Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection

*European Mycophenolate Mofetil Cooperative Study Group**

Summary

Preliminary studies suggested that mycophenolate mofetil (MMF), which inhibits proliferation of T and B cells, may reduce the frequency of acute rejection after renal transplantation. Our randomised, double-blind, multicentre, placebo-controlled study compared the efficacy and safety of MMF with placebo for prevention of acute rejection episodes after first or second cadaveric renal allograft transplantation.

491 patients were enrolled; 166 were assigned placebo, 165 MMF 2 g, and 160 MMF 3 g. Patients also received cyclosporin and corticosteroids. Significantly fewer ($p \leq 0.001$) patients had biopsy-proven rejection or withdrew early from the trial (for any reason) during the first 6 months after transplantation with MMF 2 g (30·3%) or 3 g (38·8%) than with placebo (56·0%). The corresponding percentages for biopsy-proven rejection were 17·0%, 13·8%, and 46·4%. 28·5% of MMF 2 g and 24·4% of MMF 3 g patients needed full courses of corticosteroids or antilymphocyte agents for treatment of rejection episodes in the first 6 months, compared with 51·8% of placebo recipients. By 6 months, 10·2%, 6·7%, and 8·8% of the patients in the placebo, MMF 2 g, and MMF 3 g groups, respectively, had died or lost the graft. Overall, the frequency of adverse events was similar in all treatment groups, although gastrointestinal problems, leucopenia, and opportunistic infections were more common in the MMF groups and there was a trend for more events in the 3 g than the 2 g group.

MMF significantly reduced the rate of biopsy-proven rejection or other treatment failure during the first 6 months after transplantation and was well tolerated. The 3 g dose was somewhat less well tolerated.

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Introduction

Acute allograft rejection remains an important clinical problem in renal transplantation. It occurs in up to 60% of recipients, and most first episodes occur within 3 months of transplantation.[1-3] The frequency of acute rejection during the first 6 months after transplantation may directly reflect the efficacy of the prophylactic immunosuppressive regimen used, and is associated with lower 1-year, and possibly long-term, graft survival.[1-7]

Mycophenolate mofetil (MMF), the morpholinoethyl ester of mycophenolic acid, has been developed as an immunosuppressant for prevention of rejection in renal transplantation. In vivo, MMF is de-esterified to mycophenolic acid (the active immunosuppressive component), which is a potent and specific inhibitor of the synthesis of guanosine nucleotides, and thus a selective suppressor of proliferation of both T and B lymphocytes. MMF, given alone or with corticosteroids or cyclosporin, lowers the frequency of acute rejection after allogeneic organ transplantation in animals.[8-12] Open-label clinical studies suggested that MMF as adjunctive therapy to cyclosporin and corticosteroids was effective for prevention of acute renal allograft rejection at doses of 2 g and 3 g per day.[13-16]

This European, multicentre, double-blind, and placebo-controlled study of 1 year's duration was carried out to establish the efficacy of MMF as an immunosuppressive agent, when given with cyclosporin and corticosteroids. We compared the efficacy and safety of two oral doses of MMF with placebo for prevention of acute rejection episodes during the first 6 months of transplantation.

Patients and methods

Eligible patients were male or female recipients of first or second cadaveric renal allografts, aged 18 years or older, and able to take oral medication within 72 h of the operation, who would be given dual immunosuppressive therapy with cyclosporin and corticosteroids. Randomisation to the three study groups was done before or shortly after renal transplantation and was stratified by first or second transplant. Daily doses of cyclosporin and corticosteroids were standardised according to the individual hospital protocol; cyclosporin blood concentrations were used to determine and adjust the dose. Azathioprine use was prohibited. At the analysis of the primary efficacy endpoint, evaluated 6 months after transplantation, the study was continuing.

The protocol excluded from the study patients with a history of malignant disorders, serological evidence of HIV or HBsAg, systemic infections that required therapy at the time of entry, severe diarrhoea, gastrointestinal disorders, active peptic ulcer disease, or inadequate contraceptive measures, and pregnant and lactating women.

Formal approval from the ethics committees of the individual centres and written informed consent according to the institutional guidelines were obtained for each patient enrolled. The study was carried out according to the Declaration of Helsinki.

Enrolled patients were equally and randomly assigned within the centres to one of three treatment groups—placebo, MMF 2 g (1 g twice daily), or MMF 3 g (1·5 g twice daily). The dose of cyclosporin was adjusted to maintain a stable whole-blood concentration in the target range as established at each centre. The protocol called for the initial daily dose to range between 5 and 15 mg/kg daily. The corticosteroid dose was also dictated by the routine practice of each participating centre.

*Participants listed at end of paper

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	Placebo (n=166)	MMF 2 g (n=165)	MMF 3 g (n=160)	p*
Mean (range) age in years	45·7 (19–73)	46·6 (18–71)	46·6 (19–72)	0·297/0·279
Sex				
Male	102 (61%)	92 (56%)	110 (69%)	0·049
Female	64 (39%)	73 (44%)	50 (31%)	
Mean (range) weight in kg†	67·6 (44–113)	68·1 (38–107)	70·1 (40–107)	0·229/0·994
Primary cause of renal failure				
Glomerulonephritis	78 (47%)	78 (47%)	49 (31%)	
Pyelonephritis/interstitial nephritis	25 (15%)	21 (13%)	20 (13%)	
Polycystic kidney disease	17 (10%)	19 (12%)	33 (21%)	
Diabetes mellitus	9 (5%)	8 (5%)	9 (6%)	
Hypertension	6 (4%)	11 (7%)	11 (7%)	
Renal vascular disease	4 (2%)	1 (1%)	1 (1%)	
Other	27 (16%)	27 (16%)	37 (23%)	
Renal transplant				
First	151 (91%)	149 (90%)	148 (93%)	0·733
Second	15 (9%)	16 (10%)	12 (7%)	
Blood transfusions				
Yes	68 (41%)	59 (36%)	57 (36%)	
No	98 (59%)	106 (64%)	103 (64%)	
Mean (range) donor age in years†	41·1 (4–73)	40·6 (1–77)	41·2 (7–74)	0·676/0·120
HLA A+B+DR mismatch†				
0	10 (6%)	13 (8%)	16 (10%)	0·782
1–2	58 (35%)	58 (36%)	50 (32%)	
3–4	82 (50%)	71 (44%)	79 (50%)	
5–6	14 (9%)	20 (12%)	13 (8%)	
Last PRA measurement (%)†				
0	116 (76%)	124 (82%)	115 (77%)	0·925
1–19	23 (15%)	18 (12%)	23 (15%)	
>20	13 (9%)	9 (6%)	11 (7%)	
Donor/recipient CMV serological status (%)†				
Positive/negative	36 (24%)	30 (20%)	33 (23%)	0·825
Positive/positive	63 (43%)	59 (39%)	62 (43%)	
Negative/negative	25 (17%)	37 (24%)	26 (18%)	
Negative/positive	24 (16%)	26 (17%)	24 (17%)	
Mean (range) cold ischaemia time in hours†	20·9 (5·1–44·4)	22·8 (8·0–40·0)	21·3 (4·0–40·3)	0·133/0·777

PRA=panel-reactive antibodies, CMV=cytomegalovirus. *Single values=Cochran-Mantel-Haenszel general association χ^2 stratified by investigator; two values=two-factor ANOVA with effects for treatment, investigator, and treatment-by-investigator interaction. †Data not available for all patients.

Table 1: **Baseline characteristics of allograft recipients**

In the protocol, first-line treatment for acute rejection was high-dose, intravenous corticosteroids. Rejection episodes resistant to this treatment were to be treated with monoclonal (OKT3) or polyclonal antilymphocyte agents (antithymocyte or antilymphocyte globulin). A full course of antirejection therapy was defined as at least 3 days of corticosteroids and a total cumulative dose of more than 600 mg (not concomitantly administered with antilymphocyte agents) or at least one dose of antilymphocyte agent.

The primary efficacy variable was the proportion of patients who experienced at least one episode of biopsy-proven allograft rejection or treatment failure (defined as premature withdrawal from the study for any reason) during the first 6 months of treatment. Since several patients had acute rejection episodes and were also withdrawn from the study because of adverse events, unsatisfactory therapeutic responses, or other reasons, the patients were classified according to the first event that occurred. Because we had to standardise the diagnosis of acute rejection across all 20 centres, initial clinical or biochemical evidence of acute rejection had to be confirmed by a core renal biopsy, unless it was clinically contraindicated or logistically impossible. Pathologists at the individual centres were asked to use uniform criteria to assess renal biopsy material. A classification of kidney transplant pathology[17] was made part of the protocol and used to confirm the diagnosis of acute allograft rejection. If no biopsy was done, the presumptive diagnosis of rejection was based on clinical and laboratory criteria, in particular an otherwise unexplained rise in serum creatinine.

Secondary efficacy variables were the percentage of patients with presumed rejection (treatment with corticosteroids or antilymphocyte agents without biopsy confirmation), the proportion of patients requiring full courses of antirejection therapy, renal function (assessed by serum creatinine), and graft loss.

The safety assessment focused on spontaneously reported adverse events and laboratory investigations. All adverse events, opportunistic and other infections, irrespective of intensity of reaction or relation to study medication, were recorded. We distinguished between infections that can be regarded as opportunistic infections and more conventional infections.

The overall power available for a comparison at significance of 0·05 of an acute rejection rate of 15% or better with a rate of 30% or worse is 80% for 160 patients per treatment group. This estimate incorporates a Bonferroni adjustment of the significance level, assuming a comparison of each MMF dose with the standard.[18]

The primary efficacy analyses were intention-to-treat (biopsy proven and presumed rejection). Other efficacy summaries included only patients who received study medication. All patients who received at least one dose of study medication were included in the safety summaries. All efficacy analyses and summaries were based on the first 6 months of the study. Safety summaries included all data available at the time that the last patient in the study completed 6 months of treatment (time of data cut-off).

Possible prognostic factors were identified and tested for imbalances across treatment groups. The Cochran-Mantel-Haenszel row mean score stratified by centre was applied to ordered categorical data and the general association test to binary data and unordered categorical data. Two-factor ANOVA models with factors for treatment, centre, and centre-by-treatment interaction were applied to continuous data. Tests of interaction were assessed at significance of p=0·10.

The primary efficacy endpoint of biopsy-proven rejection (acute rejection, grades I–III[17]) or treatment failure were analysed by the Cochran-Mantel-Haenszel general association test, stratified by investigator. Two pairwise comparisons (each MMF

dose compared with placebo) were done and statistical significance was assessed with the Bonferroni adjustment for two comparisons at significance of 0·025. The analysis of presumed rejection (at least one full course of treatment for rejection), biopsy-proven rejection, or treatment failure was done in a similar way. Time to first biopsy-proven rejection or treatment failure was calculated as the time to the event (in days) from the date of transplant (day 1) and summarised by the Kaplan-Meier product limit estimator. Time to graft loss or patient death was also summarised in this way.

Results

Between July, 1992, and August, 1993, 491 patients (304 men, 187 women, aged 18–73 years) were enrolled in the study. 448 were recipients of a first renal allograft and 43 had received a second renal cadaveric transplant. 166 patients were assigned placebo, 165 MMF 2 g, and 160 MMF 3 g daily.

The mean ages and mean weights of the patients in the three treatment groups were similar (table 1). There were more male (62%) than female patients (38%), reflecting the distribution of end-stage renal disease in the population. The proportions of male and female patients differed among the three treatment groups (p=0·049). There was no imbalance between the treatment groups as regards cause of end-stage renal disease, previous renal transplant, blood transfusions, mean donor age, HLA A, B, and DR mismatches, latest measurement of panel-reactive antibodies, donor/recipient cytomegalovirus serostatus, or cold ischaemia time.

151 (30·8%) patients withdrew from the study (58 [34·9%] placebo, 37 [22·4%] MMF 2 g, 56 [35·0%] MMF 3 g). The proportion of patients with adverse events causing premature withdrawal was higher in the two MMF groups than in the placebo group (17·6% MMF 2 g, 25·6% MMF 3 g, 13·9% placebo). Conversely, the proportion of patients who withdrew prematurely because of unsatisfactory therapeutic response was higher in the placebo group (13·3%) than in the groups receiving MMF 2 g (1·8%) or 3 g (3·1%).

	Placebo	MMF 2 g	MMF 3 g
Biopsy-proven rejection, graft loss or death, or other treatment failure	93 (56·0%)	50 (30·3%)*	62 (38·8%)*
Biopsy-proven rejection	77 (46·4%)	28 (17·0%)	22 (13·8%)
Grade I	29/77 (37·7%)	12/28 (42·9%)	14/22 (63·6%)
Grade II	39/77 (50·6%)	12/28 (42·9%)	7/22 (31·8%)
Grade III	9/77 (11·7%)	4/28 (14·3%)	1/22 (4·5%)
Other treatment failure	16 (9·6%)	22 (13·3%)	40 (25·0%)
Graft loss/death	4 (2·4%)	3 (1·8%)	4 (2·5%)
Unsatisfactory therapeutic response	0	0	1 (0·6%)
Adverse event	6 (3·6%)	14 (8·5%)	29 (18·1%)
Non-compliance	3 (1·8%)	3 (1·8%)	5 (3·1%)
Other remaining reasons	3 (1·8	2 (1·2%)	1 (0·6%)
Presumed or biopsy-proven rejection or treatment failure	104 (62·7%)	68 (41·2%)*	72 (45·0%)*
Presumed or biopsy-proven rejection	91 (54·8%)	50 (30·3%)	42 (26·3%)
Other treatment failure	13 (7·8%)	18 (10·9%)	30 (18·8%)
Graft loss/death†	2 (1·2%)	2 (1·2%)	3 (1·9%)
Unsatisfactory therapeutic response	0	0	0
Adverse event	5 (3·0%)	12 (7·3%)	22 (13·8%)
Non-compliance	3 (1·8%)	2 (1·2%)	4 (2·5%)
All remaining reasons	3 (1·8%)	2 (1·2%)	1 (0·6%)
All graft loss or death‡	17 (10·2%)	11 (6·7%)	14 (8·8%)
All graft losses	15 (9·0%)	7 (4·3%)	10 (6·3%)
Deaths with functioning kidney	2 (1·2%)	4 (2·4%)	4 (2·5%)

*p≤0·001 for difference from placebo. †On study; graft loss or death as cause of treatment failure (without previous presumed or biopsy-proven rejection).
‡On study drug and after end of study.

Table 2: **Biopsy-proven rejection, treatment failure, graft and patient survival by 6 months**

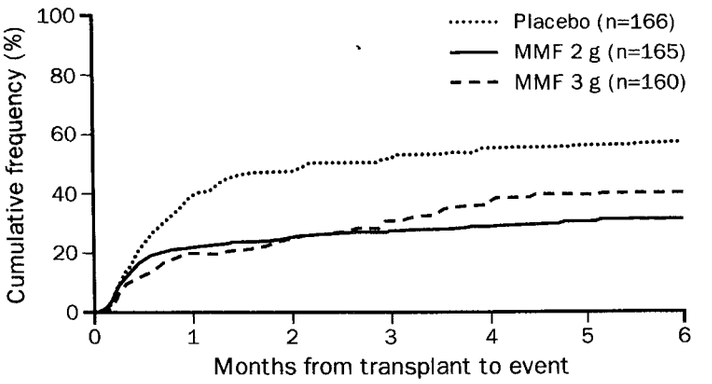

Figure: **Cumulative frequency of first biopsy-proven rejection or treatment failure during months 0–6**

Efficacy analysis

Significantly more patients from the placebo group than from either MMF group had biopsy-proven rejection or withdrew prematurely from the study (primary efficacy endpoint; table 2). The addition of MMF to cyclosporin and corticosteroids was associated with a 60–70% reduction in the frequency of acute rejection episodes. The main causes of treatment failures without biopsy-proven rejection were graft loss or death, unsatisfactory therapeutic response, adverse events and non-compliance.

The two pairwise comparisons for the primary efficacy endpoint showed that the placebo group had a significantly higher proportion of patients with biopsy-proven rejections or treatment failures than either of the MMF treatment groups (p≤0·001, table 2). Compared with placebo, MMF treatment reduced the risk of biopsy-proven rejection or treatment failure (relative risk 0·535 [97·5% CI 0·399–0·718] for MMF 2 g; 0·658 [0·494–0·875] for MMF 3 g).

Patients were classified as having presumed rejection if they received a full course of antirejection therapy without a confirmatory core renal biopsy. Secondary analyses of presumed and biopsy-proven rejection and treatment failure confirmed the results of the primary efficacy analysis with identical pairwise comparisons and p values. Similar outcomes were observed for the primary efficacy endpoint and frequency of acute rejection for first and second renal transplants.

Because of the sex imbalance at baseline we did an analysis of the primary efficacy variable by sex. The percentage of biopsy-proven rejections or treatment failures in both men and women was similar to that for the whole population. The two pairwise comparisons of MMF with placebo confirmed the overall conclusions and showed similar results for male and female transplant recipients.

Kaplan-Meier estimates for the primary efficacy endpoint (figure) show the time to biopsy-proven rejection or treatment failure during the first 6 months in the study. There was a significant difference between the placebo group and the two MMF treatment groups (p<0·001 and p=0·001 for MMF 2 g and 3 g, respectively). The two MMF treatment groups had similar results up to 10 weeks after transplantation. After month 3 the MMF 3 g group had the higher cumulative percentage of biopsy-proven rejection or treatment failure.

	Number (%) of patients		
	Placebo	MMF 2 g	MMF 3 g
One or more full courses	86 (51·8%)	47 (28·5%)	39 (24·4%)
Corticosteroids only	51 (30·7%)	38 (23·0%)	34 (21·3%)
Corticosteroids and antilymphocyte agents	31 (18·7%)	5 (3·0%)	4 (2·5%)
Antilymphocyte agents only	4 (2·4%)	4 (2·4%)	1 (0·6%)

Table 3: **Full courses of immunosuppressive therapy for rejections during first 6 months of study**

86 patients in the placebo group, 47 in MMF 2 g, and 39 in MMF 3 g received at least one full course of immunosuppressive treatment for rejection (table 3). The numbers of patients who were given one or more courses of antilymphocyte preparations (with or without corticosteroids) were substantially lower in the MMF treatment groups than in the placebo group.

The average serum creatinine concentration was lower in the MMF groups than in the placebo group at 1, 3, and 6 months after transplantation (table 4). This analysis was subject to survivor bias, since at 6 months more patients had been withdrawn after rejection (unsatisfactory therapeutic response) from the placebo group than from the two MMF groups. The percentage of patients who needed dialysis during the first postoperative week (study definition for delayed graft function) was lower in the MMF 3 g group (20·6%) than in the placebo (24·8%) or MMF 2 g (27·4%) groups. This difference was not thought to have influenced the outcome of the primary efficacy endpoint, nor to be related to use of MMF.

By 6 months after transplantation, 17 patients in the placebo group, 11 in the MMF 2 g group, and 14 in the MMF 3 g group had lost the graft or died (table 2). The reasons for graft loss were rejection (10 placebo patients, 2 MMF 2 g, 5 MMF 3 g), technical complications (0, 2, 1), recurrence of underlying disease (1 MMF 3 g patient), and other reasons (5, 3, 3). A further 10 patients died with functioning kidneys (2 placebo patients, 4 MMF 2 g, 4 MMF 3 g).

15 patients had died by 6 months after transplantation. 6 patients in the placebo group died (2 cardiovascular events, 3 infection/sepsis, 1 intra-abdominal bleeding). The 4 deaths in the MMF 2 g group were due to a cardiovascular event (1), infection/sepsis (2), and multiple organ failure (1). In the MMF 3 g group (5 deaths), the causes of death were cardiovascular events (2), infection/sepsis (2), and haemorrhagic pancreatitis (1).

Safety analysis

In the placebo group, 23 (13·9%) patients experienced adverse events that resulted in premature discontinuation of study drug compared with 29 (17·6%) in the MMF 2 g group and 41 (25·6%) in the MMF 3 g group. Gastrointestinal adverse events (table 5) were more common in the MMF groups. Gastrointestinal haemorrhage, large-bowel perforation, and pancreatitis were seen in the MMF groups only, but total numbers were small. Leucopenia and anaemia (table 5) were reported in larger proportions of the MMF treatment groups than of the placebo group. 3 patients (all MMF 2 g group) developed pancytopenia and 2 others (MMF 3 g group) developed agranulocytosis. The observed haematological adverse events resolved within about a week. Laboratory data revealed a slightly different pattern: although there was only a small difference between the groups in the frequency of anaemia or thrombocytopenia, the proportion of patients with leucopenia between 31 and 180 days after transplantation was three times higher in the MMF groups.

	Placebo	MMF 2 g	MMF 3 g	p*
1 month				
n	154	149	149	
Creatinine (μmol/L)	216 (11)	165 (12)	187 (12)	0·0106/0·2418
3 months				
n	130	139	124	
Creatinine (μmol/L)	158 (5)	131 (5)	136 (5)	0·0006/0·5265
6 months				
n	114	126	108	
Creatinine (μmol/L)	142 (4)	126 (4)	130 (4)	0·0284/0·0392

*Two-factor ANOVA with effects for treatment and treatment-by-investigator interaction.

Table 4: **Mean (SD) serum creatinine after transplantation**

	Placebo (n=166)	MMF 2 g (n=165)	MMF 3 g (n=160)
Gastrointestinal			
Diarrhoea	21 (12·7%)	21 (12 7%)	25 (15·6%)
Abdominal pain	18 (10·8%)	19 (11·5%)	18 (11·3%)
Dyspepsia	9 (5·4%)	5 (3·0%)	8 (5·0%)
Nausea	4 (2·4%)	7 (4·2%)	10 (6·3%)
Gastroenteritis	2 (1·2%)	4 (2·4%)	7 (4·4%)
Vomiting	2 (1·2%)	4 (2·4%)	6 (3·8%)
Stomach ulcer	3 (1·8%)	2 (1·2%)	2 (1·3%)
Duodenal ulcer	1 (0·6%)	2 (1·2%)	1 (0·6%)
Gastrointesinal haemorrhage	0	0	2 (1·3%)
Rectal haemorrhage	0	1 (0·6%)	1 (0·6%)
Duodenal ulcer haemorrhage	0	1 (0·6%)	0
Haemorrhagic pancreatitis and gastritis	0	0	1 (0·6%)
Large-intestine perforation	0	2 (1·2%)	2 (1·3%)
Total	69 (41·6%)	75 (45·5%)	84 (52·5%)
Haematological/lymphatic			
Leucopenia	7 (4·2%)	18 (10·9%)	22 (13·8%)
Anaemia	3 (1·8%)	7 (4·2%)	11 (6·8%)
Thrombocytopenia	8 (4·8%)	7 (4·2%)	5 (3·1%)
Pancytopenia	0	3 (1·8%)	0
Agranulocytosis	0	0	2 (1·3%)
Other	8 (4·8%)	17 (10·3%)	8 (5·0%)
Total with ≥1 event	22 (13·3%)	42 (25·5%)	38 (23 8%)
Opportunistic infections			
CMV viraemia/syndrome	22 (13·3%)	26 (15·8%)	24 (15·0%)
CMV tissue-invasive disease	4 (2·4%)	5 (3·0%)	11 (6·9%)
Herpes simplex	10 (6·0%)	24 (14·5%)	18 (11·3%)
Herpes zoster	3 (1·8%)	11 (6·7%)	8 (5·0%)
Candida	13 (7·8%)	16 (9·7%)	9 (5·6%)
Pneumocystis carinii pneumonia	4 (2·4%)	0	0
Aspergillus/mucor	1 (0·6%)	0	0
Total with ≥1 infections	46 (27·7%)	63 (38·2%)	55 (34·4%)

CMV=cytomegalovirus.

Table 5: **Adverse events and opportunistic infections**

Opportunistic infections were slightly more common in the MMF groups than the placebo group. Although the proportions with cytomegalovirus viraemia/syndrome were similar in all three groups, cytomegalovirus tissue-invasive disease was diagnosed in a higher percentage of patients in the MMF 3 g group (table 5). The proportions of patients with herpes zoster or simplex were higher in the MMF treatment groups. *Pneumocystis carinii* pneumonia and aspergillus infections occurred only in the placebo group.

3 patients (2 placebo group, 1 MMF 2 g group) developed malignant disorders during the observation period. 1 of the placebo patients was found to have a hypogastric liposarcoma during renal transplantation, which was therefore regarded as pre-existing. The other patient (male, of Mediterranean origin) in the placebo group had Kaposi's sarcoma of the skin of both legs. The

MMF 2 g patient had a squamous-cell carcinoma of the skin of the nose. 1 patient in the placebo group was diagnosed with a carcinoma of the lung more than 6 months after transplantation.

Discussion

An episode of acute allograft rejection may be associated with significant morbidity because of the treatment needed and also with possible hospital admission, impairment of renal graft function, and decreased short-term and long-term graft survival. The estimated half-life of renal grafts is shorter in patients who need treatment for one or more acute rejection episodes than in those who do not.[5]

The primary efficacy variable of our study was the number of patients with a biopsy-proven rejection episode or treatment failure. Treatment with MMF at both doses (2 g and 3 g daily) significantly reduced the number of patients with this endpoint compared with placebo. Patients in the placebo group experienced more biopsy-proven rejection episodes for which they received more courses of corticosteroids and antilymphocyte preparations. Fewer patients in the MMF 3 g group than in the MMF 2 g group had biopsy-proven rejection. However, more patients were judged to be treatment failures because of early termination for adverse events in the MMF 3 g group than in the MMF 2 g or placebo groups. Twice as many placebo patients as MMF-treated patients had to be treated with high doses of corticosteroids to abort an acute rejection episode; moreover, there were four-fold and seven-fold differences in favour of the MMF 2 g and 3 g groups for the number of patients who required antilymphocyte therapy for corticosteroid-resistant rejection, which may represent a distinct clinical advantage.

A greater frequency of gastrointestinal adverse effects and leucopenia was noted in the two MMF treatment groups. The frequency was slightly higher in the MMF 3 g group, and the findings were consistent with a dose response. The addition of a powerful immunosuppressant to an already accepted regimen for rejection control carries the risk of over-immunosuppression, which may make the patient susceptible to opportunistic infections. The treatment groups in this study had been well balanced for pretransplant cytomegalovirus serostatus of donor and recipient. The frequency of cytomegalovirus tissue-invasive disease was highest in the MMF 3 group. Herpes virus infections occurred more frequently in the MMF treatment groups.

The addition of MMF to a dual-therapy regimen with cyclosporin and corticosteroids offers improved immunosuppressive treatment after renal allograft transplantation, with a safety profile typical of a triple-therapy regimen. Besides gastrointestinal toxic effects and leucopenia, a higher frequency of cytomegalovirus disease could be associated with the use of MMF, in particular with the 3 g dose. Long-term benefits on graft survival remain to be established. If the frequency of acute rejection during the first 6 months is one of the main determinants of long-term graft survival, the long-term effect should also be good.

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