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Enteric-Coated Mycophenolate Sodium can be Safely Administered in Maintenance Renal Transplant Patients: Results of a 1-Year Study

Klemens Budde[a,*], John Curtis[b], Gregory Knoll[c], Lawrence Chan[d], Hans-Hellmut Neumayer[a], Yodit Seifu[e] and Michael Hall[e] on behalf of the ERL B302 Study Group*

[a] *University Hospital Charité, Berlin, Germany*
[b] *University of Alabama, Birmingham, AL*
[c] *University of Ottawa, Ottawa, Ontario, Canada*
[d] *University of Colorado, Denver, CO*
[e] *Novartis Pharmaceuticals, East Hanover, NJ*
**Corresponding author: Klemens Budde, klemens.budde@charite.de*

With the objective of enhancing upper gastrointestinal (GI) tolerability, enteric-coated mycophenolate sodium (EC-MPS, *myfortic*®, Novartis Pharma AG, Basel, Switzerland) has been developed. This double-blinded, 12-month study investigated whether renal transplant patients taking mycophenolate mofetil (MMF) can be safely converted to EC-MPS. Stable kidney transplant patients were randomized to receive EC-MPS (720 mg b.i.d.; n = 159) or continue receiving MMF (1000 mg b.i.d.; n = 163). The incidence of GI adverse events (AEs) was similar at 3 months (primary endpoint: EC-MPS 26.4%; MMF 20.9%; p = NS) and at 12 months (EC-MPS 29.6%; MMF 24.5%; p = NS). The increase from baseline in mean GI AE severity score, adjusted for duration, tended to be lower in EC-MPS patients (3 months: 0.15 vs. 0.20; 12 months: 0.23 vs. 0.47; p = NS). Neutropenia (<1500 cells/mm^3) within the first 3 months (coprimary endpoint) was low in both groups (EC-MPS 0.6%; MMF 3.1%; p = NS). Although the overall incidence of infections was similar, the number of serious infections was significantly lower in EC-MPS patients (8.8% vs. 16.0%; p < 0.05). Similar rates of efficacy failure (EC-MPS 2.5%; MMF 6.1%; p = NS), biopsy-proven acute rejection (EC-MPS 1.3%; MMF 3.1%; p = NS) and biopsy-proven chronic rejection (EC-MPS 3.8%; MMF 4.9%; p = NS) were observed in both groups. In conclusion, renal maintenance patients can be converted from MMF to EC-MPS without compromising the safety and efficacy profile associated with MMF.

Key words: EC-MPS, efficacy, enteric-coated mycophenolate sodium, immunosuppression, MMF, MPA, mycophenolate mofetil, mycophenolic acid, *myfortic*®, renal transplant

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Introduction

Mycophenolate mofetil (MMF) therapy has been shown to be effective in the prevention of acute rejection in renal transplantation (1–3) and in liver transplantation (4). The use of MMF as part of immunosuppressive therapy in heart transplantation also prevents the occurrence of acute rejection (5). The combination of mycophenolic acid (MPA), in the form of MMF, with cyclosporine and corticosteroids has proven to be one of the most successful strategies used in transplantation, allowing improved long-term patient and graft survival in Caucasian as well as African-American renal transplant populations (6–8).

Enteric-coated mycophenolate sodium (EC-MPS; *myfortic*®, Novartis Pharma AG, Basel, Switzerland) is an advanced formulation of MPA, developed with the objective of reducing upper gastrointestinal (GI) tract side-effects (9). Enteric-coated-MPS 720 mg and MMF 1000 mg deliver near equimolar doses of MPA, the active immunosuppressive moiety. Pharmacokinetic analysis has shown that the administration of EC-MPS 720 mg and MMF 1000 mg resulted in a similar maximal plasma concentration (C_{max}) and MPA exposure ($AUC_{0-\infty}$). Consistent with the EC design, delivery of MPA was delayed (delayed t_{max}) (10). Furthermore, in a controlled clinical study in *de novo* renal transplant patients, EC-MPS 720 mg b.i.d. has been shown to be therapeutically equivalent to MMF 1000 mg b.i.d. (11).

The objective of this study was to compare the incidence of GI adverse events (AEs) at 3 months and the occurrence of neutropenia within the first 3 months of treatment, and to evaluate whether maintenance renal transplant patients receiving MMF could be converted to EC-MPS therapy without compromising the safety and efficacy profile associated with MMF.

Methods

This phase III, international, randomized, double-blinded, double-dummy, multicenter, parallel group 12-month study was carried out in 34 centers in Austria, Belgium, Canada, Germany, Italy, Spain and the USA. Written informed consent was obtained from all patients and the study was conducted in full compliance with EEC Directive 91/507, the US 21 Code of Federal Regulations and the amended Declaration of Helsinki.

The study consisted of a screening visit, an open-label run-in period, and a double-blinded treatment period. During the run-in period, all patients received open-label MMF capsules (2000 mg/day) plus cyclosporine microemulsion (ME-CsA; Neoral®, Novartis Pharma AG, Basel, Switzerland) with or without corticosteroids for 2 weeks before randomization. Upon successful completion of the run-in period, patients who fulfilled the inclusion/exclusion criteria were randomized equally into one of two treatment groups: MMF 2000 mg/day (1000 mg b.i.d) or EC-MPS 1440 mg/day (720 mg b.i.d) for 12 months of treatment. Patients were randomized according to the protocol randomization procedure, resulting in 159 patients being assigned to the EC-MPS treatment group and 163 patients to the MMF treatment group for 12 months.

Inclusion criteria

Patients of either sex, aged 18–75 years, that had undergone primary or secondary cadaveric or living donor kidney transplantation, and were at least 6 months post-transplant and receiving an immunosuppressive regimen consisting of MMF 2000 mg/day (1000 mg b.i.d) and ME-CsA with or without corticosteroids for at least 4 weeks before screening could be included in the study. Patients were to be stable in terms of graft function, defined as serum creatinine $\leq$204 μmol/L at screening or at baseline and an increase in serum creatinine <20% between screening and study baseline visit. Females of childbearing age were required to test negative for pregnancy to be eligible for inclusion.

Exclusion criteria

Patients were excluded if they were recipients of three or more kidney grafts, had previously been transplanted with another organ, or were multiorgan recipients. Additional exclusion criteria included thrombocytopenia (<75 000 cells/mm^3), absolute neutrophil count of <1500 cells/mm^3, and/or leukocytopenia (<2500 cells/mm^3), and/or hemoglobin <9 g/dL, clinically significant infections requiring continued therapy, the presence of severe diarrhea, active peptic ulcer disease, uncontrolled diabetes mellitus, positive human immunodeficiency virus status, malignancy (other than local basal or squamous cell carcinoma of the skin) within the last 5 years, and the use of any other investigational drug within 2 weeks before screening. Female patients of childbearing potential that were unwilling to use an effective form of contraception for the duration of the study and for 6 weeks following discontinuation of study medication were also excluded.

Immunosuppression

During the 14-day run-in period, patients received MMF 1000 mg b.i.d. After randomization, patients were to receive, in a blinded manner, either MMF 1000 mg b.i.d. or EC-MPS 720 mg b.i.d. plus the matching placebo. At the discretion of the investigator, the dose of study medication could be reduced by half or eliminated completely if a patient had a leukocyte count <4000 cells/mm^3 or a neutrophil count <1500 cells/mm^3 or experienced other moderate/severe AEs, until these events resolved.

The basic immunosuppressive regimen was ME-CsA, with or without corticosteroids. Target therapeutic ranges for whole blood cyclosporine concentration (trough levels) were 100–200 ng/mL. Oral corticosteroids were given according to local practice, however, if the patient was receiving corticosteroids, the dose was to remain unchanged during the first 3 months of the double-blinded treatment.

Other concomitant therapy

When GI prophylactic treatment was administered, it was to be consistently given to all patients at a given center, and was to be unchanged for the first 3 months of each patient's participation in the study.

Safety evaluations

The primary safety endpoint was the evaluation of the incidence and severity of GI AEs at 3 months and neutropenia (defined as a low absolute neutrophil count <1500 cells/mm^3) within the first 3 months of study drug administration. Secondary safety endpoints included the evaluation of the incidence and severity of GI AEs and neutropenia, the incidence and severity of AEs and infections, and discontinuations due to AEs and serious AEs for the entire duration of the study. Laboratory evaluations were performed at a central laboratory. A comprehensive set of blood and urine tests were performed routinely at each study visit.

Gastrointestinal AEs were recorded on a separate case report form. Severity scores were recorded for each GI AE using a 0–3 scale: 0 (no event), 1 (mild), 2 (moderate) and 3 (severe). The investigator was asked to record any change in severity. Severity scores, adjusted by duration, were cumulated and summarized to obtain weighted mean scores compared against baseline for each patient. These were further summarized by treatment group. Determination of severity score included all GI AEs that occurred up to 7 days after discontinuation of the study drug.

Efficacy evaluations

Efficacy was evaluated as a secondary endpoint by measuring the incidence of efficacy failure, a composite variable of biopsy-proven acute rejection (BPAR), graft loss or death at 6 months and 12 months. Incidence of biopsy-proven chronic rejection was also evaluated at 6 months and 12 months.

Statistical analyses and study size determination

Efficacy was analyzed in the intent-to-treat (ITT) population, and safety was analyzed in the safety population. The ITT and safety patients were randomized patients that had received at least one dose of study medication. The ITT patients were required to have had one postbaseline assessment, whilst safety patients were required to have had one tolerability/safety assessment. The incidence rates of efficacy events were analyzed, as well as the associated 95% confidence intervals (95% CIs) for the difference in rates between the two treatment groups. Safety variables were evaluated by means of frequency distributions and descriptive statistics. Continuous variables were tested for baseline comparability using the Wilcoxon rank-sum test, and categorical variables were tested using the Chi-square or Fisher's exact test. Confidence intervals for differences in incidence rates were obtained using exact or asymptotic normal approximation methods. All significance tests were conducted at the 0.05 significance level and were two-sided. Only p-values less than 0.05 are reported.

The sample size of 150 patients per treatment arm yielded the following power considerations and assumptions: individual GI AE (e.g. nausea, vomiting, dyspepsia, diarrhea, constipation) and neutropenia (<1500 cells/mm^3) incidence rates will be between 10% and 25% for each individual AE for both MMF and EC-MPS; the one-sided type I error was set at 0.025; clinical equivalence was established when the upper limit of the 97.5% CI of the difference in incidence rate of the AE was less than 10%; and no adjustment for multiple significance was made. Under these assumptions, the power for claiming clinical equivalence ranged between 51% and 82%.

Randomization and blinding procedure

Patients were randomized according to a computer-generated schedule in order to guarantee that patients were distributed equally between the two treatment groups and within each center. Study medication was packaged so as to maintain the double-blinded trial design and to allow dose reduction. The patients, investigators, study center personnel and any Novartis personnel in direct contact with the study centers were blinded until the 12-month analysis was completed.

Results

The ITT and safety populations were identical, comprising 322 patients: 159 patients randomized to the EC-MPS group and 163 patients randomized to the MMF group. Patient baseline characteristics between the two groups were comparable (Table 1). The majority of patients in both groups were recipients of a first renal transplant. At the time of entry into the study, 84.9% of patients were receiving corticosteroids in the EC-MPS group and 85.3% in the MMF group. Mean dose of corticosteroids, mean ME-CsA trough levels and mean dose of ME-CsA at study entry are also summarized in Table 1.

During the study, 10.1% of patients discontinued treatment prematurely in the EC-MPS group and 11.7% in the MMF group. In total, 5.7% of patients in the EC-MPS group and 2.5% of patients in the MMF group discontinued their study drug as a result of AEs. The major differences in incidence of discontinuation between the two groups resulted from infection (EC-MPS, four patients) and leukopenia (EC-MPS, two patients). The other reasons for discontinuation occurred with similar proportions in the EC-MPS and MMF groups, namely death (MMF 1.2%), abnormal laboratory values (0.6% in each group), protocol violation (EC-MPS 0.6% and MMF 1.2%), loss to follow up (0.6% in each group), study administrative reasons (EC-MPS 0.6%) and withdrawal of consent (1.9% and 5.5% for EC-MPS and MMF, respectively).

Table 1: Patient baseline characteristics of the intent-to-treat population

	EC-MPS (n = 159)	MMF (n = 163)
Age (years)*	48.6 ± 11.43	46.8 ± 12.13
Kidney transplantation (%)		
First	90.6	87.7
Second	8.8	11.7
Gender (%)		
Male	61.0	70.6
Female	39.0	29.4
Race (%)		
Caucasian	74.2	73.0
Black	17.6	20.9
Oriental	3.1	2.5
Other	5.0	3.7
Time post-transplantation (days)*	843.9 ± 764.6	863.9 ± 830.9
Serum creatinine at study entry (μmol/L)*	141.2 ± 30.2	138.8 ± 35.7
Patients receiving corticosteroids at study entry (%)	84.9	85.3
Corticosteroid dose at study entry (mg/kg/day)*	0.1 ± 0.05	0.1 ± 0.06
ME-CsA trough level at study entry (ng/mL)*	188.9 ± 102.27	190.1 ± 139.65
ME-CsA dose at study entry (mg/kg/day)*	3.1 ± 1.23	3.3 ± 1.47

*Mean ±SD.
ME-CsA = cyclosporine microemulsion, MMF = mycophenolate mofetil, EC-MPS = enteric-coated mycophenolate sodium.

Safety

With the exception of serious infections, there were no statistically significant differences between EC-MPS and MMF in the safety parameters measured. At 3 months, the incidence of GI AEs was not statistically significantly different between EC-MPS patients and MMF patients (26.4% vs. 20.9%, respectively) (Table 2). The incidence of upper GI AEs, defined by the occurrence of nausea, dyspepsia, abdominal upper pain, gastroesophageal reflux disease, esophageal reflux, gastritis and anorexia, was similar for both groups (13.2% and 13.5% for EC-MPS and MMF, respectively). The incidence of nonupper GI AEs was 18.2% for EC-MPS and 12.9% for MMF (Table 2). The incidence of diarrhea was also similar in both groups (5.0% for EC-MPS vs. 4.9% for MMF). At 6 months, the incidence was similar between the EC-MPS and MMF treatment groups for any GI AE (28.9% vs. 27.6%), upper GI AEs (15.7% vs. 16.6%) and nonupper GI AEs (20.1% vs. 18.4%). Similar figures were observed at the 12-month visit, with no between-group difference apparent in the incidence of upper or nonupper GI AEs (Table 2). The overall incidence of GI AEs occurring during the 12 months postrandomization was similar for both groups (60.4% vs. 61.3% for EC-MPS and MMF, respectively).

The incidence of dose reductions and/or interruptions resulting from any GI AE was comparable between each treatment group, occurring in 8.2% of EC-MPS patients and 6.1% of MMF patients. Dose discontinuation resulting from GI AEs were similarly comparable, occurring in 1.9% of patients in the EC-MPS group and 1.8% of patients in the MMF group. The composite of dose interruption, adjustment or discontinuation due to upper GI AEs occurred in 4.4% of EC-MPS and 5.5% of MMF patients, respectively. Dose interruption, adjustment or discontinuation resulting from diarrhea occurred in 5.0% of EC-MPS patients (0.6% dose discontinued) and 4.3% of MMF patients (1.2% dose discontinued), respectively.

The increase from baseline in mean GI AE severity score (0 – no event; 1 – mild; 2 – moderate; 3 – severe), adjusted for duration of symptoms, was 0.15 and 0.20 for EC-MPS and MMF, respectively, at 3 months (mean difference in change from baseline –0.05; 95% CI: [–0.19,

Table 2: Percentage of patients experiencing gastrointestinal adverse events at 3, 6 and 12 months

	3 months		6 months		12 months	
	EC-MPS (n = 159)	MMF (n = 163)	EC-MPS (n = 159)	MMF (n = 163)	EC-MPS (n = 159)	MMF (n = 163)
Any GI AE	26.4	20.9	28.9	27.6	29.6	24.5
Upper GI AE	13.2	13.5	15.7	16.6	15.1	14.1
Dyspepsia	3.1	3.1	5.7	2.5	3.8	3.7
Nausea	6.3	3.7	8.2	7.4	5.7	5.5
Gastro-esophageal reflux disease	1.9	1.2	1.9	1.2	3.1	3.1
Vomiting	0.6	0.6	3.8	4.9	1.9	3.7
Non-upper GI AE	18.2	12.9	20.1	18.4	18.9	19.0
Diarrhea	5.0	4.9	5.0	6.7	3.8	6.7

GI = gastrointestinal, AE = adverse event, MMF = mycophenolate mofetil, EC-MPS = enteric-coated mycophenolate sodium.

+0.09]) (Figure 1). At 6 months, the increase from baseline in the mean GI score was 0.19 and 0.27 for EC-MPS and MMF, respectively (mean difference in change from baseline –0.08; 95% CI: [–0.25, +0.09]), and at 12 months, it was 0.23 and 0.47 for EC-MPS and MMF, respectively (mean difference in change from baseline –0.24; 95% CI: [–0.51, +0.03]) (Figure 1).

The occurrence of neutropenia, defined as a low absolute neutrophil count of <1500 cells/mm^3 (combined primary endpoint) within the first 3 months was similar in EC-MPS patients and MMF patients (0.6% for EC-MPS and 3.1% for MMF; 95% CI: [–6.74, +0.80]), remaining unchanged through the remainder of the 12-month study.

At 1 year, the incidence of overall AEs was similar in both groups: 93.7% and 92.6% for EC-MPS and MMF, respectively. Only 29.5% of patients in each treatment group had AEs that were suspected to be drug related.

The incidence of serious AEs was 23.3% in the EC-MPS group compared with 30.1% in the MMF group (p = NS) (Figure 2). The overall incidence of infections was similar in both groups (58.5% and 58.9% for EC-MPS and MMF, respectively), however, there were approximately 50% fewer serious infections associated with EC-MPS (8.8% vs. 16.0%; p < 0.05) (Figure 2). The incidence of serious pneumonia was 1.9% in patients receiving EC-MPS compared with 4.9% in patients receiving MMF (p = NS) (Figure 2). Most frequently reported serious infections are summarized in Table 3. Serious infections were related to bacterial agents (3.1% and 5.5% for EC-MPS and MMF, respectively), then viral agents (EC-MPS, 0.6% and MMF, 1.8%), or fungal agents (EC-MPS, 1.3% and MMF, 0.6%). As expected, the overall incidence of cytomegalovirus (CMV) infection was very low and was similar in both treatment groups (1.9% and 1.8% for EC-MPS and MMF,

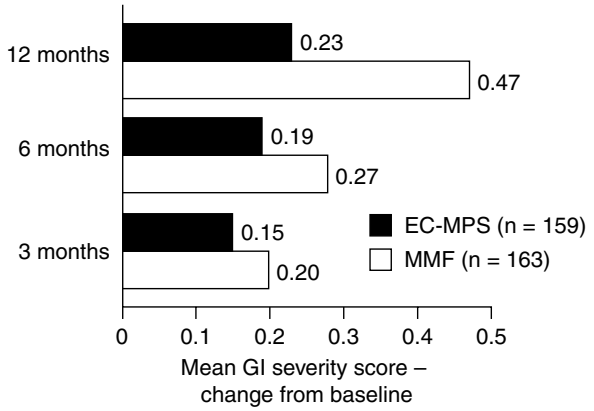

Figure 1: Changes from baseline in gastrointestinal (GI) adverse event severity score at 3, 6 and 12 months (p = NS). Severity scores for all GI adverse events were recorded, including: 0 (no event), 1 (mild), 2 (moderate) and 3 (severe). For each patient, the individual scores, weighted by duration, were summed to obtain a total severity score. Mean severity score and changes from baseline were recorded.

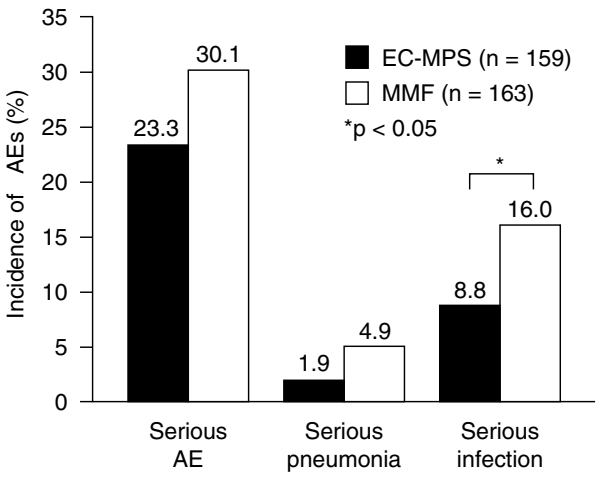

Figure 2: Frequency and severity of adverse events (AEs) and infections during the 12-month study period.

Table 3: Incidence of most frequently reported serious infections during the 12-month study period

	Number of patients (%)	
	EC-MPS (n = 159)	MMF (n = 163)
Total serious infections	14 (8.8)*	26 (16.0)
Pneumonia	3 (1.9)	8 (4.9)
Urinary tract infection/ pyelonehritis/urosepsis	4 (2.5)	9 (5.5)
Cytomegalovirus infection/ pneumonia cytomegaloviral	0	2 (1.2)
Sepsis	2 (1.3)	0
Upper respiratory tract infection	2 (1.3)	1 (0.6)
Gastroenteritis	1 (0.6)	2 (1.2)

*$p < 0.05$ compared with MMF.
MMF = mycophenolate mofetil, EC-MPS = enteric-coated mycophenolate sodium.

Table 4: Renal function throughout the study and concomitant immunosuppressive therapy at 12 months

	EC-MPS (n = 159)	MMF (n = 163)
Serum creatinine concentration (μmol/L)		
3 months (day 100–146)*	145.6 ± 34.87	138.7 ± 41.73
6 months (day 147–226)*	139.5 ± 31.42	140.0 ± 46.37
12 months (day 312–450)*	139.5 ± 37.76	138.0 ± 43.59
Immunosuppressive therapy		
ME-CsA (mg/kg/day)*	2.9 ± 1.18	3.1 ± 1.47
ME-CsA trough level (ng/mL; min–max)	164.6 (42–329)	160.1 (57–306)
Oral corticosteroids (mg/kg/day)*	0.1 ± 0.12	0.1 ± 0.07

*Mean ±SD.
ME-CsA = cyclosporine microemulsion, MMF = mycophenolate mofetil, EC-MPS = enteric-coated mycophenolate sodium.

respectively), with CMV disease occurring only in one patient in the MMF arm.

Two lymphomas were reported in the EC-MPS treatment group, one being related to AIDS from which the patient died. The incidence of nonmelanoma skin carcinoma and of other types of malignancies were similar between the EC-MPS and MMF groups. Anemia, leukopenia and thrombopenia were reported as AEs with a similar incidence between the two treatment groups. No difference was observed between treatment groups for liver function tests. Mean serum creatinine concentrations were similar during the course of the study for both groups (Table 4).

In total, 90.6% of the patients in the EC-MPS arm and 88.3% of the patients in the MMF arm were on study medication for more than 311 days. No apparent differences in the dose of ME-CsA administered, in the ME-CsA blood trough level achieved, or in the oral corticosteroid dose administered were noted between the two treatment groups during the study (Table 4).

Efficacy

Efficacy was evaluated as a secondary endpoint. Overall, there were no statistically significant differences between EC-MPS and MMF in the efficacy parameters measured. During this 12-month study, rates of efficacy failure, defined as BPAR, graft loss or death, were 2.5% in the EC-MPS group and 6.1% in the MMF group (95% CI: [–8.0, +0.8]; p = NS) (Figure 3). One MMF patient, who had experienced vessel graft thrombosis and stenosis and was noncompliant to treatment, lost his graft following recurrence of original kidney disease combined with cyclosporine toxicity and chronic rejection. Two patients in the EC-MPS group died of multiorgan failure and AIDS and four patients in the MMF group died of cerebral bleeding, hypoglycemia/heart attack, cardiac arrest and complications of pneumonia, respectively. Biopsy-proven chronic rejection was reported in 3.8% of patients receiving EC-MPS and in 4.9% of patients receiving MMF, and BPAR was reported in 1.3% of patients receiving EC-MPS and 3.1% of patients receiving MMF (Figure 3). The Kaplan–Meier point estimates of the probability of experiencing BPAR, graft loss or death at 12 months of the initial dose of study medication were 2.7% for EC-MPS and 8.7% for MMF (95% CI: [–13.0, +1.1]). Log-rank analysis did not show a

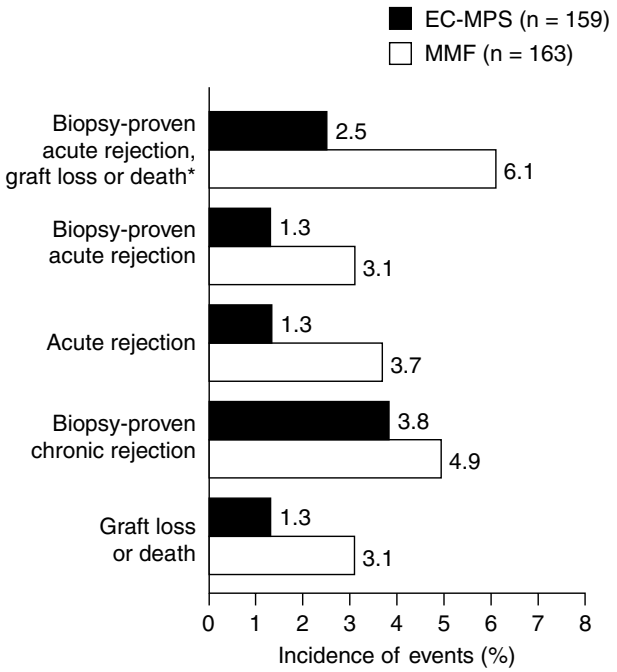

Figure 3: Efficacy of enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF) at 12 months (p = NS). *Biopsy-proven acute rejection, graft loss, death or loss to follow up: 7.5% and 12.3% for EC-MPS and MMF, respectively.

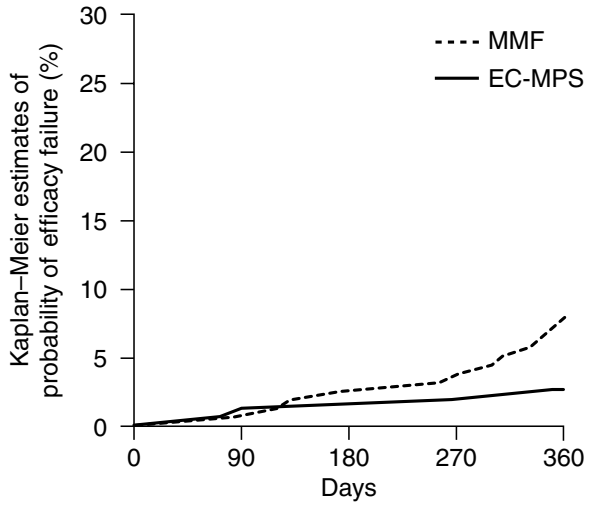

Figure 4: Kaplan–Meier estimates of the probability of biopsy-proven acute rejection, graft loss or death within 12 months (p = NS).

statistically significant difference between the two Kaplan–Meier curves (Figure 4).

Discussion

The overall results of this study clearly confirm that EC-MPS is as safe and as effective as MMF, and thus are in agreement with previous findings in *de novo* transplant patients (11). With the exception of the incidence of serious infections, no statistically significant differences between EC-MPS and MMF were identified in the safety and efficacy parameters measured. No consistent numerical or statistically significant trend in favor of either treatment group was observed for GI AEs, although the increase in GI severity score from baseline, adjusted for duration, tended to be lower in the EC-MPS group than in the MMF group (p = NS). The similarity of the overall observed rates of GI AEs in the treatment groups in this study might be explained by several factors: (i) different factors can contribute to the occurrence of GI events; (ii) the daily fluctuations as well as the subjectivity of the symptoms make documentation and interpretation of GI AEs difficult when collected in the context of standard case report forms; and (iii) patients that entered this study were already receiving and therefore tolerating MMF at a dose level of 2000 mg, which may introduce a bias as this population may not be representative of the overall transplant population. Studies more specifically designed to address GI tolerability are needed in order to better identify the impact of this new formulation of mycophenolate (enteric coated), as well as to enable the scientific community to gain a better understanding of the physiopathological mechanism linked with the occurrence of GI side-effects.

As reflected by the similar incidence of neutropenia, the hematological safety profile is comparable between the two MPA derivatives. Likewise, the overall safety profile of these two compounds is similar. The incidence/pattern of malignancies including lymphoma and nonmelanoma skin carcinoma is low in both treatment groups and corresponds to the expected incidence in this patient population. Interestingly, a nonsignificant trend towards a lower incidence of serious AEs was observed for EC-MPS compared with MMF, and the incidence of serious infections was significantly lower in the EC-MPS group ($p < 0.05$). To date, no clear explanation or hypothesis can be drawn but these findings may be considered as a potential benefit afforded by the enteric-coated formulation. Finally, converting patients receiving MMF to EC-MPS did not jeopardize efficacy as both treatment groups exhibited low rates of acute, chronic rejection or graft loss.

It can be concluded from this study that renal maintenance patients taking MMF can be safely converted to EC-MPS, as all measured safety and efficacy variables were comparable between the two treatment groups.

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Executive committee members: K Budde and H-H Neumayer (University Hospital Charité, Berlin, Germany), J Curtis (University of Alabama, Birmingham, AL), G Knoll (University of Ottawa, Ottawa, Ontario, Canada), L Chan (University of Colorado, Denver, CO), Y Seifu and M Hall (Novartis, East Hanover, NJ).

ERL B302 Study Group: D Granger, R Ouseph, and J Jones (University of Louisville, KY), J Lindberg, and J Copley (Ochsner Clinic, New Orleans, LA), L Kahana (LifeLink Foundation, Tampa, FL), E Pohanka (Universitaetsklinik Innere Medical III, Vienna, Austria), M Pescovitz (Indiana University MC, IN), P Halloran (University of Alberta, Edmonton, Canada), A Shoker (Royal University Hospital, Saskatoon, Canada), G Danovitch (UCLA Medical Center, Los Angeles, CA), S Flechner (Cleveland Clinic, Cleveland, OH), W Arns (Cologne General Hospital, Merheim Medical Center, Koln-Merheim, Germany), R Pelletier (Ohio State University, MC, Columbus, OH), S Palekar (Newark Beth Israel MC, Newark, NJ), M Weir (University of Maryland MC, Baltimore, MD), U Frei (Humboldt University of Berlin, Berlin, Germany), M Salvadori (Azienda Ospedaliera Careggi, Florence, Italy), S Yilmaz (Foothills Medical Center, Calgary, Canada), S Mulgoankar (St. Barnabas Medical Center, Livingston, NJ), S Steinberg (Sharp Kidney Transplant Center, San Diego, CA), MA Gentil (Hospital Virgen del Rocio, Seville, Spain), M Arias (Hospital Marques de Valdecilla, Santander, Spain), R Mendez (National Institute of Transplantation, Los Angeles, CA), A Guasch (Emory University, Atlanta, GA), E Alfrey, H Yang, and J Areana (Hershey Medical Center, Hershey, PA), J Shapiro (Vancouver Hospital, Vancouver, Canada), J Sennesael (AZ VUB Jette, Brussels, Belgium), HC Stummvoll (Krankenhaus der Elizabethin, Linz, Austria), F Wright (Texas Transplant Institute, San Antonio, TX), J Dunn (University of California San Diego Medical Center, San Diego, CA), D Abramowicz (ULB Erasame, Brussels, Belgium), S Greenstein

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