Patient-Reported Gastrointestinal Symptom Burden and Health-Related Quality of Life following Conversion from Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium

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Background. The benefit of converting renal transplant recipients with gastrointestinal (GI) complaints from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS) has not been evaluated using patient-reported outcomes.

Methods. A multicenter, open-label, prospective study was undertaken in MMF-treated renal transplant patients. Patients experiencing GI complaints were converted to equimolar EC-MPS (Cohort A). Patients without GI complaints remained on MMF (Cohort B). At baseline and Visit 2 (4–6 weeks postbaseline), patients completed the Gastrointestinal Symptom Rating Scale (GSRS), Gastrointestinal Quality of Life Index (GIQLI) and Psychological General Well-being Index (PGWBI). At Visit 2, patients and physicians completed the Overall Treatment Effect (OTE) scale for GI symptoms. Additionally, patients completed the OTE for health-related quality of life (HRQoL). Minimal important difference (MID) was calculated for GSRS and GIQLI based on patients' and physicians' OTE evaluation.

Results. Of 328 patients enrolled (i.e. the intent-to-treat and safety populations), 278 formed the per-protocol population (Cohort A, n=177; Cohort B, n=101). At baseline, Cohort A had significantly worse scores on all GSRS, GIQLI and PGWBI subscales compared to Cohort B (all $P<0.0001$). All GSRS, GIQLI and PGWBI subscale scores improved significantly in Cohort A between baseline and Visit 2 (all $P<0.0001$). Mean improvements in all GSRS subscales and most GIQLI subscores exceeded the calculated MID. GSRS, GIQLI and PGWBI subscales remained stable in Cohort B.

Conclusion. This first exploratory study indicates that converting patients with mild, moderate or severe GI complaints from MMF to EC-MPS significantly reduces GI-related symptom burden and improves patient functioning and well-being.

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

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With one-year kidney graft survival now exceeding 90%, and fewer than 20% of renal transplant recipients experiencing acute rejection in the first year posttransplant (*1*), there is a growing need to evaluate the impact of immunosuppressive regimens based on other health outcome measures, such as patients' physical and emotional well-being (*2*). Mycophenolic acid (MPA) administered as mycophenolate mofetil (MMF, Cellcept), is widely used as an antiproliferative agent within combination regimens following renal transplantation and offers both short-term (*3*, *4*) and long-term (*5*, *6*) efficacy benefits. However, the side-effect profile of MMF, notably gastrointestinal (GI) complications (*7*), can limit its clinical benefits. GI complications frequently necessitate dose reduction, interruption, or even discontinuation of MMF, increasing the risk of acute rejection or graft loss (*8–10*) and incurring additional healthcare costs (*11*).

An enteric-coated formulation of mycophenolate sodium (EC-MPS, *myfortic*) has been designed specifically to reduce MPA-related GI adverse events. EC-MPS and MMF show equivalent efficacy (*12*) and similar safety (*12*, *13*) in renal transplant recipients. In a one-year, multicenter, randomized study of 423 de novo renal transplant patients, although the incidence of GI complaints was comparable in the MMF and EC-MPS groups, there was a trend towards fewer dose changes for GI side effects in patients receiving EC-MPS (*12*). Among maintenance renal transplant recipients randomized either to remain on MMF or be converted to EC-MPS, the increase in mean GI adverse event severity score from baseline, after adjustment for duration, tended to be lower among patients randomized to EC-MPS (*13*).

The influence of GI symptoms on health-related quality of life (HRQoL) has been described in a range of disease conditions (*14–16*). In kidney transplantation, the use of patient-reported outcomes measures to assess the impact of GI symptoms on patients' HRQoL and symptom burden has recently been validated in a cross-sectional study (*17*). However, the effect of MPA therapy in general, and EC-MPS in particular, on patient-reported GI symptoms and HRQoL has yet to be investigated. We hypothesized that among renal transplant patients who were experiencing GI complaints while receiving MMF, conversion from MMF to EC-MPS

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would improve their functioning and well-being, as measured by patient-reported outcomes such as symptom impact and HRQoL. Accordingly, the present study was undertaken with two objectives: firstly, to determine if patients with GI complaints who are converted from MMF to EC-MPS experience improvements in GI symptom severity and HRQoL; and secondly, to evaluate the impact of GI symptoms on patients' perceptions of symptom severity, GI-specific HRQoL, and general HRQoL.

MATERIALS AND METHODS

Study Design and Conduct

The study was a longitudinal, multicenter, international, open-label, prospective trial in which MMF-treated adult renal transplant patients were evaluated for their GI symptom burden and HRQoL. 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 ICH Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles laid down in the Declaration of Helsinki.

Patient Population

Patients ≥18 years of age were eligible to enter the study if they had received a renal transplant at least one month previously and had been receiving an immunosuppressive regimen that included MMF for ≥2 weeks at the time of study entry. Patients were excluded if they were experiencing GI symptoms that were not known or assumed to be due to MMF, if they had experienced an episode of acute rejection <1 week prior to the start of the study, or were undergoing acute medical intervention or hospitalization. All patients were screened by their physicians, who used their clinical judgment to identify patients in whom GI complications qualified them for conversion from MMF to EC-MPS, as well as to evaluate the severity of the GI symptoms. Subsequently, patients entered one of two cohorts: Cohort A (patients with GI complaints who were converted to equimolar dose of EC-MPS) or Cohort B (patients without GI complaints who remained on MMF) (Fig. 1). Patients in both cohorts continued to receive concomitant immunosuppressive therapy throughout the study as per local practice. Patients in Cohort A were converted from MMF to an equimolar dose of EC-MPS at baseline. EC-MPS doses of 360 mg, 720 mg, 1080 mg, 1440 mg and 2160 mg corresponded to MMF 500 mg, 1000 mg, 1500 mg, 2000 mg and 3000 mg, respectively.

The intent-to-treat (ITT)/safety population consisted of all enrolled patients who completed the baseline visit and received ≥1 dose of EC-MPS or MMF. The per-protocol population consisted of those patients who completed the study with no protocol violations.

Patient-reported Outcomes

Three self-administered questionnaires were used, each of which has previously been validated in renal transplant recipients (*17*). The Gastrointestinal Symptom Rating Scale (GSRS) (*18–20*) is a 15-item instrument designed to assess the symptoms associated with common GI disorders. It has five subscales (reflux, diarrhea, constipation, abdominal pain and indigestion). Subscale scores range from 1–7 and higher scores represent higher symptom burden i.e. more discomfort. The Gastrointestinal Quality of Life Index (GIQLI) (*21*) is a 36-item GI-specific HRQoL instrument designed to assess HRQoL in clinical practice and in clinical trials of patients with GI disorders. It has five subscales (GI symptoms, emotional status, physical function, social function and use of medical treatment), with scores ranging from 0–4, as well as a total score ranging from 0–144. Higher scores indicate better GI-specific HRQoL. The third scale used was the Psychological General Well-being Index (PGWBI) (*22*), which is a 22-item instrument designed to evaluate general HRQoL through assessment of psychological well-being and distress. It has six subscales (anxiety, depressed mood, positive well-being, self-control, general health and vitality) each of which are scored 0–100, and also a total score ranging from 0–100. Higher scores indicate better HRQoL and psychological well-being.

Patients' overall evaluation of treatment was assessed by the Overall Treatment Effect (OTE) Scale (*23–26*) at Visit 2. The first question asks the respondent to indicate whether GI symptoms or overall HRQoL have improved, remained the same, or worsened since the last visit. Respondents who indicate improvement or worsening are then asked further questions to identify the extent of the change on a 7-point scale from 1 (almost the same) to 7 (very great deal better/worse). Physicians completed the OTE scale for GI symptoms only.

Evaluation Schedule

Patients were evaluated at baseline (Visit 1) and at a second study visit (Visit 2) which took place 4–6 weeks after baseline. At baseline, all patients completed the GSRS, GIQLI and PGWBI questionnaires at the trial site in their native languages prior to physician interaction, after which physicians categorized the severity of the patient's disease according to their clinical judgment as none, mild, moderate or severe. Those patients who were allocated to Cohort A because of mild, moderate or severe GI symptoms were converted to EC-MPS. The others were allocated to Cohort B and

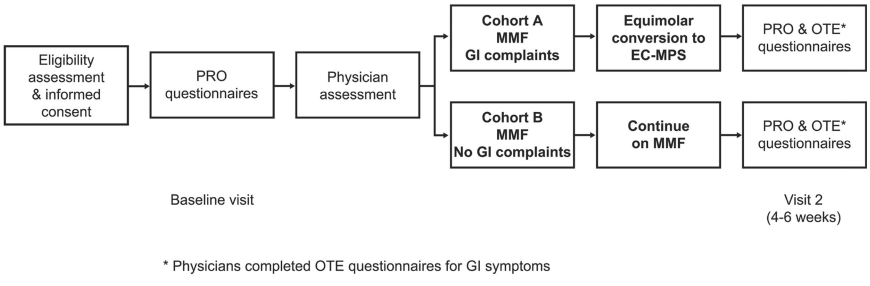

FIGURE 1. Schematic of study design. PRO, patient-reported outcomes; OTE, overall treatment effect.

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remained on MMF. At Visit 2, all patients again completed GSRS, GIQLI and PGWBI and the OTE questionnaire for symptoms and HRQoL. Physicians completed the OTE at Visit 2 for symptoms only.

Information on immunosuppressive therapies, GI-related concomitant medication and adverse events were collected throughout the study. All data were collected by investigators and transferred to an electronic database for analysis.

Statistical Analyses

A minimum sample size of 102 patients per cohort was determined in order to provide 80% power to detect a minimal important difference (MID) of 0.50 on the GSRS diarrhea and indigestion subscales between baseline and Visit 2, based on a 0.05 significance level (paired t-test). For statistical, therapeutic and ethical reasons, double that number was selected for patients with GI complications (Cohort A). The ITT/safety population consisted of all enrolled patients who completed the baseline visit and received at least one dose of EC-MPS or MMF. The per-protocol population consisted of those patients who completed the study with no protocol violations. All analyses were undertaken for both the ITT/safety and per-protocol populations. Adverse event analyses are reported for the ITT/safety population. Clinical and patient-reported outcomes are reported for the per-protocol population.

The MID is the smallest difference in score in the domain of interest (i.e. subscales of questionnaires) that either patients or clinicians perceive to be important, either as beneficial or harmful (*27*). MIDs for the GSRS and GIQLI total and subscale scores were defined as the difference in the change in patient-reported outcomes scores from baseline to Visit 2 between the patients with 'no change' and the patients with an improvement rated 'a little better' or 'somewhat better' on the OTE scale, for the per-protocol population (*27*). For the GSRS, MIDs were estimated based on the OTE for symptoms assessed by clinicians, whereas MIDs for GIQLI scores were based on the OTE for HRQoL assessed by patients. MID values were not calculated for PWGBI because the scale is not specific to GI disorders.

All patient-reported outcomes results are reported as mean±SD. Scoring of instruments including imputations for missing data, if necessary, was performed following the instructions of the developers of these patient-reported outcomes questionnaires. The main analyses were performed in Cohort A, comprising change in GSRS, GIQLI, and PGWBI scores from baseline to Visit 2. Paired t-tests, Wilcoxon Rank Sum test, analysis of variance (ANOVA) and co-variance (ANCOVA) techniques were used to examine differences over time within each cohort for continuous variables. Fisher's Exact Test and Chi-Square Test were used for categorical variables. Time since transplant, country, type of immunosuppressive regimen and the use of medication for GI complaints (i.e. number of medications for treatment or prophylaxis) were included as covariates in the ANCOVA models. All statistical tests used were two-sided with 0.05 level of significance.

RESULTS

Patient Population

Twenty-seven centers recruited patients to the study, in Argentina (four centers, 44 patients), Australia (nine centers, 90 patients), Chile (one center, 18 patients), Germany (six centers, 52 patients), Switzerland (two centers, 12 patients) and the USA (five centers, 112 patients). A total of 328 patients were enrolled (215 in Cohort A and 113 in Cohort B) and comprised the ITT/safety populations. Twelve patients (3.7%), nine in Cohort A and three in Cohort B, discontinued prematurely (five due to adverse events, four due to protocol violations, one due to withdrawal of consent and two due to loss to follow-up). During the study, 37 patients in Cohort A and 11 patients in Cohort B were protocol violators, such that the per-protocol population consisted of 278 patients (177 in Cohort A and 101 in Cohort B). In summary, 50 patients were not included into the per-protocol population, 38 because of protocol violations, two because of premature discontinuation and 10 for both reasons.

Over half of the patients were male, Caucasian and received a deceased-donor transplant (Table 1). There were no significant differences in demographics, baseline characteristics, domestic status or level of education between the two cohorts. The most frequently-reported GI complaint in Cohort A was abdominal pain, bloating or fullness (n=120, 67.8%), followed by diarrhea (n=112, 63.3%). GI bleeding was the least common GI complaint (n=4, 2.3%). According to physicians' ratings, 50 patients (28.2%) had mild, 103 patients (58.2%) moderate and 24 patients (13.6%) severe GI complaints in Cohort A.

Immunosuppression and Concomitant Medication

At baseline, 72 patients (40.7%) in Cohort A and 61 patients (60.4%) in Cohort B were receiving cyclosporine; 80 patients (45.2%) and 29 patients (28.7%), respectively, were receiving tacrolimus (P=0.0074). Twelve patients (6.8%) in

TABLE 1. Demographics and baseline characteristics (per-protocol population)

	Cohort A	Cohort B	*P* value
n	177	101	
Age (years)	47 (18–76)	46 (18–70)	0.8938
Male gender	101 (57.1%)	65 (64.4%)	0.2541
Caucasian race	143 (80.8%)	78 (77.2%)	0.1450
Weight (kg)	73 (36–151)	76 (37–133)	0.1627
Time since transplant (years)	2.5 (0.1–25.2)	2.2 (0.1–15.4)	0.4186
Deceased donor	118 (66.7%)	67 (66.3%)	1.000

Continuous variables are shown as median values (range) and binary variables are shown as n (%) of patients.

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Cohort A and three patients (3%) in Cohort B were receiving sirolimus, while 13 patients (7.3%) and seven patients (6.9%) in Cohorts A and B, respectively, were being managed by MMF monotherapy. In Cohort B, one patient (1%) received tacrolimus and sirolimus. Corticosteroids were administered to 142 patients (80.2%) in Cohort A and 87 patients (86.1%) in Cohort B. The mean daily dose of MMF was significantly lower at baseline in Cohort A than Cohort B (1453±497 mg versus 1631±463 mg, respectively, $P=0.0034$), a difference that remained significant when only patients receiving cyclosporine were included (1531±486 mg versus 1738±386 mg, $P=0.0113$). The mean daily dose of MMF was 1416±497 mg in Cohort A and 1517±538 mg in Cohort B among patients receiving tacrolimus (NS).

Patients in Cohort A were converted to equimolar dose of EC-MPS. Over the course of the study, the mean daily dose of EC-MPS in Cohort A was 1024.8±351.6 mg (71.2% of nominal dose). One hundred patients (56.5%) and 51 patients (50.5%) in Cohorts A and B, respectively, were receiving medication for the treatment or prophylaxis of GI complications.

Tolerability

Thirty-six patients (16.7%) in Cohort A and 15 patients (13.3%) in Cohort B experienced non-GI related adverse events. Infections were the most common non-GI adverse events, reported by 16 patients (7.4 %) and five patients (4.4 %) in Cohorts A and B, respectively. EC-MPS dose was adjusted or temporarily interrupted due to non-GI adverse events in five patients in Cohort A (one case each of pyrexia, anuria, leucopenia, decreased hemoglobin and decreased white blood cell count). MMF dose was adjusted in two patients in Cohort B (allograft rejection, nasopharyngitis). Four patients in Cohort A discontinued EC-MPS permanently due to a non-GI adverse event (epistaxis, leucopenia, tendon rupture and systemic mycosis). Eleven patients (5.1%) in Cohort A and two patients (1.8%) in Cohort B experienced non-GI-related serious adverse events. One patient experienced non-GI serious adverse event (pancytopenia) that was considered to be related to EC-MPS; none was considered to be related to MMF.

Thirty-eight patients (17.7%) in Cohort A experienced GI adverse events, rated mild in 17 patients (7.9%), moderate in 15 patients (7.0%) and severe in six patients (2.8%). In Cohort B, 15 patients (13.3%) reported GI adverse events; rated mild in 10 patients (8.8%), moderate in four patients (3.5%) and severe in one patient (0.9%). Diarrhea was the most frequently-occurring GI event in both cohorts of patients, being reported in 16 patients (7.4%) in Cohort A and eight patients (7.1%) in Cohort B. Seven patients (3.3%) in Cohort A and one patient (0.9%) in Cohort B experienced serious GI adverse events. Three patients experienced serious GI adverse events (two diarrhea and one GI hemorrhage) that were considered to be related to EC-MPS; none was considered to be related to MMF.

No episodes of acute rejection were reported in patients converted to equimolar doses of EC-MPS (Cohort A). Two patients in Cohort B experienced acute rejection. There were no graft losses or deaths during the study; one patient in Cohort A died on the day after the end of the study from a hemorrhage which the investigator did not consider to be related to EC-MPS.

Patient-Reported Outcomes at Baseline

At baseline, Cohort A had significantly higher scores on all GSRS subscales, and lower scores on GIQLI total and subscale scores compared to Cohort B (all $P<0.0001$). GIQLI total score was 90.4±20.7 for Cohort A versus 122.7±14.6 for Cohort B ($P<0.0001$) (Fig. 2). PGWBI total and subscale scores were also significantly lower for Cohort A versus Cohort B (all $P<0.0001$). These differences indicate significantly worse symptom burden, more impaired GI-specific HRQoL and lower general HRQoL in patients who were later con-

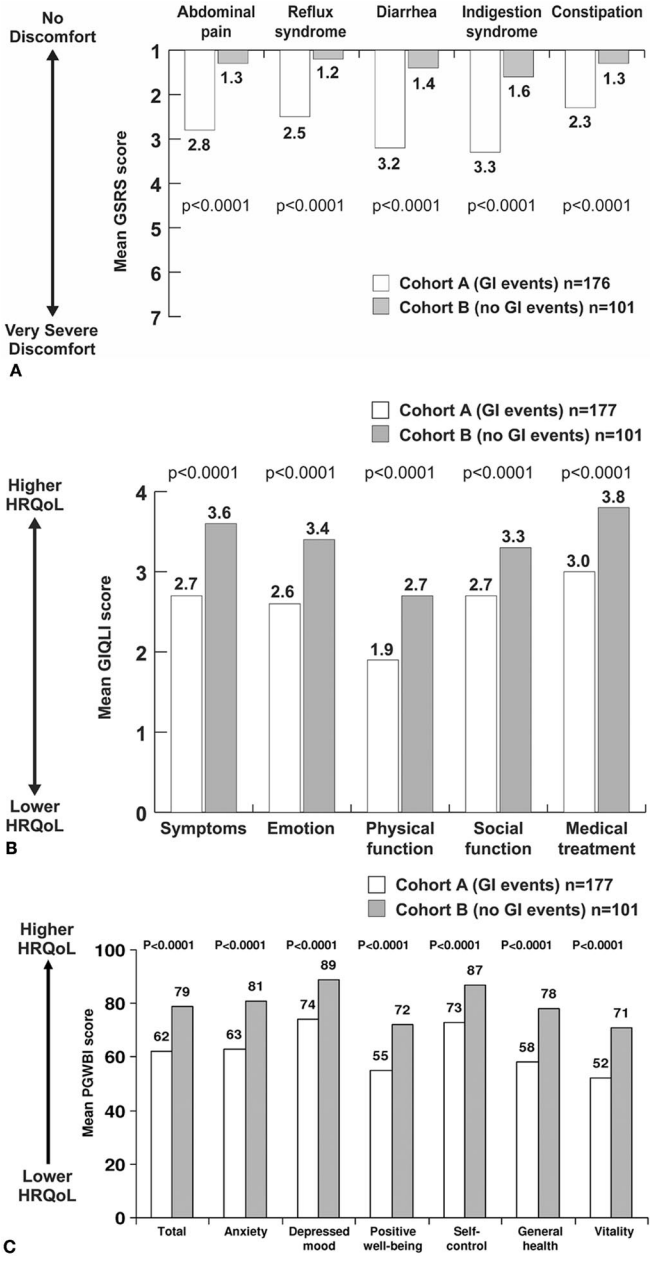

FIGURE 2. Patient-reported subscale scores at baseline for (A) GSRS, (B) GIQLI, and (C) PGWBI.

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verted to EC-MPS. All differences between cohorts remained significant after adjustment for demographic and clinical characteristics (data not shown).

Baseline GIQLI and PGWBI scores for all patients were assessed according to physicians' ranking of disease severity (Table 2). GIQLI scores were significantly different for all subscales between patients rated by their physicians as having no GI symptoms and those rated to have mild, moderate or severe GI symptoms at baseline. In addition, GIQLI total score and all subscale scores with the exception of the social function subscale were significantly different between patients with mild versus severe symptoms. GIQLI total score, symptoms and medical treatment subscales were significantly different between patients rated as having moderate versus severe symptoms. For PGWBI, there were statistically significant differences for all the subscale scores between patients with no symptoms versus patients with mild, moderate or severe symptoms. PGWBI general health subscale score was also significantly different between patients with mild versus severe symptoms.

Changes in Patient-reported Outcomes

Significant improvements were observed in Cohort A patients between baseline and Visit 2 (i.e. after conversion to EC-MPS) for all GSRS subscales, GIQLI total and subscale scores, and PGWBI total and subscale scores (all $P<0.0001$) (Fig. 3). The greatest change in GSRS score was reported for the diarrhea and indigestion subscales. On GIQLI the total score improved from 90.0±20.7 to 108.1±19.0 ($P<0.0001$), with the most pronounced improvement observed in the symptom subscale (2.7±0.6 at baseline versus 3.3±0.5 at Visit 2, $P<0.0001$). The physical function subscale also improved markedly (1.8±0.9 at baseline versus 2.3±0.9 at Visit 2, $P<0.0001$). Disparities in symptom and HRQoL scores narrowed between Cohort A and Cohort B from baseline to Visit 2, but remained significantly different (data not shown). In Cohort B, GSRS, GIQLI and PGWBI scores remained stable between baseline and Visit 2 (data not shown).

Overall Treatment Effect

At Visit 2, 117 patients (66%) in Cohort A reported an overall improvement in GI symptoms versus baseline (Fig. 4A) while only eight patients (8%) in Cohort B reported an improvement. Physicians rated symptoms to be improving, remaining unchanged or worsening in 138 patients (78%), 33 patients (19%) and five patients (3%) in Cohort A, respectively (Fig. 4A), and in one (1%), 94 (93%) and six patients (6%) in Cohort B. Regarding change in overall HRQoL, 91 patients (51%) in Cohort A reported that their HRQoL had improved over the course of the study (Fig. 4B), compared to nine patients (9%) in Cohort B.

All patient-reported outcomes analyses were also performed on the ITT/safety population, and results were similar to those shown here for the per-protocol population.

Minimal Important Differences

Estimated MIDs for GSRS scores were 0.6 for abdominal pain, 0.8 for reflux, 0.4 for diarrhea, 0.7 for indigestion and 0.7 for constipation. For GIQLI, estimated MIDs were 12.7 for total score, 0.4 for symptoms, 0.2 for emotion, 0.3 for physical function, 0.5 for social function and 0.4 for medical treatment. The mean improvements on both the GSRS and the GIQLI subscales exceeded the corresponding estimated MIDs, with the exception of the constipation subscale on GSRS as well as social function and medical treatment subscale on GIQLI.

DISCUSSION

This is the first prospectively designed longitudinal study to investigate changes in functioning and well-being in maintenance renal transplant patients with MMF-related GI

TABLE 2. Patient reported outcome scores on GIQLI and PGWBI by physicians' ranking of clinical disease severity at baseline (per-protocol population)

	None	Mild	*P* value vs none	Moderate	*P* value vs none	Severe	*P* value vs none	*P* value vs mild	*P* value vs moderate
n	101	50		103		24			
GIQLI									
Total score	122.7±14.6	97.5±18.3	<0.001	90.5±19.5	<0.001	74.4±22.6	<0.001	<0.001	<0.01
Symptoms	3.6±0.3	2.9±0.5	<0.001	2.7±0.6	<0.001	2.3±0.7	<0.001	<0.001	<0.01
Emotion	3.4±0.6	2.8±0.7	<0.001	2.6±0.8	<0.001	2.1±0.9	<0.001	<0.01	NS
Physical function	2.7±0.8	2.1±0.9	<0.001	1.9±0.9	<0.001	1.4±0.9	<0.001	<0.05	NS
Social function	3.3±0.7	2.8±0.8	<0.01	2.7±0.9	<0.001	2.2±0.9	<0.001	NS	NS
Medical treatment	3.8±0.4	3.2±1.1	<0.01	3.0±1.1	<0.001	2.3±1.3	<0.001	<0.01	<0.05
PGWBI									
Total score	79.0±13.4	64.2±15.2	<0.001	62.4±17.6	<0.001	54.8±16.7	<0.001	NS	NS
Anxiety	80.8±15.2	64.4±17.9	<0.001	64.4±20.7	<0.001	56.5±20.3	<0.001	NS	NS
Depressed mood	89.2±14.4	77.2±17.1	<0.01	74.5±22.4	<0.001	67.8±21.6	<0.001	NS	NS
Positive well-being	71.8±17.3	56.3±18.7	<0.001	56.1±20.8	<0.001	49.0±17.4	<0.001	NS	NS
Self-control	87.1±14.9	76.3±17.8	<0.05	72.6±22.4	<0.001	66.7±21.2	<0.001	NS	NS
General health	77.6±17.7	62.8±16.6	<0.001	57.6±18.2	<0.001	47.5±21.8	<0.001	<0.01	NS
Vitality	71.2±16.7	54.3±20.4	<0.001	52.7±20.6	<0.001	45.4±22.9	<0.001	NS	NS

Higher scores represent better quality of life. Values shown are mean±SD.

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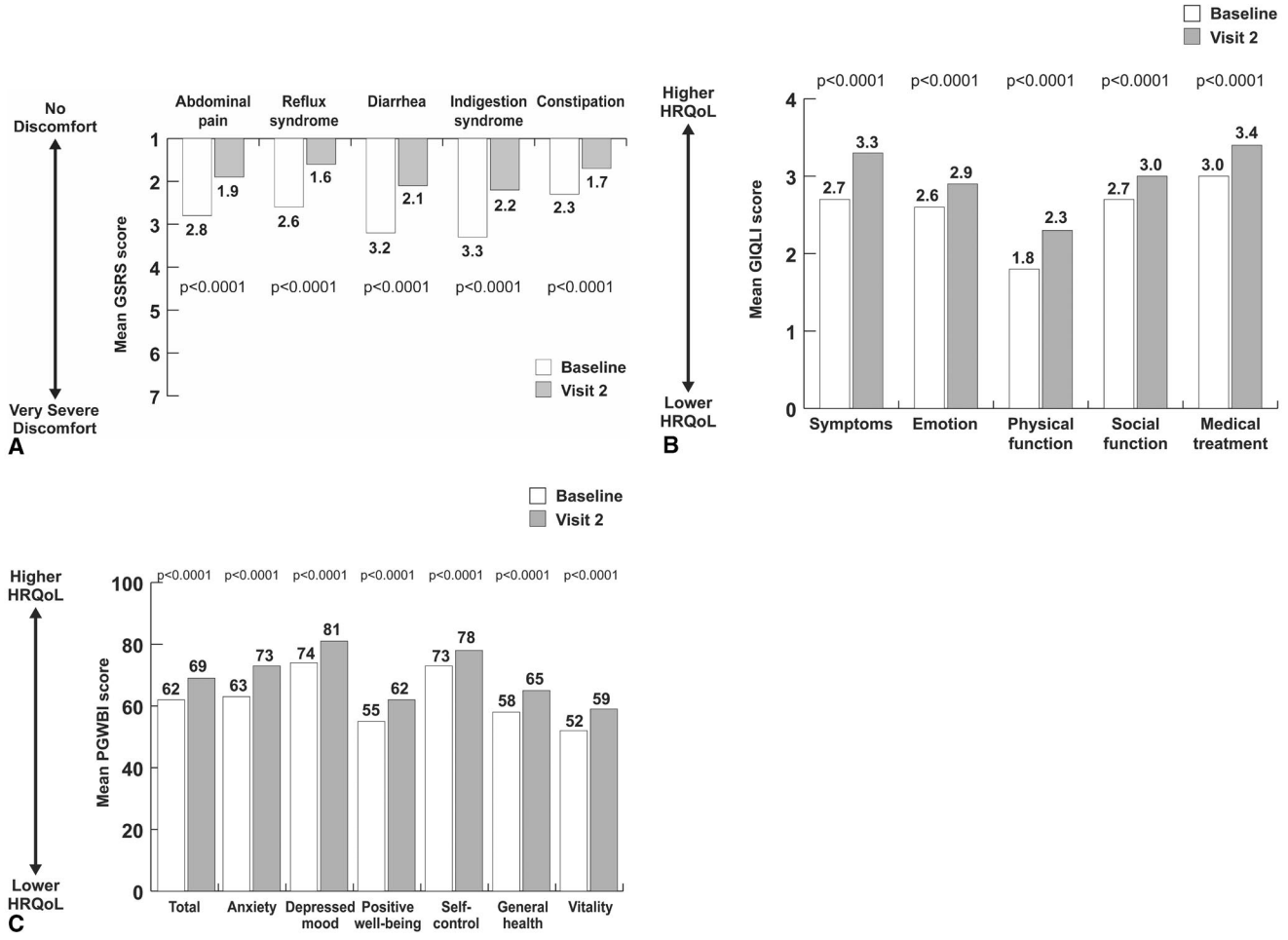

FIGURE 3. Patient-reported outcomes scores on (A) GSRS (n=176), (B) GIQLI (n=177), and (C) PGWBI (n=177) at baseline and Visit 2 in Cohort A.

complaints after conversion to EC-MPS. A two-cohort, parallel-group design was selected as an appropriate method for this exploratory study. It included a cohort of MMF-treated patients who were experiencing GI side effects, despite the fact that most of them were three to four years posttransplant and were receiving medication to treat or prevent such complications, and a cohort who were free from GI symptoms. The results demonstrated that converting maintenance patients with mild to severe GI complaints from MMF to EC-MPS significantly reduces the GI-related symptom burden and improves patient functioning and well-being within 4–6 weeks, as measured by patient-reported symptom and HRQoL questionnaires. Moreover, two-thirds of patients reported an improvement in overall treatment effect in terms of GI symptoms after conversion from MMF to EC-MPS. Significant improvements were consistently observed for all symptom and psychological measures on each of the three scales employed, providing good preliminary evidence that conversion to EC-MPS is beneficial for patient functioning and psychological well-being in this population. The greatest improvement after conversion to EC-MPS was observed in the GSRS diarrhea subscale. During the same period, patient-reported outcomes remained unchanged in the cohort of patients without GI symptoms who remained on MMF, on all the scales used.

The improvement in GI symptoms and HRQoL following conversion to EC-MPS did not result in equivalent scores to those patients who were free of MMF-related GI complaints at baseline, although mean differences were narrowed considerably. Given the marked discrepancy in symptom scores between the two groups at baseline, and the high proportion of patients with moderate (58%) or severe (14%) GI complaints in the cohort converted to EC-MPS, this was to be expected.

Comparing data from patients with or without MMF-related GI complaints at baseline provides a useful insight into the impact of GI side effects on patients. In addition to the expected increase in patient-reported symptom burden and GI-related quality of life, the cohort with GI complaints reported significantly worse general HRQoL, including increased anxiety, depressed mood and vitality. Total score on the PGWBI scale, which assesses general HRQoL based on psychological well-being, was 20% lower in the cohort with GI complaints. As would be anticipated, increased symptom severity was associated with greater impairment of patient-reported functioning and well-being.

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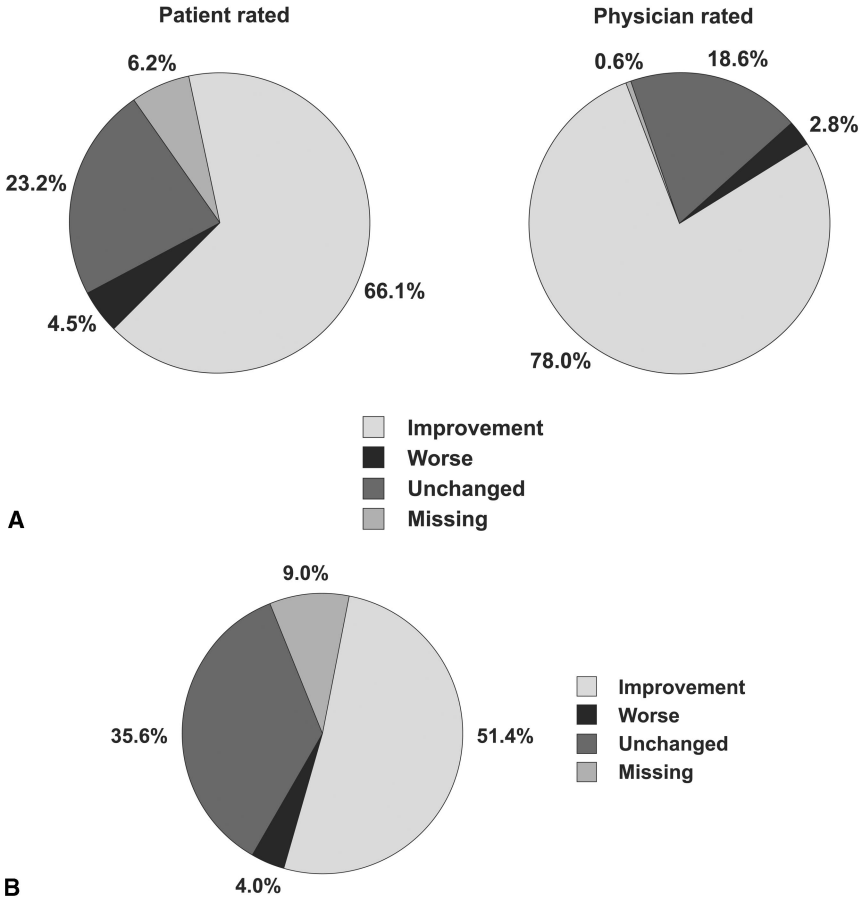

FIGURE 4. Overall treatment effect scores in Cohort A (n=177) at Visit 2 for (A) patient-rated and physician-rated GI symptoms (B) overall health-related quality of life.

All patient-reported outcome data were analyzed based on the ITT/safety and per-protocol population. Although the results were comparable for the two populations we reported only the per-protocol results which excluded protocol violators and patients who did not complete the patient-reported outcomes instruments at Visit 2 in order to avoid bias in the patient-reported outcomes results due to therapeutic changes during the study period or missing data.

Although the study was not randomized, and data can only be regarded as indicative, the two cohorts were well-matched for all characteristics other than the presence of GI complaints, and all differences in symptom and HRQoL ratings remained significant after adjustment for demographic and clinical characteristics. Other important design considerations should be taken into account when interpreting the results of this exploratory study. Neither investigators nor patients were blinded, and the placebo effect is likely to have contributed to some extent to the improvements reported in the cohort converted to EC-MPS. However, the consistently large and meaningful changes in GI symptom scores and HRQoL over time in the EC-MPS conversion group suggest that the observed improvements cannot be explained solely by the placebo effect or by regression to the mean. In addition, the three scales selected for patient-reported outcomes measures corresponded well with patients' and physicians' ratings of OTE, and patient-reported outcomes using GIQLI and PGWBI generally corresponded well with physicians' subjective ratings of disease severity (the correlation was not assessed for GSRS). Scores on both the GIQLI and PGWBI scales differed significantly between patients with or without GI complaints, although significant differences in scores were not generally discernible between grades of severity. The proportion of patients and physicians reporting an improvement in overall treatment effect was also comparable. This confirms that these patient-reported outcome instruments are applicable, reliable and responsive in this setting, as previously reported (*17*). Accordingly, these instruments appear appropriate for future trials in renal transplant populations, in addition to their current use in fields such as gastrointestinal reflux disease (*15*, *16*), hypertension (*28*), diabetes (*29*), congestive heart failure (*30*), dyspepsia (*31*) and constipation (*32*). Our results have shown a significant reduction in GI symptom burden ($P<0.0001$) and significant improvement in GI-specific and general psychological HRQoL ($P<0.001$). This improvement in health-related quality of life translates into a lower psychological burden and an improved functional health status, and may be linked to increased medication belief, which is an important factor in compliance and adherence (*33*).

The results of this first study into the relative GI tolerability of MMF and EC-MPS based on patient-reported outcomes require further confirmation. Additional investigations are ongoing to confirm the effect of conversion to EC-MPS for GI symptoms over a longer period of time, which will help to determine whether patient-reported symptoms and

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HRQoL converge with MMF-treated renal transplant patients who do not suffer GI symptoms.

In conclusion, these preliminary results suggest that converting MMF-treated renal transplant patients with GI complaints to EC-MPS significantly reduces their symptom burden and improves their HRQoL, functioning and psychological well-being. These findings also confirm the significant deleterious effect that GI complaints exert on patients' functioning and overall well-being.

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