceeded those of azathioprine (phase A €2665 [SD 586] *vs* €184 [62]; phase B €5095 [2658] *vs* €322 [170], p<0·0001 for both).**

Interpretation **In recipients of cadaver kidney-transplants given ciclosporin microemulsion, mycophenolate mofetil offers no advantages over azathioprine in preventing acute rejections and is about 15 times more expensive. Standard immunosuppression regimens for transplantation should perhaps include azathioprine rather than mycophenolate mofetil, at least for kidney grafts.**

Introduction

Mycophenolate mofetil, an ester prodrug of mycophenolic acid that acts by inhibiting the synthesis of purines, has been advocated as a novel drug for acute graft rejection.[1] It can specifically suppress proliferation of T and B lymphocytes, theoretically leaving haemopoiesis and polymorphonuclear neutrophil number and activity unchanged; this feature has been presented as a major advantage over azathioprine.[1]

Mycophenolate mofetil reduced acute rejections of organ transplantation in animals[2] and in people in open-label studies that also included ciclosporin.[3,4] Three large registration trials found that mycophenolate mofetil reduced acute rejection by 30 to 50% compared with azathioprine[5,6] or placebo[7] at 6 months after transplantation. These findings served to launch mycophenolate mofetil as part of standard treatment for preventing rejection of transplanted kidneys and, more recently, of heart, liver, lung, and bone marrow.[8] Nowadays, this drug is used by most transplant centres worldwide as part of maintenance immunosuppression regimens.

However, since the introduction of mycophenolate mofetil, a microemulsion preparation of ciclosporin, Neoral (Novartis, Basel, Switzerland), has become available. Because it is more rapidly, completely, and reproducibly absorbed than Sandimmune (Novartis, Basel, Switzerland), Neoral has become the preferred form of ciclosporin in many centres.[9–11] Whether mycophenolate mofetil retains its better antirejection activity over azathioprine with the present microemulsion preparation of ciclosporin has not been tested. Nor is solid evidence available on whether, in view of current protocols, steroids still have a fundamental role in maintenance immunosuppression regimens. Because of the well recognised adverse effects of long-term steroid use, withdrawal of steroids at some point after transplantation is desirable. Attempts to do so have been made,[12–23] but results have been disappointing so far. The benefits of low-dose or no-steroid protocols included less growth retardation in children,[12] and reductions in hypertension,[13,14] dyslipidaemia.[15,16] and glucose intolerance,[16] but also more rejections[18,19] so some of

the trials had to be prematurely stopped for safety reasons.[19]

The mycophenolate steroids sparing (MYSS) study—a multicentre, randomised, parallel-group trial—was designed to clarify whether mycophenolate mofetil is better than azathioprine in regimens that include ciclosporin microemulsion, and whether it offers advantages over azathioprine in the opportunity to reduce or stop steroids. Our aim was to compare the risk-benefit profile of mycophenolate mofetil and azathioprine combined with this form of ciclosporin, with or without concomitant steroid therapy.

Methods

Patients

Eligible patients were men and women aged 18–70 years who were to receive a first kidney transplant from a cadaver donor. We excluded those with a history of malignant disorders (apart from successfully treated non-metastatic basal or squamous-cell carcinoma of the skin), serological evidence of infection with HIV or hepatitis B virus, systemic infections requiring continued antibiotic therapy, haematological abnormalities (white-blood-cell count $<3\times10^9$/L, platelet count $<1\times10^{11}$/L, or haemoglobin <50 g/L), severe gastrointestinal disorders, active peptic-ulcer disease, or inability to take oral medication long term, pregnant women, nursing mothers, women who did not agree to use adequate contraception, and patients who did not fully understand the purposes of the study or were already involved in other studies. All patients selected provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the ethics committees of all participating centres.

Study design

The study was organised in two sequential phases: phase A, from kidney transplantation to 6 months afterwards; and phase B, from months 6 to 21 after transplantation (figure 1). In phase A, selected patients were randomly assigned equally within each centre to receive treatment with 1 g mycophenolate mofetil twice daily, or azathioprine once daily according to bodyweight (100 mg if bodyweight <75 kg, 150 mg if ⩾75 kg). Both treatments were started within the first 3 days after transplantation, as soon as intestinal transit was restored. Randomisation was centralised at the Laboratory of Biostatistics of the Clinical Research Centre for Rare Diseases Aldo e Cele Daccò of the Mario Negri Institute for Pharmacological Research, under the responsibility of an independent investigator who was not involved in design or performance of the study. Ciclosporin microemulsion and steroids were given concomitantly to all patients as maintenance immunosuppressive therapy. From day of transplantation (day 0) to day 3, ciclosporin (5 mg/kg daily) was infused intravenously. From day 4, ciclosporin microemulsion (10 mg/kg daily) was given orally in two divided

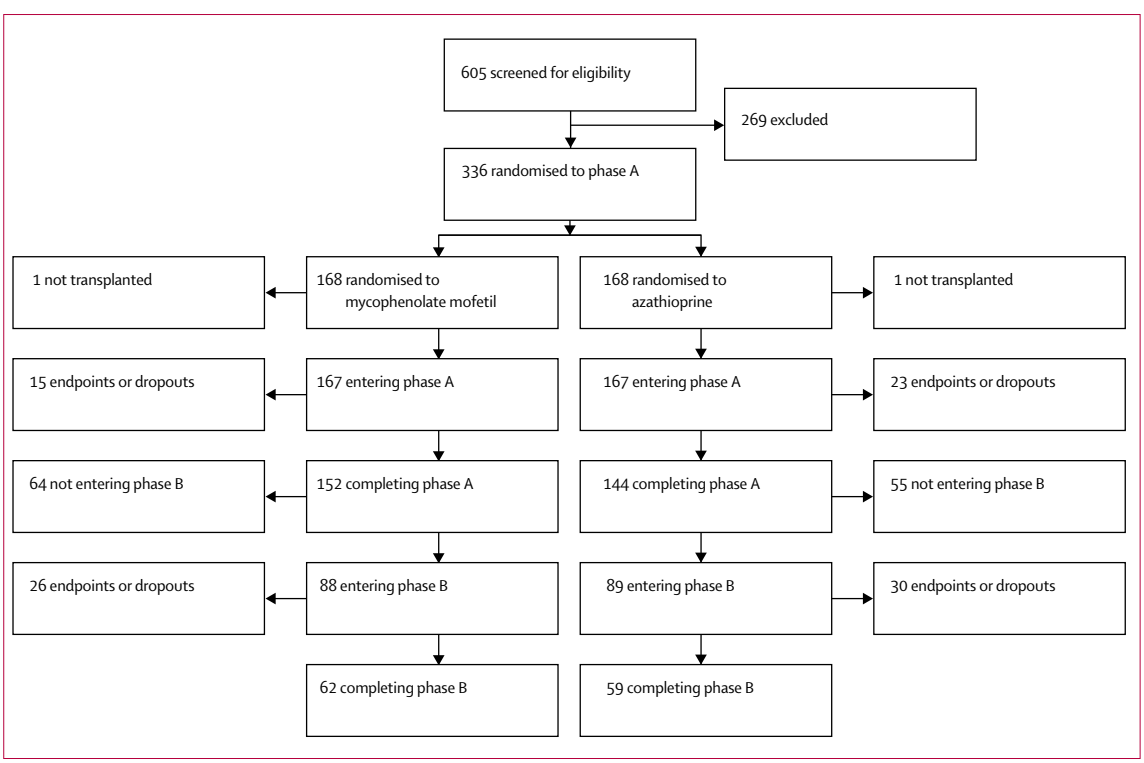

Figure 1: **Trial profile**

	Mycophenolate mofetil (n=168)	Azathioprine (n=168)
Recipients		
Men	119 (71%)	101 (60%)
Age (years)	43·3 (12·9)	45·9 (11·5)
Weight (kg)	67·2 (11·9)	66·2 (11·3)
Primary cause of renal failure		
Diabetes mellitus	0	2 (1%)
Hypertension, renovascular disease	9 (5%)	11 (7%)
Glomerulonephritis	72 (43%)	64 (38%)
Polycystic kidney disease	16 (10%)	18 (11%)
Pyelonephritis/interstitial nephritis	20 (12%)	22 (13%)
Other	11 (7%)	12 (7%)
Uncertain	40 (24%)	38 (23%)
Donors		
Men	96 (57%)	97 (58%)
Age (years)	43·5 (16·6)	43·1 (15·9)
Weight (kg)	70·1 (12·0)	70·9 (11·3)
B-cell crossmatch		
Negative	163 (97%)	162 (96%)
Positive	1 (1%)	1 (1%)
Not done	4 (2%)	5 (3%)
HLA A, B, or Dr mismatches		
0	3 (2%)	6 (4%)
1	42 (25%)	40 (24%)
2	71 (42%)	82 (49%)
3	45 (27%)	33 (20%)
Missing	7 (4%)	7 (4%)

Data are number (%) or mean (SD).

Table 1: **Baseline characteristics of phase A patients**

doses. The dose of intravenous or oral ciclosporin was adjusted to maintain trough blood concentrations within 250–440 μg/L from days 0 to 7, within 200–300 μg/L from days 8 to 28, and within 150–250 μg/L up to study end. The steroid regimen was intravenous methylprednisolone from days 0 to 4 (500 mg on day 0, 200 mg on days 1 and 2, 150 on day 3, and 100 mg on day 4), oral prednisone (75 mg on day 5 and 50 mg on day 6), then oral methylprednisolone (20 mg daily from days 7 to 11, 16 mg daily from days 12 to 60, 12 mg daily from days 61 to 120 and 8 mg daily up to end of phase A). No patient was given induction therapy.

At the completion of phase A, patients entered phase B if they had had no more than two acute rejection episodes and no episodes of steroid-resistant rejection during phase A, had stable serum creatinine concentrations (changes ⩽30% over the last 3 months of phase A), and had a serum creatinine concentration of 177 μmol/L or less and a urinary protein excretion rate less than 1g per 24 h at the end of phase A (figure 1). In these patients, the steroid dose was progressively tapered and discontinued over the next 90 days. From days 181 to 225 after transplantation, oral prednisone was progressively tapered to 8 mg every other day, and from days 226 to 270 the dose was further reduced to 2 mg every other day. The steroid was then discontinued. If an acute rejection episode was diagnosed, oral steroid was renewed at the dose preceding the last reduction (if the patient was in the tapering phase) or at 6 mg every other day (if the patient had already discontinued the medication). The steroid doses were then maintained up to study end. All patients were also maintained on their previous (phase A) dose of mycophenolate mofetil or azathioprine. Oral ciclosporin was adjusted to maintain trough blood concentrations within 150–250 μg/L up to study end.

For all patients, serum creatinine concentration was monitored according to each centre's practice up to discharge and every month until study end. For those entering phase B, serum creatinine was measured weekly during the steroid-tapering protocol and for at least 2 months after steroid discontinuation, every 2 weeks over the next 4 months, and every month up to study end. Concentrations of ciclosporin in blood were measured daily for the first 15 days after transplantation, and every month thereafter. Blood samples were taken just before (trough concentration or C0) and 2 h after (C2) the morning dose of ciclosporin microemulsion. Other routine clinical and laboratory measurements were made monthly as per each centre's practice. Additional assessments were done whenever deemed clinically appropriate.

Acute rejection episodes were diagnosed if three or more of these criteria were present: temperature 38°C or higher without obvious signs of infection; graft swelling; graft tenderness; a rise of 26·5 μmol/L or more in serum creatinine concentration in the presence of low or therapeutic ciclosporin trough concentrations; oliguria; increased resistive index on doppler ultrasonography; and clinical response to steroid treatment consistent with rejection. Kidney biopsy samples were taken whenever appropriate to confirm the diagnosis, and for all steroid-resistant rejection episodes. The treatment of rejection

	Overall	Mycophenolate mofetil	Azathioprine	p
Acute rejection episodes				
Clinical diagnosis	114 (34%)	56 (34%)	58 (35%)	0·91
Biopsy proven	68 (20%)	30 (18%)	38 (23%)	0·34
Steroid resistant	27 (8%)	9 (5%)	18 (11%)	0·11
Refractory*	4 (1%)	2 (1%)	2 (1%)	0·99
Banff score ⩾2	66 (20%)	28 (17%)	38 (23%)	0·22
Adverse events				
Deaths	8 (2%)	4 (2%)	4 (2%)	0·99
Delayed graft function	111 (33%)	52 (31%)	59 (35%)	0·49
White blood-cell count $<3{\cdot}5\times10^9$/L	54 (16%)	32 (19%)	22 (13%)	0·18
Platelet count $<60\times10^9$/L	7 (2%)	2 (1%)	5 (3%)	0·45
Anaemia	22 (7%)	10 (6%)	12 (7%)	0·82
Diarrhoea	4 (1%)	3 (2%)	1 (1%)	0·99
Urinary tract infection	17 (5%)	11 (7%)	6 (4%)	0·32
CMV reactivations	85 (25%)	43 (26%)	42 (25%)	0·99
Ganciclovir-treated	79 (24%)	40 (24%)	39 (23%)	0·99
Pneumocystis carinii pneumonia	1 (1%)	0	1 (1%)	0·99
Systemic candidosis	10 (3%)	4 (2%)	6 (4%)	0·75

CMV=cytomegalovirus. Data are number (%). *Resulting in graft loss despite rescue therapy.

Table 2: **Patients with events on phase A**

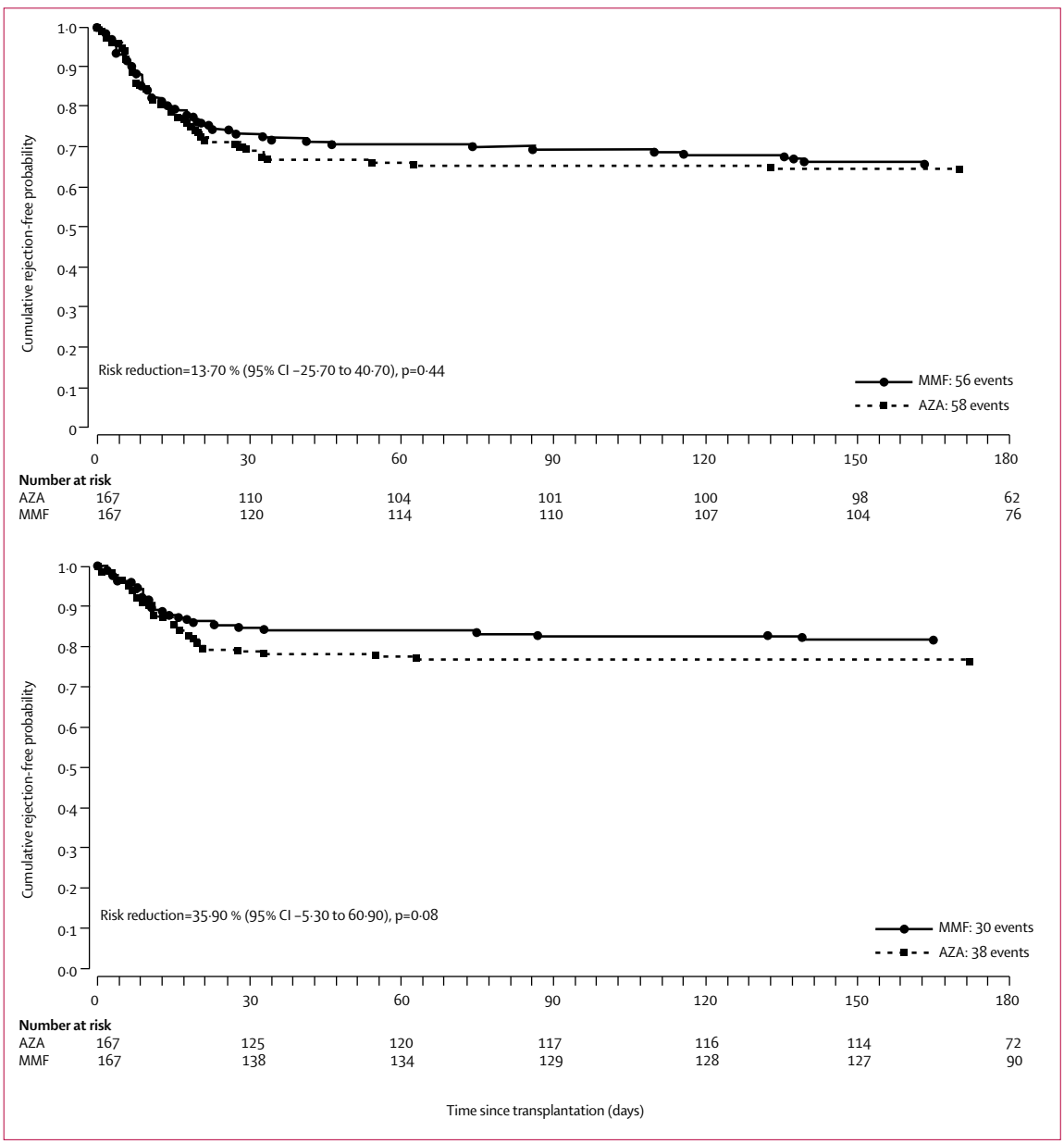

***Figure 2*: Clinically diagnosed (upper) and biopsy-proven (lower) acute rejection episodes during phase A**
MMF=mycophenolate mofetil. AZA=azathioprine.

episodes was initially intravenous pulse steroids (methylprednisolone, 500 mg daily for 3 days, tapered to maintenance dose over 10 days). Biopsy-proven steroid-resistant rejections were treated by intravenous infusion of antilymphocyte immunoglobulins or monoclonal antibodies to CD3 (OKT3) according to each centre's practice.

The MYSS study was designed as a superiority trial according to data available at the time the protocol was finalised.[6] The primary efficacy outcome was occurrence of acute rejection episodes (clinically diagnosed). Sample size was calculated on the basis of the frequency of events expected in the two treatment groups during phase A. On the basis of the results of the Tricontinental Mycophenolate Mofetil Renal Transplantation Study,[6] a 48% frequency of acute rejections was predicted in the control group assigned azathioprine, and a 33% reduction (eg, from 48% to 32%) was expected in the experimental group assigned mycophenolate mofetil. To give the study 80% power to detect a statistically significant ($p<0·05$) reduction, and accounting for a predicted 13% dropout rate, 168 patients per group had to be randomised.

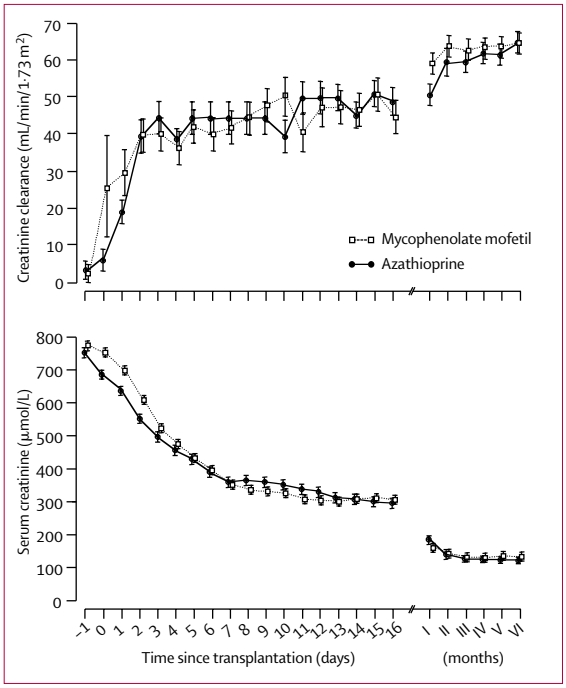

Figure 3: **Creatinine clearance values (upper) and serum creatinine concentrations (lower) at different visits during phase A**
Error bars indicate SE.

Statistical analysis

Primary and secondary endpoints were analysed by intention to treat. Analyses were based on the full analysis set (ie, all patients randomly assigned the study medications), excluding two patients who were randomised but did not undergo transplantation. The hazard ratio for the primary endpoint and its 95% CI was calculated by a Cox's regression model, which included the site as a covariate. The risk reduction was obtained as a percentage equal to: (1–hazard ratio)×100. Survival curves were based on Kaplan-Meier estimates.

Results

336 patients (168 per group) were randomly assigned. Table 1 shows patients' and donors' characteristics at randomisation. Cold ischaemia time was 16·3 h (SD 6·6) in the mycophenolate mofetil group and 16·1 h (7·6) in the azathioprine group. Two patients (one per group) did not receive the transplant for technical reasons. Thus, 334 patients (167 per group) received the study drugs. A similar proportion of patients in both groups (52 [31%] mycophenolate mofetil *vs* 59 [35%] azathioprine, p=0·42) had delayed recovery of renal function and required one or more dialysis sessions in the post-transplantation period. Four of these patients (one assigned mycophenolate mofetil and three assigned azathioprine) did not recover renal function and remained dependent on dialysis.

Phase A

145 rejections were clinically diagnosed in 114 (34%) of the 334 patients entering phase A. 87 had only one episode and 27 two or more. 89 (61%) of the clinically diagnosed rejections were also biopsy proven. The proportion of patients with clinical or biopsy-proven rejection episodes (table 2), time-courses to first acute (clinical or biopsy-proven) rejection (figure 2), mean Banff scores of all biopsy-proven rejections (mycophenolate mofetil 3·23 [SD 0·19], azathioprine 3·63 [0·12], p=0·12), and occurrence of rejections with Banff score of 2 or more (table 2) did not differ significantly. The average doses of mycophenolate mofetil and azathioprine in patients with or without rejections were similar (data not shown).

All rejections were initially treated with intravenous steroids. 87 patients (76%) recovered with steroids, but 27 (24%) needed rescue therapy with intravenous immunoglobulins or OKT3. Four (15%) of the patients with steroid-resistant rejections did not recover despite rescue therapy, and irreversible graft loss resulted. There was a non-significant trend towards fewer steroid-resistant rejections in the mycophenolate mofetil group, but the number of graft losses due to refractory rejection was identical in the two groups (table 2). Serum creatinine concentrations and creatinine clearance at different

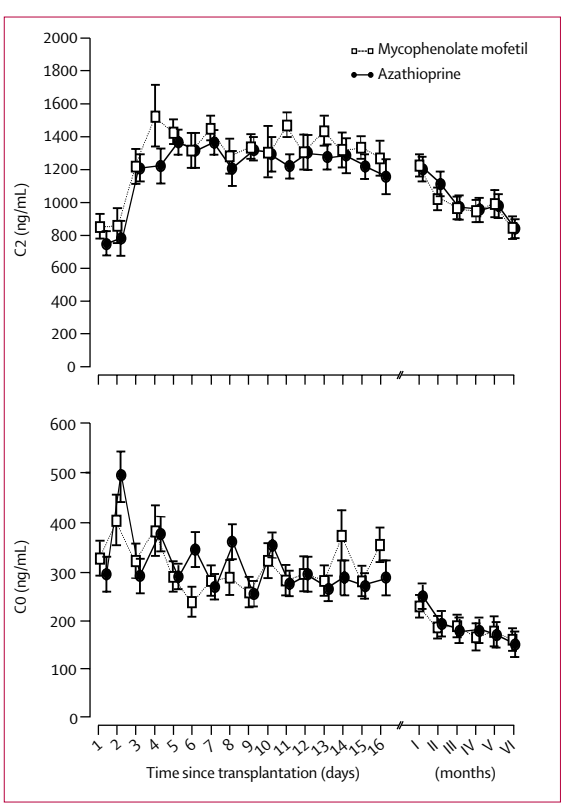

Figure 4: **C2 and C0 concentrations at different visits during phase A**
Error bars indicate SE.

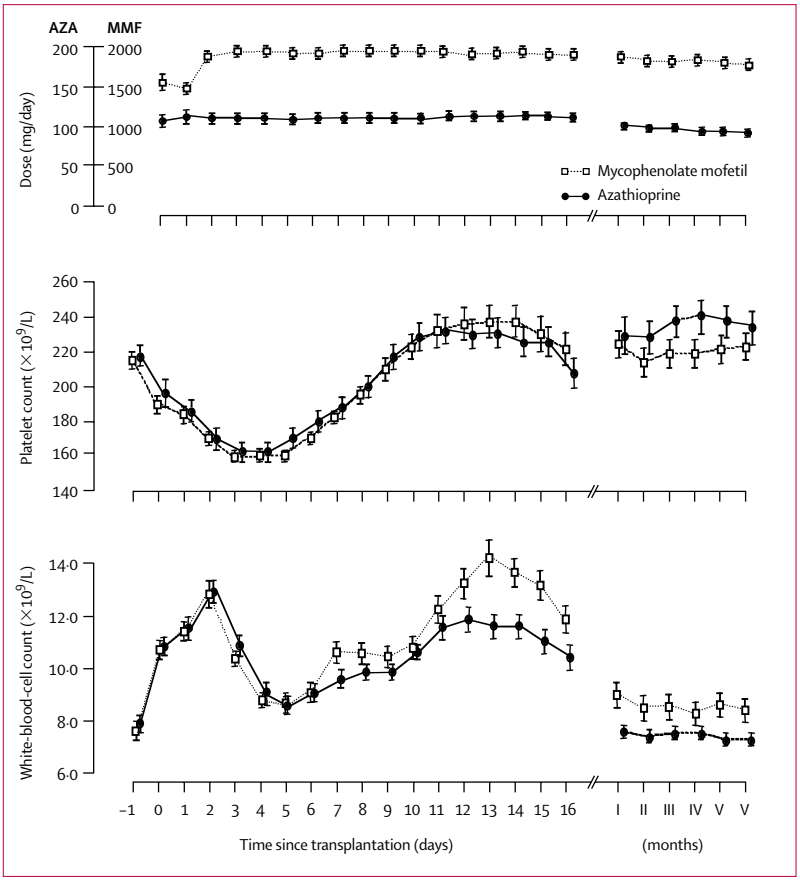

Figure 5: **Doses of study drugs, white blood cell counts, and platelet counts at different visits during phase A**
MMF=mycophenolate mofetil. AZA=azathioprine. Error bars indicate SE.

time points were similar in the two groups (figure 3). C0 and C2 values were also similar in the two groups (figure 4), as were the proportions of patients who had C0 and C2 values in target ranges (data not shown).

Four patients per group died. Overall, the frequency and severity of adverse events were similar in the two groups (table 2). Leucopenia episodes were more frequently reported for the azathioprine group than for the mycophenolate mofetil group (31 [19%] *vs* 13 [8%], p=0·006). However, the cases with white-blood-cell counts less than $3·5\times10^9$/L showed an opposite trend, and the number of patients with at least one white-blood-cell count less than $3·5\times10^9$/L (table 2) was similar in the two groups (22 [13%] *vs* 32 [19%], p=0·18). Thrombocytopenia was very uncommon in both groups (table 2). Average white-blood-cell and platelet counts did not differ between the treatment groups during the early phases of the study. In the long term, however, the white-blood-cell counts were higher for mycophenolate mofetil and the platelet counts were higher for azathioprine (figure 5). Throughout the observation period the average daily doses of the two drugs were more or less constant (figure 5).

	Mycophenolate mofetil (n=88)	Azathioprine (n=89)
Recipients		
Men	61 (69)	55 (62)
Age (years)	41·3 (12·1)	45·5 (11·8)
Weight (kg)	67·0 (12·4)	65·3 (11·6)
Primary cause of renal failure		
Diabetes mellitus	0	1 (1%)
Hypertension, renovascular disease	4 (5%)	6 (7%)
Glomerulonephritis	40 (45%)	36 (40%)
Polycystic kidney disease	7 (8%)	11 (12%)
Pyelonephritis/interstitial nephritis	10 (11%)	12 (14%)
Other	5 (6%)	6 (7%)
Uncertain	22 (25%)	17 (19%)
Donors		
Men	54 (61%)	55 (62%)
Age (years)	40·8 (16·9)	41·3 (16·0)
Weight (kg)	69·0 (11·8)	70·7 (10·5)
B-cell crossmatch		
Negative	88 (100%)	88 (99%)
Positive	0	1 (1%)
Not done	0	0
HLA A, B, or Dr mismatches		
0	1 (1%)	4 (4%)
1	25 (28%)	20 (22%)
2	42 (48%)	46 (52%)
3	20 (23%)	19 (21%)
Missing	0	0

Data are number (%) or mean (SD).

Table 3: **Baseline characteristics of phase B patients**

An identical proportion of patients in the two treatment groups had at least one episode of cytomegalovirus reactivation and received ganciclovir therapy (table 2). The average duration of the episodes (mycophenolate mofetil 21·0 [3·5] days, azathioprine 25·8 [4·9] days, p=0·40) and of ganciclovir therapy (mycophenolate mofetil 21·4 [11·9] days, azathioprine 24·2 [4·6] days, p=0·12) was similar in the two groups.

Phase B

177 (60%) of the 296 patients completing phase A entered phase B of the trial (figure 1 and table 3). Cold ischaemia time was similiar in those assigned mycophenolate mofetil (16·0 h [6·5]) and those assigned azathioprine (15·1 h [6·7]). Of the remaining 119 patients, 67 (56%) did not enter phase B (35 of mycophenolate mofetil and 32 of azathioprine groups) because they did not satisfy the inclusion criteria. The remaining 52 (44%) were not included because of safety concerns (eight and six), consent withdrawal, or non-compliance (nine and three), protocol violations (four and four), need for medications prohibited by the study protocol (three and four), adverse events (three and two), or for other practical reasons (two and four).

25 (14%) of the 177 patients entering phase B had one clinical diagnosis of acute rejection. In 12 (7%) of the patients the rejections were biopsy proven. The frequency of clinical rejections and of biopsy-proven rejections (table 4), time courses to first (clinical or

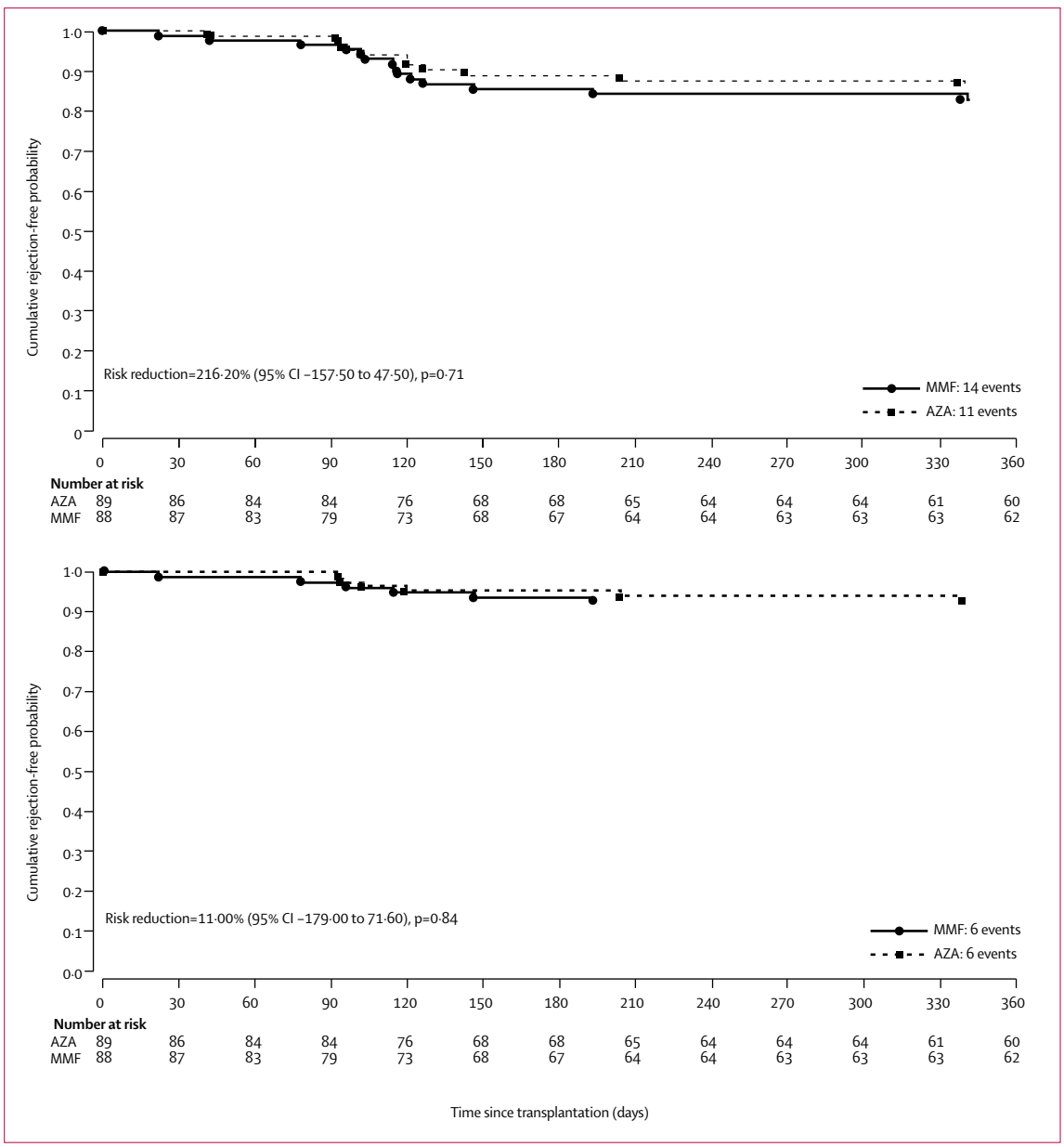

Figure 6: **Clinically diagnosed (upper) and biopsy-proven (lower) acute rejection episodes during phase B**
MMF=mycophenolate mofetil. AZA=azathioprine.

biopsy-proven) rejection (figure 6), mean Banff scores of all biopsy proven-rejections (mycophenolate mofetil 3·00 [SD 1·41], azathioprine 3·00 [0·89], p=0·99), and frequency of rejections with a Banff score of 2 or more did not differ significantly between the two groups (table 4).

All rejections were initially treated with intravenous steroids. 24 (96%) rejection episodes recovered with steroids. One (4%) steroid-resistant rejection arose in the mycophenolate mofetil group and resulted in irreversible graft loss despite rescue therapy. Serum creatinine concentrations were similar in the two groups up to study end (table 5), as were creatinine clearance and C0 and C2 values (data not shown).

No patient died during phase B. The overall frequency and severity of adverse events were similar in the two groups. However, more patients in the azathioprine group had at least one episode of leucopenia (white-blood-cell count <3·5×109/L) after steroid withdrawal (table 4). No patient had severe thrombocytopenia or anaemia. 11 (6%) had at least one opportunistic infection. Eight cytomegalovirus reactivations (four mycophenolate mofetil and four azathioprine) arose in seven patients (four mycophenolate mofetil and three

	Overall	Mycophenolate mofetil	Azathioprine	p
Acute rejection episodes				
Clinical diagnosis	25 (14%)	14 (16%)	11 (12%)	0·64
Biopsy proven	12 (7%)	6 (7%)	6 (7%)	0·78
Steroid resistant	1 (1%)	1 (1%)	0	0·49
Refractory*	1 (1%)	1 (1%)	0	0·49
Banff score ⩾2	11 (6%)	5 (6%)	6 (7%)	0·98
Adverse events				
White blood-cell count <3·5×10⁹/L	38 (21%)	13 (15%)	25 (28%)	0·05
Diarrhoea	1 (1%)	1 (1%)	0	0·49
Urinary-tract infection	1 (1%)	0	1 (1%)	0·99
CMV reactivations	7 (4%)	4 (5%)	3 (3%)	0·62
Ganciclovir-treated	3 (2%)	2 (2%)	1 (1%)	0·62
Systemic mycosis	1 (1%)	0	1 (1%)	0·99

CMV=cytomegalovirus. Data are number (%). *Resulting in graft loss despite rescue therapy.

Table 4: **Patients with events on phase B**

azathioprine). Three of these patients received ganciclovir treatment (table 4). The two groups had similar mean durations of episodes (mycophenolate mofetil 131·7 [SD 232·2], median 18·0 days, azathioprine 43·5 [18·3], median 27·5 days, p=0·48) and of ganciclovir therapy (mycophenolate mofetil 17·5 [3·5] days, azathioprine 26·5 [12·0] days, p=0·42).

Estimated costs of treatment

Mean (SD) daily doses of mycophenolate mofetil and azathioprine were 1893 (188) mg and 106 (22) mg for phase A, and 1760 (410) mg and 89 (24) mg for phase B, respectively. The cost of 1 mg mycophenolate mofetil and azathioprine is €0·0081 and €0·0103, respectively. Thus, the estimated costs of 1 day of mycophenolate mofetil versus azathioprine treatment were €15·3 versus €1·1 and €14·3 versus €0·92 during phase A and phase B, respectively.

In phase A there were 163 patients in the mycophenolate mofetil group and 163 in the azathioprine group with available information. Their mean treatment duration was 173 (34) days and 167 (45) days, respectively. Thus, the average costs for mycophenolate mofetil versus azathioprine treatment for phase A patients were €2665 (586) versus €184 (62) (p<0·0001). Overall treatment costs were €434 368 for the mycophenolate mofetil group and €30 053 for the azathioprine group.

	Mycophenolate mofetil	Azathioprine	p
Time since transplantation (weeks)			
25	121·1 (33·6)	118·5 (30·9)	0·66
44	129·1 (34·5)	122·9 (38·0)	0·32
64	122·9 (28·3)	119·3 (30·1)	0·53
84	125·5 (30·1)	121·1 (33·6)	0·54

Data are mean (SD).

Table 5: **Serum creatinine concentration (μmol/L) in patients throughout phase B**

In phase B there were 88 patients in the mycophenolate mofetil group and 89 in the azathioprine group with available information. Their average treatment duration was 351 (157) days and 347 (153) days, respectively. Thus, for phase B patients the average costs for mycophenolate mofetil were €5095 (2658) versus €322 (170) for azathioprine treatment (p<0·0001). The overall treatment costs were €448 416 for the mycophenolate mofetil group and €27 716 for the azathioprine group. The overall estimated costs for the whole study period (phase A plus phase B) were €882 784 for the mycophenolate mofetil group and €57 770 for the azathioprine group.

Discussion

Mycophenolate mofetil was no better than azathioprine in limiting acute rejection episodes. Graft losses due to refractory rejections and adverse events did not differ between the treatment groups. These findings suggest that mycophenolate mofetil does not have a better risk-benefit profile than azathioprine, even in the setting of a dual immunosuppressive regimen that does not include oral steroids. Of note, there were fewer acute rejections in our controls than in controls from similar studies that compared the same two drugs in the context of conventional immunosuppressive regimens.[5,6,13,20,21] By contrast, the occurrence of acute rejections in the mycophenolate mofetil group was similar in the present and previous series.[5,6]

In previous studies comparing mycophenolate mofetil and azathioprine in a regimen including ciclosporin Sandimmune, average trough ciclosporin concentrations at different times after transplantation were not given.[5,6] In our protocol, we used a well defined scheme for ciclosporin dosing that was targeted to trough blood concentrations of this drug.[24] This scheme was based on the results of a logistic regression model generated to predict the trough concentrations associated with low occurence of rejection and negligible toxicity.[24] Most patients in the MYSS study had trough ciclosporin concentrations within the target range (330–430 μg/L) soon after transplantation, and these patients had fewer rejections.[25] Thus, the achievement of target concentrations in most patients could explain the low frequency of rejection in our series, particularly for controls assigned azathioprine treatment. Our present results, however, do not exclude the possibility that mycophenolate mofetil provides better antirejection activity in those patients whose target ciclosporin concentrations are not achieved, at least over the first days post-transplantation.

An additional important finding of our study was that both drugs were equally well tolerated, with similar occurrences of cytomegalovirus reactivation in the two treatment groups. In particular, although leucopenia was more common in the azathioprine group, there was no objective evidence of more bone-marrow

toxicity for azathioprine than for mycophenolate mofetil.

These findings challenge the current practice of most transplant centres to regard mycophenolate mofetil as a key component of immunosuppressive drug regimens based on ciclosporin microemulsion. Since the costs for standard treatment with mycophenolate mofetil exceed those for azathioprine by 15 times (€5416 *vs* €354 per patient during both phase A and B), if azathioprione were used instead of mycophenolate mofetil, more then €4000 per patient per year could be saved. With a population of 14 888 renal transplant patients in Europe and 12 630 in the USA in 2002 (Council of Europe, International data on organ donation, transplantation and waiting list, 2002), and treatment costs for the two drugs similar to those we have calculated, use of azathioprione rather than mycophenolate mofetil should give a net yearly saving of about €75 million in Europe and US$77 million in the USA.

Whether, as suggested,[26] mycophenolate mofetil might have a role in reducing late allograft loss independently of its effect on acute rejection remains to be proved. In view of the cost, standard immunosuppression regimens for transplantation should perhaps include azathioprine rather than mycophenolate mofetil, at least for kidney grafts.

Contributors

G Remuzzi, N Perico, and P Ruggenenti participated in all stages of the study, data interpretation, and preparation of the report. S Sandrini, G Segoloni, and U Valente contributed to study design and organisation, and to recruitment and management of patients. E Gotti, D Donati, M Salvadori, G Mourad, S Federico, P Rigotti, V Sparacino, and J-L Bosmans contributed to recruitment and management of patients. M Lesti and G Gherardi monitored all phases of the study. M Ganeva and B Dimitrov did statistical analyses. B Ene-Iordache prepared the database and contributed to data management. All authors critically revised the first draft and approved the final report.

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Conflict of interest statement

None declared.

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