Enteric-Coated Mycophenolate Sodium Versus Mycophenolate Mofetil in Renal Transplant Recipients Experiencing Gastrointestinal Intolerance: A Multicenter, Double-Blind, Randomized Study

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Background. Two open-label studies demonstrated that conversion from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS) significantly reduces gastrointestinal (GI) symptom burden and improves GI-specific health-related quality of life. Using a randomized design, this study evaluated changes in GI symptoms and health-related quality of life in patients converted from MMF to EC-MPS versus patients who continued with MMF-based treatment.

Methods. In this 4-week, multicenter, randomized, prospective, double-blind, parallel-group trial, renal transplant recipients with GI symptoms receiving MMF plus a calcineurin inhibitor±corticosteroids were randomized to an equimolar dose of EC-MPS+MMF placebo or continue on their MMF-based regimen+EC-MPS placebo. The primary efficacy outcome was a change from baseline in total Gastrointestinal Symptom Rating Scale score of a minimally important difference of more than or equal to 0.3.

Results. Three hundred ninety-six patients (EC-MPS group: n=199; MMF group: n=197) were included. A greater proportion of EC-MPS patients (62%) reached the primary efficacy outcome compared with MMF patients (55%); however, the difference was not statistically significant ($P=0.15$). EC-MPS patients had a significantly greater decrease in the Gastrointestinal Symptom Rating Scale indigestion syndrome dimension versus MMF patients. Within the subgroups of patients with diabetes, patients transplanted 6 to 12 months of study enrollment, and patients on steroids, a statistically significant greater proportion of EC-MPS versus MMF patients reached the primary efficacy outcome.

Conclusions. Conversion from MMF to EC-MPS may be associated with improvements in presence and severity of GI symptoms, particularly in patients with indigestion, diabetes, on steroids, and in patients converted between 6 and 12 months posttransplantation.

Keywords: Gastrointestinal, Quality of life, HRQoL, Mycophenolate mofetil, Mycophenolate sodium.

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Mycophenolate mofetil (MMF, CellCept, Nutley, NJ) is an esterified prodrug of mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase and consequently the pathway of de novo guanosine nucleotide synthesis. T and B lymphocytes are critically dependent on de novo synthesis of purines for their proliferation, whereas other cell types can use salvage pathways. As a consequence, the cytostatic effects of MPA are more selective for lymphocytes than on other cell types (*1*).

MMF is associated with excellent short- and long-term efficacy after renal transplantation (*2–5*). However, dose reductions, omissions, and impaired compliance subsequent to MMF-related gastrointestinal (GI) toxicity are associated with an increased risk of rejection (*6–8*) and graft loss (*8–10*). MMF dose adjustments are also associated with increased short-term treatment costs (*7*).

Enteric-coated mycophenolate sodium (EC-MPS [Myfortic, Novartis, East Hanover, NJ]) is an advanced formulation of MPS that delays the release of the MPA until it reaches the duodenum where the enteric pH rises above 5. EC-MPS was developed with the aim to improve GI tolerability of MPA therapy. EC-MPS is not bioequivalent to MMF (*11*), although the area under the curve is similar, and EC-MPS is equal in efficacy and safety to MMF (*12–14*). Compared with MMF, the use of EC-MPS is associated with fewer dose changes, interruptions, and discontinuations (*15*).

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Two published open-label trials concluded that GI improvements occurred after a conversion from MMF to EC-MPS. Patient Reported Outcomes in Renal Transplant Patients with or without Gastrointestinal Symptoms (PROGIS) was a 1-month, longitudinal, international, multicenter trial where GI outcomes were evaluated for patients with MMF-associated GI complaints converted to EC-MPS. Conversion to EC-MPS was associated with significantly reduced GI-related symptom burden and improved patient functioning and well being (*16*). The study also incorporated a cohort where patients without GI complaints who remained on MMF were followed up.

MyTime was a 3-month, longitudinal, US multicenter, prospective trial in adult renal transplant patients with self-reported GI symptoms considered by their physician to be related to MMF who were converted to an equimolar dose of EC-MPS. Significantly reduced GI symptom scores, improved GI-specific quality of life, and improved overall well being were observed after conversion from MMF to EC-MPS (*17*).

This study was conducted to further evaluate the potential for GI tolerability improvements in an MMF to EC-MPS conversion protocol. The aim of this study was to investigate, in a blinded, randomized fashion, the safety and tolerability of converting kidney transplant recipients with MMF-associated GI symptoms to an equimolar dose of EC-MPS. The comparator arm was composed of patients who continued on their MMF-based regimen.

RESULTS

Patient Disposition and Baseline Characteristics

Details on patient disposition are included in Table 1. Four hundred patients from 67 centers (56 United States, 6 Canada, and 5 Mexico) were enrolled in the study (200 in EC-MPS group and 200 in MMF group). The ITT and safety population included 199 (99.5%) of enrolled patients in the EC-MPS group and 197 (98.5%) of enrolled patients in the MMF group. The per-protocol population included 170 (85.0%) of enrolled patients in the EC-MPS group and 171 (85.5%) of enrolled patients in the MMF group.

Patients in the EC-MPS and MMF groups were similar in demographic characteristics with no statistically significant differences between the groups in age, gender, race, time since most recent transplant, or types of end-stage renal disease leading to transplantation (Table 2). Mean GSRS total scores at baseline were the same for EC-MPS and MMF (2.6±0.9) patients. There was no difference in the use of proton pump inhibitors (EC-MPS 105 [52.8%] and MMF 106 [53.8%]). Demographic and background characteristics in the per-protocol population were similar to those in the ITT population.

TABLE 1. Patient disposition

Category	Treatment group: EC-MPS, n (%)	Treatment group: MMF, n (%)
Screened (n=412)		
Enrolled[a]	200 (100.0)	200 (100.0)
ITT and safety population[b]	199 (99.5)	197 (98.5)
Per-protocol population[c]	170 (85.0)	171 (85.5)
Completed study medication	186 (93.0)	185 (92.5)
Discontinued study medication	13 (6.5)	12 (6.0)
Reason discontinued		
Adverse event[d]	9 (4.5)	8 (4.0)
Protocol violation	2 (1.0)	0 (0.0)
Withdrew consent	1 (0.5)	3 (1.5)
Lost to follow-up	0 (0.0)	1 (0.5)
Administrative problems	1 (0.5)	0 (0.0)
Completed study	195 (97.5)	191 (95.5)
Discontinued study	4 (2.0)	6 (3.0)
Reason discontinued		
Withdrew consent	1 (0.5)	5 (2.5)
Lost to follow-up	2 (1.0)	1 (0.5)
Administrative problems	1 (0.5)	0 (0.0)

[a] All percentages are based on the number of patients enrolled.
[b] ITT population consists of all patients who received study drug.
[c] Per-protocol population consists of all patients who completed the study without any major deviations from the protocol procedure. Reasons for exclusion from the per-protocol population included study medication taken for less than 17 d (nine EC-MPS and nine MMF), nonequimolar conversion from MMF (seven EC-MPS and six MMF), ongoing infection requiring therapy (five EC-MPS and three MMF), and MMF taken tid before enrollment in the study (two EC-MPS and two MMF).
[d] Three patients discontinued study medication early because of BK virus infections and are included in this count.
EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; ITT, intent-to-treat.

MPA Exposure

The average daily dose of MMF at baseline was similar in both groups (1410 vs. 1389 mg MMF) as was the mean and median duration of exposure to study medication. Most (>95%) of the patients received more than or equal to 2 weeks of exposure to study medication, and 59% of patients in the EC-MPS and 61% in the MMF group received 30 days of exposure. However, 90.9% had more than or equal to 27 days of exposure. At the end of the study, the average doses (equimolar) were 1053 mg EC-MPS (the equivalent of 1465 mg MMF) and 1491 mg MMF (1102 mg as MPA).

Primary and Secondary Efficacy Results

A numerically greater proportion of patients in the EC-MPS group (62%) had an improvement in GSRS total score of at least 0.3 compared with patients in the MMF group (55%). However, the difference in response rates was not statistically significant ($P=0.15$). Similarly, for the per-protocol population, a numerically greater proportion of patients in the EC-MPS group (64%) had an improvement in GSRS total score of at least 0.3 compared with patients in the MMF group (58%). However, the difference in response rates was not statistically significant ($P=0.25$).

One patient in the MMF group experienced BPAR (Banff type I-A) that was noted at visit 2 because of an increase in serum creatinine to 1.9 mg/dL. The patient was treated with methylprednisolone and rehydrated, and the event was considered resolved 10 days later. There were no cases of AR in the EC-MPS group.

TABLE 2. Baseline demographic and background characteristics by treatment group

	Treatment group		
	EC-MPS (N=199)	MMF (N=197)	*P*
Age (yr)			
Mean±SD	48.4±13.4	48.4±12.6	0.9562[a]
Sex, n (%)			
Female	105 (52.8)	95 (48.2)	0.3662[b]
Male	94 (47.2)	102 (51.8)	
Race, n (%)			
White	112 (56.3)	119 (60.4)	0.8743[b]
Black	49 (24.6)	44 (22.3)	
Asian	8 (4.0)	7 (3.6)	
Other	30 (15.1)	27 (13.7)	
Time since most recent transplant (d)[c]			
Mean±SD	1136.2±1269.2	1011±1176.0	0.4146[d]
Median	541.0	562.0	
Range	27–6141	30–7688	
End-stage disease leading to transplantation, n (%)			
Glomerulonephritis/glomerular disease	36 (18.1)	37 (18.8)	
Pyelonephritis	3 (1.5)	2 (1.0)	
Polycystic disease	26 (13.1)	19 (9.6)	
Hypertension/nephrosclerosis	34 (17.1)	37 (18.8)	
Diabetes mellitus	38 (19.1)	40 (20.3)	
Interstitial nephritis	3 (1.5)	0 (0.0)	
Vasculitis	1 (0.5)	0 (0.0)	
Obstructive disorder/reflux	5 (2.5)	3 (1.5)	
Renal hyperplasia/dysplasia	0 (0.0)	1 (0.5)	
Unknown origin	13 (6.5)	13 (6.6)	
Other	40 (20.1)	45 (22.8)	

[a] *P* value based on *t* test.
[b] *P* value based on χ^2 test.
[c] Date of study day 1 minus date of most recent transplantation.
[d] *P* value based on Wilcoxon *t* test.
SD, standard deviation; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

Secondary Safety and Tolerability Results

The Proportion of Patients With GI Adverse Events During the 30 Days of Treatment

GI adverse events (AEs) were relatively frequent (39% EC-MPS and 46% MMF) and constituted the system organ class with the highest number of AEs overall (Table 3). The proportion of patients with severe GI AEs was similar in both groups (11% EC-MPS and 13% MMF). Related GI AEs occurred at a similar frequency in both groups (20% EC-MPS and 22% MMF). Serious GI AEs occurred at a low rate in both groups (1% EC-MPS and 2.5% MMF).

Change From Baseline to Day 30 in Severity of GI Symptoms

Patients in the EC-MPS group had a statistically significant ($P=0.03$) greater improvement in total GI symptom score from baseline to day 30 than patients in the MMF group. Patients in the EC-MPS group also had a statistically significant ($P<0.05$) greater improvement in GI symptom subscale symptom scores including eructation, lower GI, constipation, and flatulence, compared with patients in the MMF group (Table 4).

Dose Changes or Interruptions

Dose changes or interruptions were relatively infrequent and did not significantly differ ($P=0.44$) between the treatment groups (11/199 [5.5%] patients in the EC-MPS group vs. 12/197 [6.1%] patients in the MMF group had dose changes or interruptions of study medication over the 30 days of treatment). Dose adjustments were most commonly made as per protocol (7 [3.5%] EC-MPS and 5 [2.5%] MMF), reflecting dose increases back to baseline levels after a decrease or interruption or because of AEs (e.g., leucopenia, thrombocytopenia, neutropenia, or anemia; 5 [2.5%] EC-MPS and 8 [4.1%] MMF), primarily affected by dose decreases in response to these laboratory values. No patients had their dose interrupted for safety reasons for more than 4 consecutive days during the first 2 weeks of the study or for more than 12

TABLE 3. Treatment-emergent GI AEs affecting ≥2% of patients in any treatment group

	Treatment group		
	EC-MPS (N=199), n (%)	MMF (N=197), n (%)	*P*
Patients with at least one GI AE[a]	77 (38.7)	91 (46.2)	0.1545
Abdominal distension	27 (13.6)	31 (15.7)	0.5719
Diarrhea	22 (11.1)	19 (9.6)	0.7420
Dyspepsia	19 (9.5)	17 (8.6)	0.8616
Nausea	11 (5.5)	23 (11.7)	0.0320
Flatulence	11 (5.5)	19 (9.6)	0.1325
Eructation	9 (4.5)	20 (10.2)	0.0348
Abdominal pain upper	9 (4.5)	18 (9.1)	0.0754
Abdominal pain lower	11 (5.5)	14 (7.1)	0.5426
Intestinal functional disorder	10 (5.0)	14 (7.1)	0.4079
Gastroesophageal reflux disease	13 (6.5)	9 (4.6)	0.5115
Constipation	7 (3.5)	15 (7.6)	0.0829
Vomiting	6 (3.0)	11 (5.6)	0.2258

[a] A patient with multiple occurrences of an AE is counted only once in the AE category for that treatment.

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

consecutive or cumulative days during the 30-day study period. The total number of patients with any amount of drug interruption was trivial. Three patients in the EC-MPS treatment arm and two patients in the MMF group interrupted the study drug for a cumulative total of 14 days among the five patients.

Change From Baseline to Day 30 in GSRS Total and Dimension Scores and in GIQLI Total and Subscale Scores

Statistically significant ($P<0.0001$) decreases from baseline in overall GSRS were seen in both the EC-MPS (mean decrease from baseline to day 30: -0.6 ± 0.9) and MMF (-0.5 ± 1.0) treatment groups. Between-group differences in change from baseline at day 30 were not statistically significant ($P>0.05$). GSRS dimension scores were similar for the EC-MPS and MMF groups at baseline and declined in both groups at day 30 compared with baseline. A statistically significant ($P=0.02$) greater decrease for the indigestion syndrome was seen in the EC-MPS group compared with the MMF group (mean change: EC-MPS: -0.7 ± 1.2 and MMF: -0.5 ± 1.4). Statistically significant changes from baseline to day 30 were not observed for diarrhea, constipation, abdominal pain, or reflux.

The baseline GIQLI scores were similar between the treatment groups ($P>0.05$). The mean overall and subscale scores significantly ($P\leq0.003$) improved in both treatment groups compared with baseline with no statistically significant difference between the EC-MPS and MMF groups in the change from baseline.

Proportion of Patients at Day 30 Who Were Free of at Least One of the GI Symptoms That Were Present at Baseline

There were no statistically significant ($P=0.62$) differences between treatment groups in the proportion of patients who were free of diarrhea, dyspepsia, acid reflux, or abdominal pain that was present at baseline (% free of symptom at day 30: EC-MPS: 65% and MMF: 62%). For diarrhea specifically, the proportion of patients who were symptom free was numerically greater in the EC-MPS group (42%) compared with the MMF group (35%), but the difference was not statistically significant ($P=0.33$). The proportion of patients whose diarrhea improved (EC-MPS: 64% and MMF: 67%), remained the same (EC-MPS: 30% and MMF: 30%), or worsened (EC-MPS: 6% and MMF: 3%) since baseline was similar in both groups ($P=0.28$). A greater proportion of patients in the MMF (43%) versus the EC-MPS (37%) group had a new or worsening GI AE during the study; however, the difference was not statistically significant ($P=0.10$).

OTE-HRQoL Scores at Day 30

The mean OTE-HRQoL score declined in both the EC-MPS (mean decrease: -1.7 ± 3.2) and the MMF (mean decrease: -1.9 ± 2.7) treatment groups compared with baseline, but there was no statistically significant difference between the treatment groups ($P=0.57$). Categorical changes from baseline (better: EC-MPS=43% and MMF=48%; same: EC-MPS=50% and MMF=46%; worse: EC-MPS=7% and MMF=6%) at day 30 were also similar between the groups ($P=0.32$).

Efficacy Results: Planned Subgroup and Post Hoc Analyses

Because CNIs can contribute significantly to GI side effects and are more likely in patients taking tacrolimus, a separate analysis was performed for cyclosporine versus tacrolimus patients. If CNIs played a role in the patient's GI symptoms at baseline, they would have been randomized equally to the EC-MPS and MMF arms. No significant difference in response rate was observed between EC-MPS and MMF patients using tacrolimus (61.4% EC-MPS and 54.3% MMF, $P=0.32$), patients using cyclosporine (66.7% EC-MPS and 60.0% MMF, $P=0.60$), patients not taking steroids (53.0% EC-MPS and 77.0% MMF, $P=0.10$), patients without diabetes (58.6% EC-MPS and 62.0% MMF, $P=0.97$), patients with transplant dates less than or equal to 6 months (58.5% EC-MPS and 56.5% MMF, $P=0.91$) or more than 12 months of study start (60.4% EC-MPS and 55.9% MMF, $P=0.74$), or between EC-MPS, and MMF African American patients (63.3% EC-MPS and 52.3% MMF, $P=0.29$).

A statistically significantly better response rate was observed for EC-MPS versus MMF patients in the subgroup of patients with diabetes (EC-MPS: n=70 and MMF: n=76) present pretransplantation (EC-MPS: 69.6% vs. MMF: 44.7%, $P=0.009$). There were no differences in time since transplant, study drug dosing, MPA levels, GI medication, or insulin use between the EC-MPS- and MMF-treated patients with diabetes. Other subgroups with statistically significant better response rates included patients who had a transplant date between more than 6 months and less than or equal to 12

TABLE 4. Change from baseline to day 30 in severity of GI symptoms

	Treatment group						
	EC-MPS			MMF			
	BL (N=198)	Day 30 (N=193)	Change from BL (N=193)	BL (N=195)	Day 30 (N=191)	Change from BL (N=189)	P^a
Overall total score[b]	0.7±0.4	0.4±0.4	−0.3±0.4	0.6±0.4	0.4±04	−0.2±0.4	0.026
Upper GI subtotal[c]	0.6±0.5	0.3±0.4	−0.3±0.5	0.6±0.4	0.4±0.4	−0.2±0.4	0.057
Eructation[d]	0.9±1.0	0.4±0.7	−0.4±0.8	0.7±0.8	0.5±0.8	−0.2±0.7	0.001
Lower GI subtotal[e]	0.8±0.5	0.5±0.5	−0.4±0.5	0.8±0.5	0.5±0.5	−0.2±0.5	0.038
Constipation[d]	0.4±0.8	0.2±0.6	−0.2±0.7	0.3±0.7	0.3±0.7	0.0±0.5	0.004
Flatulence increased[d]	1.0±1.0	0.6±0.9	−0.4±0.8	1.0±1.0	0.7±0.9	−0.2±0.8	0.007

Data are presented as mean±standard deviation.

[a] *P* value for treatment group comparison for change from BL based on analysis of covariance; model includes baseline severity score, center, and treatment group.

[b] Mean of severity ratings of 16 individual symptoms; severity rating: 0=absent, 1=mild, 2=moderate, and 3=severe.

[c] Mean of severity ratings of 10 individual symptoms for upper GI tract; severity rating: 0=absent, 1=mild, 2=moderate, and 3=severe.

[d] Severity rating: 0=absent, 1=mild, 2=moderate, and 3=severe.

[e] Mean of severity ratings of six individual symptoms for lower GI tract; severity rating: 0=absent, 1=mild, 2=moderate, and 3=severe.

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; BL, baseline; GI, gastrointestinal.

months of the study start date (EC-MPS: 75.8% vs. MMF: 50.0%, $P=0.035$) and patients taking steroids (EC-MPS: 65.0% vs. MMF: 50.6%, $P=0.012$; Fig. 2).

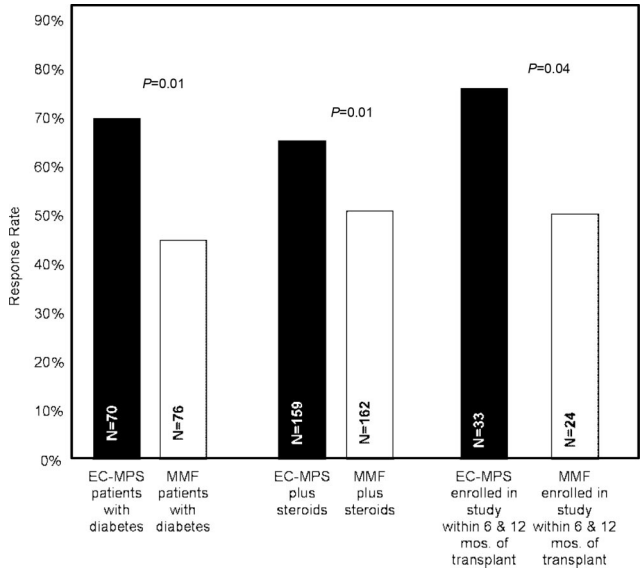

FIGURE 2. Response rates at day 30, enteric-coated mycophenolate sodium (EC-MPS) versus mycophenolate mofetil (MMF), by specific subgroups. *Black bars*: EC-MPS; *gray bars*: MMF; response=an improvement in Gastrointestinal Symptom Rating Scale total score of at least 0.3. The response rate for EC-MPS patients with diabetes identified by the transplant center pretransplant was significantly greater than MMF patients with diabetes. The response rate for EC-MPS patients who also received steroids was significantly greater than MMF patients who also received steroids. The response rate for EC-MPS patients who had their transplant between more than 6 months to less than or equal to 12 months from the start of the study was significantly greater than MMF patients with a transplant date between more than 6 months to less than or equal to 12 months at the start of the study.

DISCUSSION

This is the first randomized, double-blinded study to compare GI symptom burden between maintenance renal transplant patients with MMF-related GI symptoms converted to EC-MPS and patients maintained on MMF. In this study, 62% of patients converted from MMF to EC-MPS reached the primary efficacy endpoint of a clinically important improvement in GSRS score of at least 0.3 compared with 55% of patients maintained on MMF. However, the difference between the groups was not statistically significant ($P=0.15$). Patients converted to EC-MPS did have a statistically significant greater decrease in the GSRS indigestion syndrome dimension. In addition, patients converted to EC-MPS had a statistically significant improvement in severity of overall and specific GI symptoms (eructation, lower GI, constipation, and flatulence) during the 30-day course of the study compared with patients maintained on MMF. Patients in the EC-MPS group had numerically lower frequencies of GI-related AEs, new or worsening GI AEs during the study, and a numerically greater frequency of freedom from GI symptoms present at baseline. The pattern of data regarding improvements in GI-related outcomes tended to favor conversion from MMF to EC-MPS, despite that some of these differences were not statistically significant. This improvement in GI outcomes with EC-MPS is consistent with previously published open-label studies (*16*, *17*). Similar to other studies, the incidence of AR was low and comparable between the EC-MPS and MMF groups.

Independent of anticipated confounding variables, a significantly greater proportion of patients with diabetes in the EC-MPS conversion group had an improvement in GSRS score of at least 0.3 compared with those in the MMF-maintained group. Diabetes was the second leading primary cause of kidney failure for kidney transplants performed between 1997 and 2006. Within the deceased-donor, expanded criteria donor-kidney population, diabetes is the leading primary cause of kidney failure (*27*). The true prevalence of diabetes in the renal transplant population may be higher, as a

significant proportion of recipients reported as having a primary underlying condition of glomerular disease (the leading underlying condition) likely have diabetes. Thus, the population of kidney transplant recipients with pretransplant diabetes represents a large segment of the kidney transplant population that could uniquely benefit from the tolerability of an EC-MPS-based immunosuppressive regimen. Analysis of three clinical trials of EC-MPS versus MMF found that clinical efficacy outcomes (BPAR, death, and graft loss) were comparable between EC-MPS-treated and MMF-treated renal transplant recipients with diabetes (*28*).

The lack of statistical significance between the ITT EC-MPS and MMF groups for the primary efficacy endpoint may reflect a true lack of difference between EC-MPS and MMF in GI effects, or alternatively true differences may have been masked by factors that were not anticipated a priori. Post hoc subgroup analysis based on time since transplant identified a potential bias that may have precluded finding statistically significant improvements in the primary endpoint between the EC-MPS and MMF groups. Within the subgroup of patients who were transplanted between more than 6 months and less than or equal to 12 months of their enrollment in the study, a statistically significant greater proportion of EC-MPS-converted patients had an improvement in GSRS score of at least 0.3. It is possible that the patients with a transplant date between more than 6 months and less than or equal to 12 months of study enrollment may represent the patients with GI symptoms most clearly attributable to MMF, and therefore, the subgroup most likely to benefit from a conversion to EC-MPS. No significant difference in the primary endpoint was observed between the EC-MPS and MMF groups for patients transplanted 1 to 6 months or those transplanted more than 12 months from their study enrollment date. There was a wide range of time since transplantation in the group of patients with a transplant date more than 12 months of study enrollment; in fact, some patients were several years posttransplant at the time of enrollment. It is hypothesized that these patients may have had GI complaints because of reasons other than, or in addition to, MMF. This supposition stems from the notion that MMF-related GI symptoms would likely occur and lead to MMF dose changes or cessation with the early use of MMF (i.e., within the first year) and that patients more than a year posttransplant would have already had their immunosuppressive regimens altered in response to MMF intolerability. An analysis of the Scientific Registry of Transplant Recipients data found that the majority of immunosuppressive regimen changes for kidney transplant recipients transplanted between 1998 and 2002 occurred within the first year posttransplantation (*29*). Conversely, GI complaints of patients who are newly transplanted (<6 months) are often because of the use of other medications with GI side effects that are ultimately tapered or removed. Magnesium and phosphorous supplementation, with their innate GI toxicity, will wane in the majority of transplant patients the further they are from their date of transplantation. In addition, the target levels of the CNIs, which are inherently GI toxic, will decrease in time when target trough levels are lowered. Prophylactic antibiotics that may contribute to GI symptoms would be removed or dose reduced by 6 months at all centers. Finally, the postoperative period is fraught with GI concerns such as constipation because patients are exposed to GI slowing narcotics and nauseating anesthesia.

In addition, 55% of patients maintained on MMF achieved the primary endpoint. The high response rate suggests that many patients in the study had transient GI symptoms because of reasons other than MMF. The large number of centers participating gives strength to the overall results as it is less likely that a few centers that might make poor choices with recruitment would significantly influence the overall results. The entry criteria allowed physicians per their clinical acumen and standard of practice to exclude patients with non-MMF–related GI symptoms without dictating how this was done (e.g., stool culture or abdominal ultrasound). Previously completed open-label studies (PROGIS and MyTime) used this entry criteria, and MyGain was designed to confirm in a double-blind study the results observed in these studies.

The double-blind, randomized nature of this study was a strength of this study over the two previous studies that evaluated changes in GI complaints after conversion from MMF to EC-MPS (*16*, *17*). However, some patients may have experienced a placebo benefit from the possibility of being switched to another medication or from their participation in a clinical trial. Finally, we evaluated changes in GI symptoms and HRQoL at 1 month postconversion to MMF. It is possible that additional significant differences between the groups would have been realized with a longer follow-up period. This was suggested in MyTime where the majority of improvements in GI complaints were seen in the first month; however, the decrease in GSRS score was found to further decline at 3 months (*17*). In PROGIS, the follow-up occurred at 4 to 6 weeks posttransplant, and in fact, GI improvements in some patients were captured at 6 weeks (*16*).

A positive effect of myfortic was observed in patients taking steroids. Although the study was not stratified for steroid use, the majority of patients were taking steroids (80% EC-MPS and 82% MMF), and the steroid analysis was planned before the study initiation. Results from this trial indicate that intervention in patients with self-reported and personally concerning GI symptoms that are considered to be related to the use of MMF is associated with improvements in the presence and severity of GI symptoms and that conversion from MMF to EC-MPS shows a numerical advantage that does not reach significance. Statistically significant improvements in the presence and severity of GI symptoms were detected in patients with pretransplant diabetes and in patients converted to EC-MPS between 6 and 12 months posttransplantation. The results from the post hoc analyses suggest future modifications to the experimental design that may potentially lead to better characterization of patients with GI symptoms who may benefit from conversion of MMF to EC-MPS. It should be emphasized that these statistically significant benefits were discovered on post hoc analysis and might not prove to hold true whether these specific populations are vetted in a prospective study.

MATERIALS AND METHODS

Study Design and Conduct

MyGAIN (Myfortic [Novartis, East Hanover, NJ] and MMF [CellCept, Nutley, NJ] when administered in combination with calcineurin inhibi-

tors [CNI] in renal transplant recipients experiencing GI intolerance) was a 4-week, multicenter, randomized, prospective, double-blind, parallel-group trial in which MMF-treated and EC-MPS-treated adult renal transplant patients were evaluated for GI symptom burden and health-related quality of life (HRQoL) (clinical trial NCT00400400). The follow-up of 4 weeks was chosen because it was adequate in the PROGIS and US02 (myTIME) studies to demonstrate a statistical change in response.

Patients with self reported and personally distressing GI complaints, which the investigators determined to be related to MMF, were randomly assigned to one of the following two treatment arms in a 1:1 ratio: group 1: equimolar dose of EC-MPS+MMF placebo+CNI±steroids; group 2: MMF+EC-MPS placebo+CNI±steroids (Fig. 1). Twelve-hour trough MPA concentrations in peripheral blood were measured at baseline and day 30 to monitor compliance with study medication.

Randomization

Study medications were double blinded. Patients, investigator staff, persons performing the assessments, and data analysts were blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) randomization data were kept strictly confidential until the time of unblinding and (2) the identity of the treatments was concealed by using study drugs with matching placebos that were identical in packaging, labeling, schedule of administration, appearance, and odor. A double-dummy design was used because the identity of the study drugs could not be disguised because of their different forms.

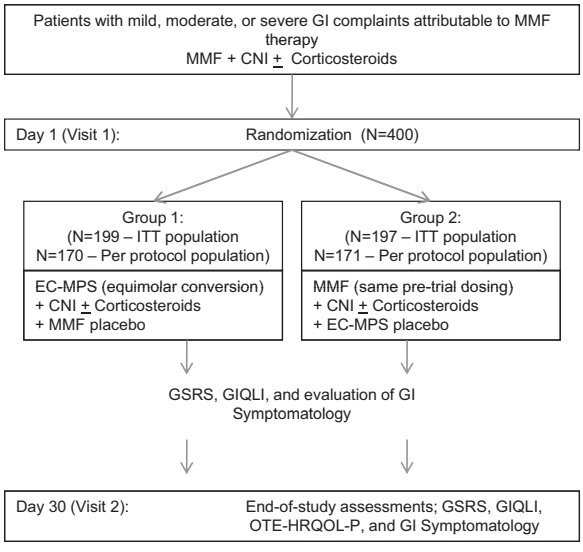

FIGURE 1. Schematic of study design. GI, gastrointestinal; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; GSRS, Gastrointestinal Symptom Rating Scale, a 15-item instrument assessing symptoms associated with common GI disorders. It has five subscales/dimensions (reflux, diarrhea, constipation, abdominal pain, and indigestion). Subscale scores range from 1–7, and higher scores represent higher symptom burden (i.e., more discomfort). Each of the GSRS dimensions was summarized by determining the mean of the individual questions within that dimension. The total score was also determined by computing the mean of all 15 questions. GIQLI: Gastrointestinal Quality of Life Index, a 36-item GI-specific health-related quality of life (HRQoL) instrument with five subscales (GI symptoms, emotional status, physical function, social function, and stress of medical treatment), and scores ranging from 0 to 4, and a total score ranging from 0 to 144. Higher scores indicate better GI-specific HRQoL. OTE-HRQL-P, overall treatment effect for health-related quality of life; the OTE was used to assess change in HRQoL since the baseline visit. Higher scores represent greater improvement or deterioration, depending on the scale. GI symptomotology: the severity of any GI condition was assessed by the attending physician as 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. In addition, total scores were determined for upper GI tract symptoms, lower GI symptoms, and overall symptoms.

At the baseline visit, all patients who fulfilled the inclusion or exclusion criteria for the study and provided informed consent were assigned a randomization number in the order in which they were enrolled, each successive patient receiving the lowest number available at the site. The randomization list was generated by Novartis Drug Supply Management using a validated system that automated random assignment of treatment arms to randomization numbers in a 1:1 ratio. The randomization numbers ranged from 1001 to 2268 and were assigned to sites in blocks of 4; numbers were entered on the randomization case report form only. On all other case report forms, patients were identified only by their 9-digit patient identification number.

Patient Population

Eligible patients were those aged 18 to 75 years who had undergone renal transplants at least 4 weeks from baseline and had been receiving an immunosuppressive regimen that included MMF (up to 3 g/day dosage allowed)+Neoral (Novartis, East Hanover, NJ) (or its generic equivalent, cyclosporine United States Pharmacopeia [MODIFIED]) or tacrolimus, with or without corticosteroids, and with self-reported but personally distressing GI symptoms determined to be associated with MMF therapy. The study was not stratified for steroid use, and steroid doses were permitted to be altered during the study. Major exclusion criteria included: multiorgan transplant patients, severe GI disorder, preexisting significant GI conditions without a presumed causal relationship with MMF, modification of GI medication or MMF dose within 1 week before baseline, evidence of graft rejection, treatment of acute rejection (AR), unstable renal function within 4 weeks before the baseline visit, inability to self-administer the study questionnaires, and patients receiving generic formulations of MMF.

The intent-to-treat (ITT) population, defined as all enrolled patients who took at least one dose of blinded study medication, was the primary population for analysis; the safety population was identical to the ITT population. The per-protocol population included all patients who received at least 17 days of study drug and completed the study without any major deviations from the protocol. Planned subgroup analyses were conducted by specific CNI (tacrolimus and cyclosporine) and for patients with and without steroids; post hoc analysis was conducted for patients with pretransplant diabetes, African American patients, and by time since transplantation to study enrollment (i.e., ≤6 months, >6 to ≤12 months, and >12 months).

Patient-Reported Outcomes

Three self-administered questionnaires were used: the Gastrointestinal Symptom Rating Scale (GSRS) (*18–20*), the Gastrointestinal Quality of Life Index (GIQLI) (*18*, *21*), and the Overall treatment effect (OTE) in HRQoL (*22–25*) (Fig. 1); each have been previously validated in renal transplant recipients (*18*). The severity of any GI condition was also assessed by the attending physician.

Primary and Secondary Efficacy Outcomes

The primary efficacy outcome was the proportion of EC-MPS versus MMF patients with MMF-associated GI intolerance that responded to the intervention of conversion of MMF to EC-MPS therapy. Response to intervention was defined as meeting or exceeding the minimal important difference of 0.3 in change from baseline in GSRS total score at day 30. The minimal important difference is the smallest difference in score in the domain of interest (i.e., subscales of questionnaires) that patients or clinicians perceive to be important, as beneficial or harmful (*26*). The secondary efficacy outcomes were the proportion of EC-MPS versus MMF patients with biopsy-proven acute rejection (BPAR) and treated AR.

Secondary Safety Outcomes

Secondary safety outcomes included: the proportion of patients with no new or worsening GI symptoms within 30 days, the change from baseline in the severity of GI symptoms at day 30, the proportion of patients with dose changes or interruptions of study medication within 30 days, the change from baseline in GSRS total and subscale scores at day 30, the change from baseline in GIQLI total and subscale scores at day 30, the proportion of patients at day 30 who were free of at least one GI symptoms that was present at baseline (diarrhea, dyspepsia, acid reflux, and abdominal pain), the proportion of patients at day 30 who were free of diarrhea that was present at baseline, HRQoL OTE scores at day 30, and the change in the severity of diarrhea from baseline to day 30.

Statistical Analyses

For the primary efficacy outcome, response rates were summarized as number and percent of responders in each treatment group. A Cochran-Mantel-Haenszel test, adjusting for center was used to test for a significant difference between groups in response to treatment. For the secondary efficacy evaluations, the proportion of patients with BPAR or AR-treated patients at day 30, the number and percent of AR per patient, and the severity of BPAR, assessed according to the Banff '97 criteria, were summarized descriptively.

For the continuous secondary safety evaluations, the change from baselines were compared between treatment groups using an analysis of covariance model with baseline measurement as a covariate and treatment and center as main effects. The statistical significance of the mean change from baseline was assessed using a paired *t* test. HRQoL OTE scores at day 30 were compared between treatment groups using an ANOVA model with treatment and center as main effects when analyzing the score and by Cochran-Mantel-Haenszel test for association, adjusting for centers, when analyzing the categorical outcome of better, about the same, or worse. The categorical secondary safety evaluations were compared between treatment groups using Cochran-Mantel-Haenszel tests adjusting for center.

The sample size was calculated to detect at least a 15% difference in response rates between the EC-MPS treatment group and the MMF treatment group using a two-sided, chi-square test with a significance level of 0.05 and 80% power. Chi-square was chosen because of the larger sample size and not the Fisher's exact test, which can be used for 2×2 tables if the population number were smaller. Assuming an MMF response rate of 45%, 173 patients per treatment group would be needed. Assuming a dropout rate of 10%, 384 randomized patients would ensure approximately 346 completed patients.

Statistical analyses were performed using SAS, version 9.1 (SAS, Inc., Cary, NC) and were based on the pooled data from the individual study centers. All statistical tests were conducted under a two-sided alternative hypothesis, using a significance level of 0.05. Institutional review board approval was obtained at each participating center, and informed consent was obtained from all patients. The study was undertaken in accordance with the The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.

APPENDIX

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