Improvement in 3-Month Patient-Reported Gastrointestinal Symptoms After Conversion From Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium in Renal Transplant Patients

Paul Bolin,[1,10] Bekir Tanriover,[2] Gazi B. Zibari,[3] Melissa L. Lynn,[4] John D. Pirsch,[5] Laurence Chan,[6] Matthew Cooper,[7] Anthony J. Langone,[8] and Stephen J. Tomlanovich[9]

Background. The benefit of conversion from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS) in terms of gastrointestinal symptom burden has been evaluated previously using patient-reported outcomes. However, data are lacking concerning the sustained effect of conversion over time, and the potential impact of concomitant calcineurin inhibitor.

Methods. In this 3-month, prospective, multicenter, longitudinal, open-label trial, MMF-treated renal transplant patients with gastrointestinal symptoms receiving cyclosporine or tacrolimus were converted to equimolar doses of EC-MPS. Change in gastrointestinal symptom burden was evaluated using a validated Gastrointestinal Symptom Rating Scale (GSRS).

Results. A significant improvement in GSRS score was observed from baseline (2.61, 95% CI 2.54–2.68) to month 1 (1.87, 95% CI 1.81–1.93) after conversion to EC-MPS and was sustained to month 3 (1.81, 95% CI 1.74–188; both $P<0.0001$ versus baseline). The mean change in overall GSRS score from baseline to month 1 was −0.74 overall (cyclosporine: −0.73 and tacrolimus: −0.74; all $P<0.0001$ versus baseline), with a slight further improvement (−0.79) at month 3 (cyclosporine: −0.82 and tacrolimus: −0.78; all $P<0.0001$ versus baseline). A significant improvement in GSRS subscale scores was also observed in the total population regardless of calcineurin inhibitor at month 1, sustained to month 3 (all $P<0.0001$ versus baseline). The improvement in GSRS score postconversion was similar in African-American and non-African-American patients, and in diabetic and nondiabetic patients.

Conclusions. This exploratory study in 728 patients demonstrates that following conversion from MMF to EC-MPS, regardless of concomitant calcineurin inhibitor, GSRS is improved and sustained over 3 months.

Keywords: Mycophenolate mofetil, Enteric-coated mycophenolate sodium, Myfortic, Gastrointestinal symptoms, Quality of life.

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Mycophenolic acid (MPA) therapy has become routine after renal transplantation, based on evidence from pivotal trials (*1–3*) and large-scale registry analyses (*4*, *5*) showing a significant reduction in acute rejection and graft loss. Gastrointestinal (GI) complications, however, are common in MPA-treated patients (*6*), and a high proportion of renal transplant patients (40–50%) who experience GI symptoms while receiving mycophenolate mofetil (MMF) require a dose reduction or MMF discontinuation (*7*, *8*). Inadequate MPA dosing is associated with an increased risk of acute rejection after renal transplantation (*9–11*) and retrospective analyses have demonstrated that patients receiving MMF dose reductions or discontinuation experience a higher rate of rejection (*7*, *12*) and graft loss (*13*). Large-scale registry analyses have confirmed that patients receiving MMF dose changes associated with GI complications are at greater risk of graft loss (*8*, *14*). Bunnapradist et al. reported a 1.8-fold increase in graft loss among patients receiving a GI-associated MMF dose reduction and a 2.2-fold increase in patients with GI-related MMF discontinuation (*8*). Moreover, in addition to physician-initiated dosing changes, patients with GI complications are less likely to adhere to their prescribed MMF dosing schedule (*15*). Therefore, strategies that reduce the GI symptom burden and risk of suboptimal MPA dosing would help to avoid the consequent adverse clinical implications.

In an attempt to limit GI complications and improve dosing, an enteric-coated formulation of mycophenolate sodium (EC-MPS, *myfortic*) has been developed. A large randomized trial conducted in de novo renal transplant patients demonstrated therapeutic equivalence of EC-MPS and MMF

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[1] Division of Nephrology and Hypertension, Brody School of Medicine at East Carolina University, Greenville, NC.
[2] Department of Renal Transplantation, Dallas Nephrology Association, Dallas, TX.
[3] Department of Surgery, Willis Knighton/Louisiana State University Health Science Center, Shreveport, LA.
[4] Northwest Louisiana Nephrology Research, Shreveport, LA.
[5] Department of Surgery, University of Wisconsin Hospital and Clinics, Madison, WI.
[6] Department of Transplant Nephrology, University of Colorado Health Sciences Center, Denver, CO.
[7] Department of Surgery, University of Maryland Medical Center, Baltimore, MD.
[8] Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN.
[9] Department of Surgery, University of California San Francisco, School of Medicine, San Francisco, CA.
[10] Address correspondence to: Paul Bolin, M.D., Division of Nephrology and Hypertension, Brody School of Medicine, East Carolina University, 2355 West Arlington Blvd, Greenville, NC 27834.
E-mail: bolinp@ecu.edu

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(*16*), and that conversion from MMF to EC-MPS can be undertaken safely without compromising efficacy (*17*, *18*). Data from maintenance renal transplant patients have suggested that the severity of GI adverse events may be lower with EC-MPS (*17*), and there are anecdotal reports in the literature that conversion to EC-MPS can alleviate GI complications in MMF-treated patients (*19*), leading to interest in further comparisons of GI tolerability between the two formulations.

Recently, the PROGIS (measurement of patient reported outcomes in renal transplant recipients with and without GI symptoms) study used patient-reported outcomes measures to assess the effect of conversion to EC-MPS in renal transplant recipients experiencing mild to moderate GI complications during MMF treatment (*20*). The results demonstrated a consistent and significant reduction in GI-related symptom burden, and improved patient functioning and well-being, within the first 4–6 weeks after conversion to EC-MPS. As part of the analysis of data from PROGIS, the minimal important difference (MID) was calculated, the smallest difference in patient-reported outcomes using instruments such as the Gastrointestinal Symptom Rating Scale (GSRS) that either patients or clinicians perceive to be important, either as beneficial or harmful (*21*). MID values for the GSRS subscale scores were calculated to range from 0.4 to 0.8, and the improvement on each scale exceeded the MID (*20*).

The PROGIS study, however, did not evaluate the impact of calcineurin inhibitor choice on conversion to EC-MPS, and did not assess whether the effect of conversion was sustained beyond 4–6 weeks. To extend the findings from PROGIS, a prospective, multicenter study was undertaken with the objective of assessing the tolerability of EC-MPS after conversion from MMF in maintenance renal transplant patients considered by their physician to have MMF-related GI intolerance. The current trial involved more than 700 patients with 3 months of follow-up.

MATERIALS AND METHODS

Study Design and Conduct

The study was a 3-month, longitudinal, multicenter, open-label, prospective trial in adult renal transplant patients receiving MMF in combination with either cyclosporine or tacrolimus, and who were experiencing mild or moderate GI symptoms that were considered by their physician to be related to MMF therapy. Patients were converted to an equimolar dose of EC-MPS and were evaluated using patient-reported outcomes measures at baseline, month 1, and month 3. Patients were recruited at 55 transplant centers in the United States. 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 International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.

Patient Population

Patients aged 18–75 years were eligible to enter the study if they had received a renal transplant at least 4 weeks previously and had been receiving an immunosuppressive regimen that included MMF (at any dose) with cyclosporine or tacrolimus and with or without steroids for at least 2 weeks. All participants were required to be experiencing mild to moderate GI complications of any kind that were considered by their physician to be related to MMF therapy. GI complications were to have been present for a minimum of 2 weeks before study entry, but there was no maximum time limit for duration of symptoms. Patients experiencing GI symptoms prior to transplantation were excluded. Recipients of first or second transplants from a deceased, living-related, or living-unrelated donor could be enrolled but patients receiving a multiorgan transplant or a previous nonrenal transplant were excluded, as were those who had evidence of acute rejection within 2 weeks prior to study entry. Patients were also excluded if they had a clinically significant infection requiring continued therapy, severe diarrhea (as defined by the investigator), or active peptic ulcer disease that would interfere with the study conduct.

Immunosuppression

All patients were converted at baseline from MMF to an equimolar dose for MPA; for example, EC-MPS 360 mg corresponds to MMF 500 mg. Patients were instructed to take EC-MPS twice-daily; if MMF had been administered three times a day (t.i.d.), EC-MPS was given twice-daily with reversion to t.i.d. dosing if moderate or severe adverse events occurred. EC-MPS dose reduction or temporary interruption was permitted in cases of leukopenia (leukocyte count $<4{,}000/mm^3$), thrombocytopenia ($<75{,}000\ mm^3$), or neutropenia (absolute neutrophil count $<1{,}500\ mm^3$) or in response to moderate or severe adverse events. Patients were permitted to continue the study at a reduced dose. If EC-MPS was temporarily withdrawn, it was to be restarted once the adverse event had resolved or returned to an acceptable grading. Discontinuation was considered if EC-MPS was interrupted for safety-related considerations for more than 2 consecutive days within the first 2 weeks after conversion, or for longer than 12 days thereafter. Cyclosporine or tacrolimus administration was continued throughout the study as per local practice, with changes in dose permitted where necessary for medical reasons. Corticosteroid dosing was as per local practice.

Patient-Reported Assessments

Patients reported their perception of the change in GI symptom burden after conversion to EC-MPS using the self-administered GSRS questionnaire. The GSRS is a 15-item instrument designed to assess the severity of symptoms associated with common GI disorders (*22*, *23*), which has previously been validated in renal transplant recipients (*24*). It consists of five subscales (abdominal pain, reflux, diarrhea, indigestion, and constipation). Subscale scores range from 1–7 with higher scores representing higher symptom burden. Overall GSRS score was defined as the mean of all 15 item scores. In addition, patients provided an overall evaluation of treatment effect in terms of the change in their symptoms and health-related quality of life (HRQoL) by completing two further questionnaires: (a) Overall Treatment Effect (OTE) scale for GI symptoms and (b) OTE scale for HRQoL (*25*, *26*). Patients completed the GSRS questionnaire at each study visit, and completed the OTE questionnaires for symptoms and HRQoL at the 3-month visit. Physicians also completed

the OTE questionnaire for symptom assessment at the 3-month visit.

Physician-Reported Assessments

In conjunction with the patients' self-assessments, physicians evaluated GI symptoms using standard adverse event reporting procedures. At baseline, patients were asked by their physician what GI complications they had experienced in the previous 2 weeks, including their duration and severity. At months 1 and 3, the physician asked patients what GI complications had occurred since the previous study visit, again including duration and severity. After physicians had classified the severity of GI complications, severity was quantified as no event, 0; mild, 1; moderate, 2; and severe, 3.

Study Endpoints

The primary tolerability variable was the change in overall GSRS score from baseline within 3 months. Secondary safety and tolerability variables included the change from baseline in GSRS subscale scores; the incidence of GI complications; the change from baseline in GI symptom severity score; the proportion of patients receiving medication for GI complications; the occurrence of adverse events; and the occurrence of infections. Efficacy variables included the incidence of biopsy-proven acute rejection (BPAR), death, or graft loss.

Statistical Analysis

Sample size calculation showed that a minimum sample size of 375 patients per cohort was required to provide 90% power to detect a change from baseline of 0.2 in overall GSRS score considering a 0.05 significance level and a standard deviation of 1.1 for a paired *t* test, and allowing for a 10% dropout. All analyses were performed on the intent-to-treat (ITT) population, which consisted of all patients who received at least one dose of EC-MPS. Changes in overall GSRS and subscale scores from baseline within patients receiving either cyclosporine or tacrolimus were tested using a paired *t* test at the 0.05 level of significance.

The incidence of GI complications was calculated for the 3-month treatment period, and for three time periods: during the 2 weeks prior to first EC-MPS dose (baseline), during the 2 weeks prior to the month 1 visit (a posthoc analysis), and the month 3 visit. The incidence of GI complications at baseline and at month 3 within treatment groups was compared using McNemar's test (a posthoc analysis). Severity of GI complications was also calculated for the 3-month treatment period, the 2 weeks prior to first EC-MPS dose (baseline), the 2 weeks prior to the month 1 visit and the 2 weeks prior to the month 3 visit (the latter two are posthoc analyses). Changes from baseline in the severity of GI complications within the cyclosporine or tacrolimus cohorts were tested using paired *t*-tests.

RESULTS

Patient Population

Recruitment took place at 55 centers in the United States during the period September 2004 to September 2005, with the last patient visit taking place in February 2006. Of 742 patients screened for inclusion in the study, 734 were enrolled and 728 comprised the ITT population (224 received cyclosporine and 504 received tacrolimus; Fig. 1). Due to slower than expected enrolment of cyclosporine-treated patients, more tacrolimus-treated patients were enrolled than originally intended to ensure a total of 750 patients for pooled data analysis. Sixty-two patients were lost to follow-up or discontinued the study prematurely (Fig. 1), such that 666 patients (92%) completed the trial (211 cyclosporine, 455 tacrolimus patients). Adverse events were the most frequent reason for discontinuation (25/53 [47%]; Fig. 1). There were 34 patients with protocol violations (11 cyclosporine, 23 ta-

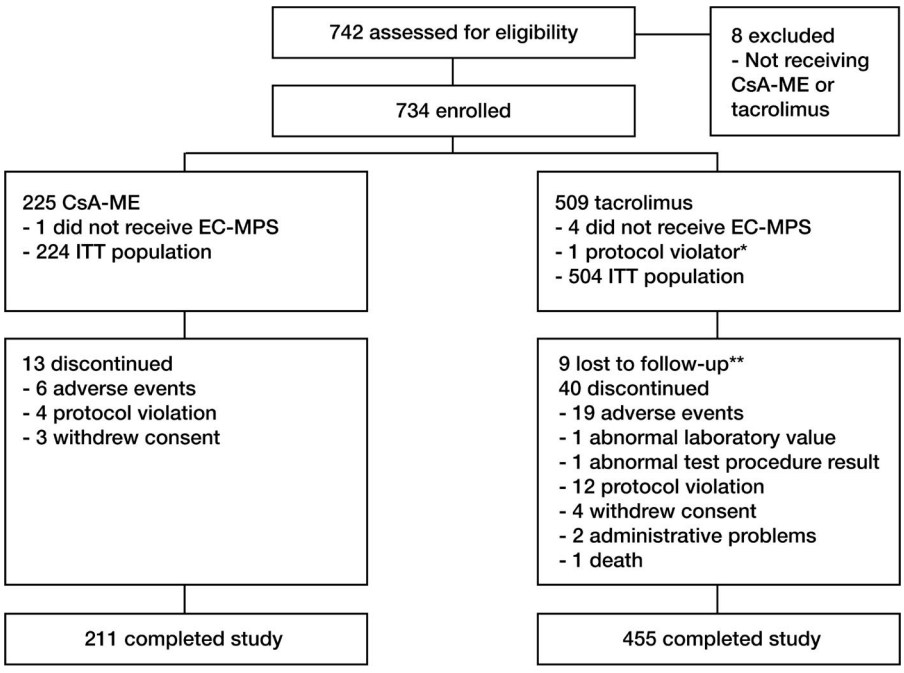

FIGURE 1. Patient disposition. ITT, intent-to-treat. *, no gastrointestinal complaints at baseline; **, reasons not recorded.

TABLE 1. Demographics and baseline characteristics

	All patients	Cyclosporine	Tacrolimus
N	728	224	504
Recipient age (years)	50 (18–81)	52 (21–75)	49 (18–81)
Recipient male sex	381 (52%)	124 (55%)	257 (51%)
Recipient race/ethnicity			
White	362 (50%)	115 (51%)	247 (49%)
African-American	272 (37%)	86 (38%)	186 (37%)
Asian	12 (2%)	4 (2%)	8 (2%)
Other	82 (11%)	19 (8%)	63 (12%)
Cause of end-stage renal failure			
Hypertension/nephrosclerosis	192 (26%)	62 (28%)	130 (26%)
Glomerulonephritis/glomerular disease	123 (17%)	49 (22%)	74 (15%)
Diabetes mellitus	141 (19%)	34 (15%)	107 (21%)
Polycystic disease	53 (7%)	16 (7%)	37 (7%)
Other/unknown	219 (30%)	63 (28%)	156 (31%)
Time since most recent transplant (days)	615 (18–7881)	1542 (28–7881)	485 (18–5988)
Donor age (years)	36 (1–72)	34 (5–67)	38 (1–72)
Duration of GI complications reported during 2 weeks prior to conversion to EC-MPS			
>2 weeks	670 (92.9%)	209 (94.6%)	461 (92.2%)
>6 months	460 (63.8%)	163 (73.8%)	297 (59.4%)
>12 months	394 (54.7%)	146 (66.1%)	248 (49.6%)

Data are n (%) or median (range).

crolimus); the most frequent cause of protocol violation was nonequimolar conversion to EC-MPS at baseline (5 cyclosporine, 10 tacrolimus). One hundred and forty-nine patients (20.5%) had experienced at least one severe posttransplant GI complication at the start of the study, an exclusion criterion; however, they were included in the ITT analyses because this was not considered a major deviation from the protocol. In terms of symptom duration, the GI symptoms reported during the 2 weeks prior to conversion to EC-MPS had been present for more than 1 year in 54.7% of patients and for more than 6 months in 63.8% of patients (Table 1). The mean time since transplant was threefold longer in cyclosporine-treated patients than in those receiving tacrolimus, but otherwise the characteristics of patients receiving either calcineurin inhibitor were similar (Table 1).

Immunosuppression and Concomitant Medication

At baseline, the mean MMF dose was 1567±560 mg/day (1697±574 mg/day in cyclosporine-treated patients and 1509±544 mg/day in tacrolimus-treated patients). The mean dose of EC-MPS remained stable after conversion (1114±393 mg/day at month 1 and 1092±393 mg/day at month 3), and was slightly lower in tacrolimus-treated patients (1072±383 mg/day versus 1209±400 mg/day in cyclosporine patients at month 1, and 1049±385 mg/day versus 1189±395 mg/day at month 3). Across the total study population, 99 of 728 patients (14%) required a dose reduction and 24 of 728 patients (3%) required a dose interruption. The most frequent reason for dose reduction or interruption was an adverse event or abnormal laboratory or test result (n=80). Of the adverse events leading to a dose reduction and/or interruption, leukopenia was the most common (n=34).

Median cyclosporine trough level was 140 ng/mL (range 5–1243; mean 162±124 ng/mL) at month 1 and 133 ng/ml (range 9–981; mean 150±106 ng/mL) at month 3; median tacrolimus trough level was 7.0 ng/mL (range 0.4–570 ng/mL; mean 9.9±32.8 ng/mL) at month 1 and 6.7 ng/mL (range 0–368 ng/mL; mean 9.0±22.7 ng/mL) at month 3.

At baseline, 605 patients (83%) were receiving one or more medications for GI complications (cyclosporine 185 [83%], tacrolimus 420 [83%]), compared to 590 patients (81%) (cyclosporine 183 [82%], tacrolimus 407 [81%]) at 3 months after conversion to EC-MPS.

Tolerability and Efficacy

Non-GI complications were reported by 326 patients (45%: 90 cyclosporine [40%], 236 tacrolimus [47%]), of which the majority were mild or moderate. In total, 140 patients (19.2%) experienced GI and non-GI adverse events with a suspected relation to EC-MPS (55 patients with non-GI events [7.6%] and 106 patients with GI events [14.6%]). Diarrhea was the most frequent GI event to be reported with a suspected relation to EC-MPS (59 patients, 8.1%). Leukopenia, neutropenia, anemia, and thrombocytopenia with a suspected relation to EC-MPS occurred in 22, 8, 1, and 1 patient, respectively. Infections were reported in 151 patients (21%: 32 cyclosporine [14%], 119 tacrolimus [24%]), including cytomegalovirus infection in two patients receiving cyclosporine and five patients receiving tacrolimus.

Ten patients (1.4%) experienced BPAR during the 3-month study: four in patients receiving cyclosporine, all of

which were graded mild (Banff Grade IA or IB [*27*]), and six in patients receiving tacrolimus (three Grade IA, one Grade IIA, and two of unknown severity). There were two graft losses (0.3%), each of which was due to acute rejection and occurred in tacrolimus-treated patients who underwent transplantation due to diabetic nephropathy. One patient receiving tacrolimus died due to a myocardial infarction after the protocol-defined final visit window.

Patient-Reported Results

The mean overall GSRS score at baseline (±SE) was 2.61±0.03 (95% CI 2.54–2.68), improving to 1.87±0.03 (95% CI 1.81–1.93) at month 1 ($P<0.0001$ versus baseline). This change was sustained at month 3 after conversion (mean 1.81±0.03, 95% CI 1.74–1.88, $P<0.0001$ versus baseline). For patients receiving cyclosporine, mean overall GSRS score was 2.57±0.07 (95% CI 2.44–2.70) at baseline, and 1.84±0.06 (95% CI 1.72–1.95) at month 1 and 1.76±0.06 (95% CI 1.64–1.87) at month 3 (both $P<0.0001$ versus baseline). For tacrolimus-treated patients, overall GSRS score was 2.62±0.04 (95% CI 2.54–2.70) at baseline, 1.88±0.03 (95% CI 1.82–1.95) at month 1 and 1.84±0.04 (95% CI 1.75–1.92) at month 3 (both $P<0.0001$ versus baseline).

GSRS subscale scores were similar in patients receiving cyclosporine or tacrolimus at baseline, other than a slightly lower score on the diarrhea subscale among cyclosporine-treated patients (Fig. 2). All GSRS subscale scores improved significantly ($P<0.0001$) after conversion from MMF to EC-MPS across the total population and in patients receiving either calcineurin inhibitor (Fig. 2).

The majority of the improvement was apparent within the first month after conversion: overall GSRS score and all subscales showed significant decreases by the end of month 1 in both the cyclosporine- and tacrolimus-treated patients (all $P<0.0001$), with further minor improvements observed at month 3 on some subscales (Fig. 2).

Patient ratings of OTE for GI symptoms 3 months after conversion from MMF to EC-MPS showed that 478 patients (66%) considered that their symptoms had improved compared to baseline. In all, 137 cyclosporine patients (61%) and 341 tacrolimus patients (68%) reported an improvement. Physicians' ratings of OTE for GI symptoms were consistent with the patient-rated results (Fig. 3). The OTE for HRQoL was also rated by patients: 397 patients (55%) reported an improvement at the end of the study versus baseline (107 cyclosporine patients [48%] and 290 tacrolimus patients [58%]; Fig. 3).

Physician-Reported Results

Physician-reported data showed GI adverse events that occurred in at least 10% of patients became significantly less frequent after conversion from MMF to EC-MPS, with the majority of the improvement being apparent by month 1 postconversion and maintained at month 3 (Fig. 4). The incidence of these GI events decreased significantly among patients receiving either cyclosporine or tacrolimus, except for constipation, abdominal pain and hard feces in cyclosporine-treated patients, and constipation and hard feces in tacrolimus-treated patients. The mean severity score improved significantly from baseline to three months for all GI complications reported by ≥10% of patients (Fig. 5); significant improvements were also observed for patients receiving cyclosporine or tacrolimus, other than for abdominal pain in cyclosporine-treated patients and constipation, abdominal pain and hard feces in tacrolimus-treated patients.

Patient-Reported Results in Subpopulations

In posthoc analyses, the change in mean overall GSRS score from baseline to month 3 did not appear to be affected by African-American origin versus non-African-American, presence of diabetes, use of proton pump inhibitor (PPI) therapy, renal function, or time since transplantation. The mean change in overall score was −0.78 in African-American recipients (n=272) and −0.80 in non-African-Americans (n=456). Patients with diabetes appeared to obtain at least as great a benefit (−0.85, n=141) as those who were diabetes-free (−0.79, n=587). The improvement in overall GSRS score was −0.83 among patients receiving PPI therapy (n=384) compared to −0.75 in those without PPI treatment (n=344). Patients with very poor renal function (creatinine clearance <30 mL/min/1.73 m^2) showed a higher improvement in overall GSRS score than those with CrCl >30 mL/min/1.73 m^2, but only 22 patients had very poor renal function so this finding should be interpreted with caution. Time posttransplant did not affect the extent of improvement in overall GSRS score; newly transplanted patients (<3 months posttransplant) reported a similar change to those >24 months posttransplant (−0.89 [n=127] versus −0.81 [n=334]). The change in incidence and severity of the most frequent GI symptoms (diarrhea, gastroesophageal reflux disease [GERD], flatulence, dyspepsia, nausea, and abdominal distension) from baseline to 3 months after conversion to EC-MPS did not appear to differ between any of the subpopulations examined.

DISCUSSION

The results from this study support those of a previous trial (*20*) demonstrating that conversion of maintenance renal transplant patients with MMF-related GI symptoms to EC-MPS significantly reduces patients' GI symptom burden. The significance of GI symptom burden has been evaluated utilizing the GSRS scale, an instrument previously validated in both transplant (*24*) and nontransplant populations (*22*, *23*, *28*). Mean GSRS scores observed in the current study ranged from 2.17 to 3.02 at baseline and, while not directly comparable, are of the same magnitude of those reported by the GERD patient population (*28*). The overall GSRS score and subscale scores improved significantly after conversion from MMF to EC-MPS for the total study population and for tacrolimus-treated patients, with the greatest benefit being observed on the diarrhea subscale. It is also noteworthy that the improvement was highly significant for cyclosporine treated patients despite lower patient numbers (n=224). Furthermore, the improvement in GSRS scores was sustained, and indeed showed a slight numerical improvement, between the first and third month postconversion. Using OTE scales, more than half of all patients considered that their GI symptoms and HRQoL had improved 3 months after conversion to EC-MPS compared to baseline. Since HRQoL relates to all aspects of health and not solely GI events, it is not unexpected that an improvement in overall HRQoL was reported by fewer patients than for GI symptoms alone, but nevertheless

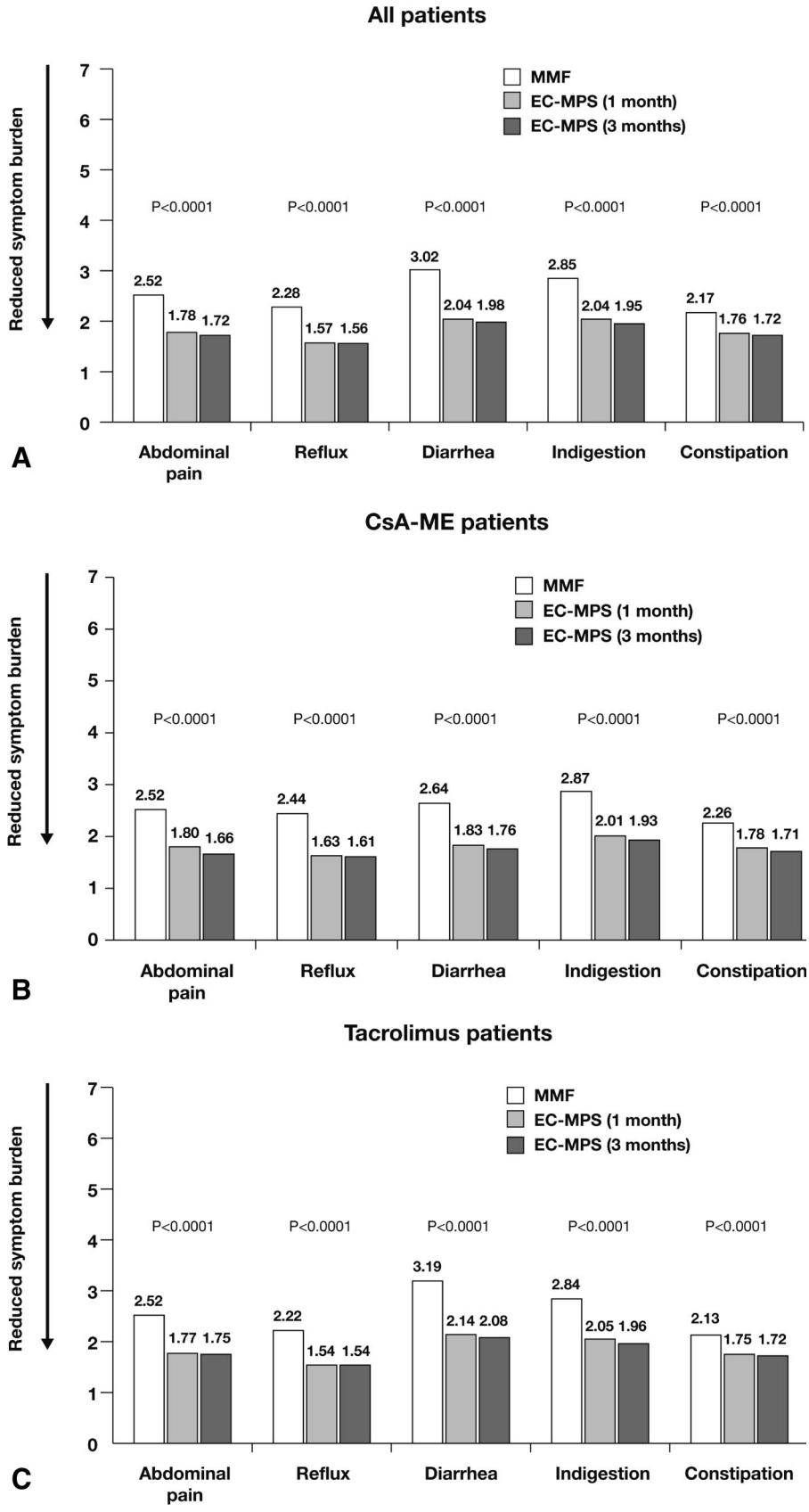

FIGURE 2. Patient-reported results: mean GSRS subscale scores at baseline (while receiving MMF) and at 1 and 3 months after conversion to EC-MPS in (A) all patients [n=728], (B) cyclosporine patients [n=224], and (C) tacrolimus-treated patients [n=504]. *P* values refer to the difference between baseline and month 1, and between baseline and month 3 (all $P<0.0001$). Mean GSRS subscale scores in patients with GERD have previously been reported to be 2.27 (abdominal pain), 3.09 (reflux syndrome), 1.74 (diarrhea), 2.48 (indigestion syndrome), and 1.75 (constipation) (*28*).

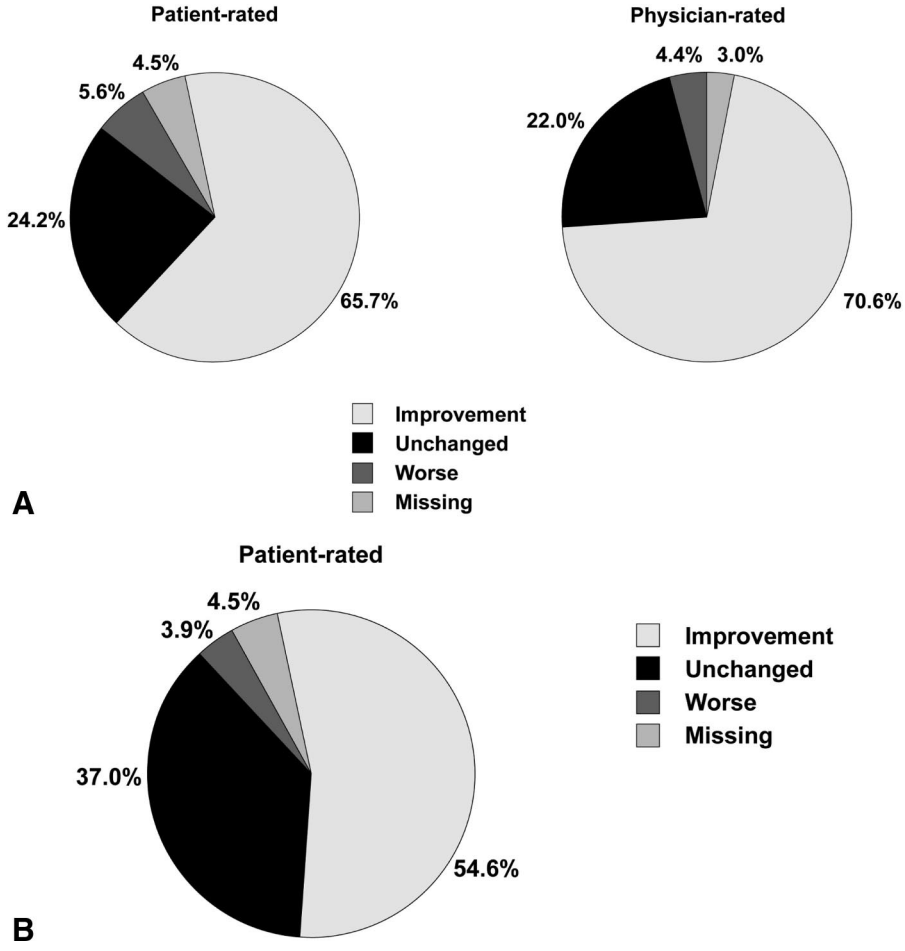

FIGURE 3. Overall Treatment Effect (OTE) ratings for (A) GI symptoms (patient-reported and physician-reporteded results) and (B) health-related quality of life (HRQoL; patient-reported results) 3 months after conversion to EC-MPS compared to baseline (i.e., while receiving MMF).

it is encouraging that 55% of patients considered their HRQoL to be better after conversion to EC-MPS.

The MID values from the PROGIS study (0.4 to 0.8) were applied to results from the current trial to assess the clinical relevance of the findings. This GSRS MID was derived from the change in baseline in patient-reported outcomes score (GSRS) between patients with "no change" and the patients with an improvement rate "a little better" or "somewhat better" on the OTE scale. The improvement in GSRS subscale scores after conversion to EC-MPS exceeded the MID for all subscales at months 1 and 3 except for reflux and constipation, suggesting that improvements in GSRS scores

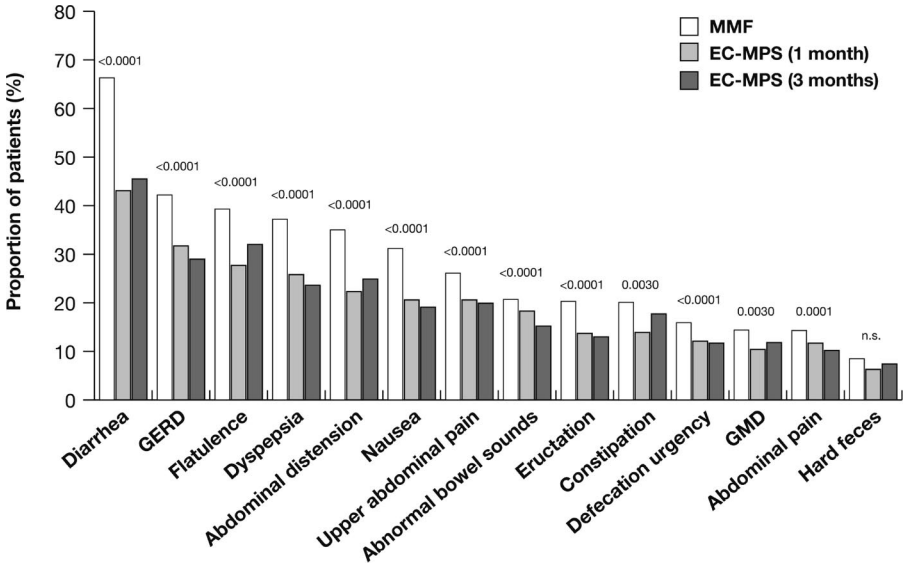

FIGURE 4. Physician-reported results: incidence of GI complications occurring in ≥10% patients at baseline (while receiving MMF), and at 1 and 3 months after conversion to EC-MPS (n=728). GERD, gastroesophageal reflux disease; GMD, gastrointestinal motility disorder. *P* values refer to the change in incidence between baseline and month 3 postconversion.

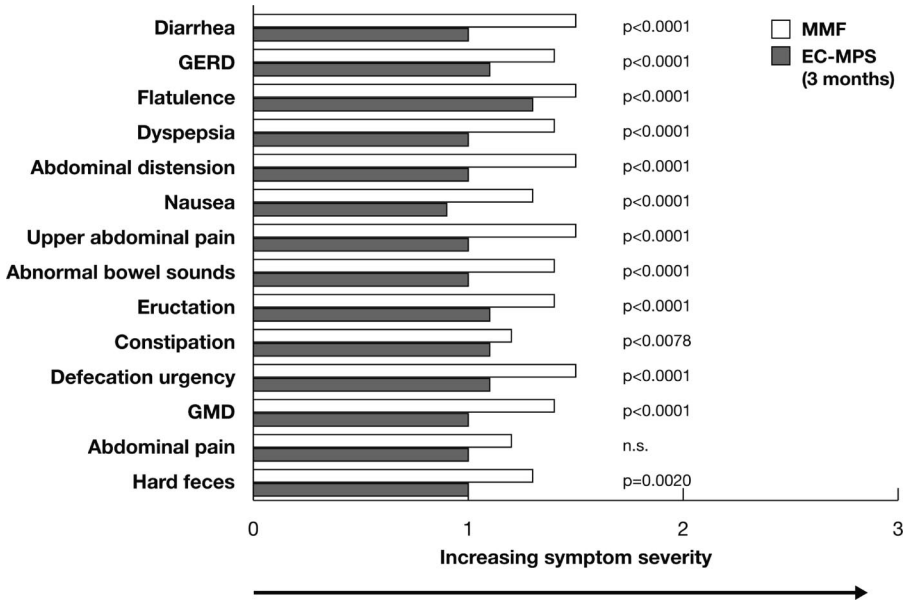

FIGURE 5. Physician-reported results: mean severity score for GI complications occurring in ≥10% patients at baseline (while receiving MMF) and 3 months postconversion to EC-MPS, based on physicians' assessment (n=778). GERD, gastroesophageal reflux disease; GMD, gastrointestinal motility disorder. Severity rating: 0=no event; 1=mild; 2=moderate; 3=severe.

after conversion to EC-MPS are clinically relevant for patients. The improvement in GSRS scores was consistent with the finding that the incidence and severity of all frequent GI complications decreased after conversion to EC-MPS. The greatest reduction in the incidence of GI events was seen for diarrhea in the tacrolimus group, consistent with the high rate of diarrhea at baseline in tacrolimus-treated patients versus cyclosporine-treated patients, as reported previously in the literature (*29*). Of note, the extent of the improvement in patient-reported outcomes in African-American patients was similar to that reported by non-African-American patients; similarly, the benefit of conversion from MMF to EC-MPS in terms of GSRS results was not affected by the presence of diabetes.

This trial was adequately powered to detect significant differences in GI symptom burden for the total population and for tacrolimus-treated patients after conversion from MMF to EC-MPS. The study design was considered appropriate since this was an exploratory trial to evaluate the impact of GI symptoms and the effect of conversion from MMF to EC-MPS on GI symptom burden, from the perspective of the patient. Although the study was open-label with no control group, it is unlikely that the improvements in GI burden could be attributed solely to the placebo effect. Notably, statistically and clinically significant changes in the overall GSRS score and subscale scores were observed, which were evident by 1 month postconversion and sustained at 3 months. The patient-reported and physician-reported OTE ratings also point to a treatment effect. Moreover, the concurrent physician-reported results were consistent with the patient-reported findings. These preliminary results await conclusive confirmation by a blinded trial currently underway in which patients suffering from MMF-related GI complications are randomized to remain on MMF therapy or be converted to EC-MPS.

In conclusion, conversion of renal transplant recipients with MMF-related GI complications to EC-MPS is safe and significantly reduces patients' GI symptom burden. Benefits were seen by the first month postconversion and maintained to the end of the 3-month study. These improvements were observed regardless of concomitant calcineurin inhibitor and appeared to be clinically relevant based on published MID data in a similar population. Conversion from MMF to EC-MPS did not appear to compromise efficacy or overall safety. The results of this trial may help to guide treatment decisions in patients experiencing MMF-related GI complications.

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