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ORIGINAL ARTICLE

Effect of conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium on maximum tolerated dose and gastrointestinal symptoms following kidney transplantation

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Summary

Despite the potential tolerability advantage of enteric-coated mycophenolate sodium (EC-MPS), no prospective, randomized trial has evaluated whether conversion from mycophenolate mofetil (MMF) to EC-MPS permits mycophenolic acid dose to be increased or gastrointestinal side-effects to be ameliorated. In a randomized, multicenter, open-label trial, kidney transplant recipients experiencing gastrointestinal side-effects either remained on MMF or switched to an equimolar dose of EC-MPS, adjusted 2 weeks subsequently to target the highest tolerated dose up to 1440 mg/day (EC-MPS) or 2000 mg/day (MMF). Patients were followed up to 12 weeks postrandomization. One hundred and thirty-four patients were randomized. The primary efficacy endpoint, the proportion of patients receiving a higher mycophenolic acid (MPA) dose at week 12 than at randomization, was significantly greater in the EC-MPS arm (32/68, 47.1%) than the MMF arm (10/61, 16.4%; $P < 0.001$). At the final visit, 50.0% (34/68) of EC-MPS patients were receiving the maximum recommended dose versus 26.2% (16/61) of MMF patients ($P = 0.007$). Kidney transplant patients receiving reduced-dose MMF because of gastrointestinal side-effects can tolerate a significant increase in MPA dose after conversion to EC-MPS. Patient-reported gastrointestinal outcomes with higher doses of EC-MPS remained at least as good as in MMF-treated controls.

Introduction

Mycophenolic acid (MPA) is now a standard component of the immunosuppressive regimen following kidney transplantation [1]. In clinical practice, however, as many as 70% of patients cannot tolerate the recommended dose of mycophenolate mofetil (MMF) (2000 mg/day) and either require a dose reduction or discontinuation [2,3]. Retrospective analyses have demonstrated a significantly increased relative risk of acute rejection in kidney transplant patients receiving MMF at a dose below 2000 mg/day in combination with a calcineurin inhibitor [2,4],

and a significantly higher risk of graft loss following MMF dose reduction or withdrawal [3]. The risk of graft failure is particularly high in patients receiving an MMF dose less than 1000 mg/day [5]. With more than half of patients who experience gastrointestinal (GI) symptoms requiring MMF discontinuation or a dose reduction of at least 50% [6], the impact of MMF dose reduction in these patients is particularly relevant. Two large-scale analyses of transplant registries have shown a marked and significant rise in graft loss among GI-intolerant patients in whom the MMF dose was reduced [6,7]. Clearly, avoiding MPA dose reductions caused by GI adverse events is desirable. Furthermore, growing interest in calcineurin inhibitor (CNI)-sparing regimens is leading to wider use of MPA-based immunosuppression following CNI withdrawal or CNI dose reduction. In this setting, maintenance of adequate MPA dose or, indeed, the ability to *increase* MPA dose to compensate for CNI minimization, is likely to be even more important.

The potential benefit of enteric-coated mycophenolate sodium (EC-MPS) in reducing GI symptom burden is of particular interest if it translates to maintenance of adequate MPA dose in a greater proportion of patients than can be achieved with MMF. The initial registration studies compared EC-MPS versus MMF only in terms of efficacy and overall safety, and did not include sensitive monitoring of GI symptoms [8,9], but subsequently two large open-label trials have investigated the effect of conversion from MMF to EC-MPS on GI symptom burden using patient-reported outcomes instruments [10,11]. Both of these studies showed a consistent improvement in the impact of GI events after conversion to EC-MPS, but were not randomized and lacked a control arm, and did not attempt protocol-driven increases in EC-MPS dose following conversion from MMF. Indeed, data from the literature comparing MPA dosing with EC-MPS versus MMF are limited [12–14]. Sollinger et al. retrospectively reviewed data from 1709 *de novo* kidney transplant patients at their center [12]. Kaplan–Meier estimates showed a lower rate of dose reductions with EC-MPS as compared with MMF (64% vs. 74%, $P < 0.001$) and fewer drug discontinuations (28% vs. 33%, $P = 0.013$); possibly related to this, there was a lower incidence of biopsy-proven acute rejection in the EC-MPS patients (22% vs. 30%, $P < 0.001$).

We report here the findings of a prospective, multicenter study in which renal transplant recipients experiencing GI disturbances while on MMF therapy were randomized to either remain on MMF or convert to EC-MPS. Randomization was followed by a dose titration phase to examine the maximum tolerated MPA dose in each treatment arm, and a range of patient-reported outcomes instruments were employed to monitor changes in GI symptom burden and health-related quality of life (HRQoL). The primary objective of the study was to investigate whether treatment with EC-MPS permits maintenance of higher MPA doses than MMF therapy in patients with GI side-effects. A secondary objective was to study the effect on GI symptoms as reported by patients.

Materials and methods

Study design and conduct

*My*QoL [A Study of the Effect of Changing to **My**fortic on **Q**uality **o**f **L**ife in Patients with Gastrointestinal (GI) Symptoms Related to MMF (Cellcept) Therapy after Kidney Transplantation] was a randomized, multicenter, controlled, open-label 13-week trial conducted at 19 transplant and renal centers in the United Kingdom. Kidney transplant recipients experiencing MMF-related GI intolerance were randomized to either remain on MMF or convert to an equimolar dose of EC-MPS. After randomization, the MPA dose in both groups was to be increased to the highest tolerated dose. Randomization was performed using telephone treatment assignment: randomized patient numbers were generated centrally by computer and issued, on request, by telephone and confirmed by fax.

The study was conducted in accordance with the principles of ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all patients following receipt of approval from the Multicentre Research Ethics Committee.

Patients

Kidney transplant patients aged ≥18 years receiving MMF as part of their immunosuppressive regimen were eligible to take part in the study if they were (i) experiencing GI side-effects that had previously necessitated a reduction in MMF dose and which were now present but tolerated, or (ii) experiencing GI events for which a reduction in MMF dose would be clinically indicated. Patients with GI symptoms assumed or known to be unrelated to MPA therapy were excluded, as were those experiencing acute rejection less than 1 week prior to study enrollment.

Immunosuppression

After screening (Visit 1), patients were randomized at the baseline visit (Visit 2). Patients randomized to the EC-MPS treatment arm were converted at Visit 2 from MMF to an equimolar dose of EC-MPS, whereby MMF 250 mg, 500 mg and 1000 mg b.i.d. were considered equimolar to EC-MPS 180 mg, 360 mg and 720 mg b.i.d. respectively.

EC-MPS was initiated on a twice-daily basis regardless of the previous MMF dosing schedule. Two weeks later (Visit 3), the dose of EC-MPS or MMF was increased at the investigator's discretion to a maximum of EC-MPS 720 mg b.i.d. or MMF 1000 mg b.i.d. if the current dose was below these thresholds. The final visit (Visit 4) took place at week 13, 12 weeks after randomization.

Patient reported outcomes

Five self-administered patient questionnaires were used in the study. The Gastrointestinal Symptom Rating Scale (GSRS) assesses GI symptoms based on responses to 15 questions grouped into five subscales (reflux, diarrhea, constipation, abdominal pain and indigestion). Scores range from 1 to 7, where higher scores represent greater symptom burden i.e. more discomfort [15–17]. The total GSRS score was calculated as the mean of all 15 scores. GI-specific HRQoL was assessed using the Gastrointestinal Quality of Life Index (GIQLI), in which a total score of up to 144 can be calculated from individual scores in response to 36 questions, with higher scores indicating better GI-specific HRQoL [18]. Both GSRS and GIQLI have previously been validated in kidney transplant patients and performed significantly better than generic patient-reported outcomes instruments [19]. The SF-36 health survey is a standardized questionnaire used to assess patient health across eight dimensions [20], from which physical and mental composite scores can be derived [21]. Patients' overall evaluation of treatment in terms of GI symptoms and HRQoL was assessed using the Overall Treatment Effect (OTE) scale, in which the respondents are asked whether status has improved, remained the same or deteriorated since the last visit. If a change was reported, a follow-up question determined the extent of the change on a 7-point scale from 1 (almost the same) to 7 (very great deal better/worse).

The Bristol Stool Chart consists of a form where the patient records details of each bowel movement, including number of movements per day and stool consistency, with consistency scored from 1–7 using the Bristol Stool Chart score (lower scores represent diarrhea, higher scores represent constipation) [22].

Evaluation

The presence of GI symptoms (abdominal pain, constipation, diarrhea, dyspepsia, flatulence and nausea) was recorded at Visits 2 and 4, graded by the clinician in terms of severity as none (0), mild (1), moderate (2) or severe (3). Mean severity was calculated excluding missing or unknown values. Patients completed the GSRS, GIQLI and SF-36 questionnaires at Visits 2, and 4; GSRS was also completed at Visit 3. At Visit 4, OTE scales for symptoms and for HRQoL were completed by patients and the OTE scale for symptoms was completed by clinicians. Patients completed questionnaires prior to any clinical evaluation or procedure, to encourage unbiased responses.

Bristol Stool Charts were given to patients at study entry, prior to randomization. These were to be completed on a daily basis at home for the seven days prior to each study visit, with results collected at Visits 2, 3 and 4.

Statistical analysis

The primary efficacy endpoint was the proportion of patients at Visit 4 maintained on a dose of EC-MPS or MMF that was at least one dose step higher than at baseline (Visit 2). A dose step was defined as EC-MPS 180 mg/day or MMF 250 mg/day. The expected proportion of patients in the MMF group achieving the primary endpoint was assumed to be low (10–25%) as patients had previously demonstrated GI intolerance at a higher dosage or were experiencing GI disturbances at the current dose. A difference of 20% between treatment groups was considered to be clinically important. Choosing a power of 80–85% and a two-sided significance level (α) of 5% led to a necessary sample size of 100 patients per arm to detect a difference of 20% in the proportion of patients achieving an increased maintenance dose at Visit 4. Hence the overall sample size required was estimated to be 200.

Fisher's exact test was used to compare the proportion of patients in each treatment group with $\geq$1 dose step higher at Visit 4 versus Visit 2. Changes in GSRS, GIQLI, SF-36 and Bristol Stool Chart scores were compared between treatment groups using an analysis of covariance (ANCOVA) model with the variables being treatment group, dose (expressed as a proportion of the target therapeutic dose), center and the value at Visit 2. Severity of GI symptoms and results from OTE scales were compared between treatment groups using Wilcoxon two-sample tests.

Results

Patient population

One hundred and thirty-five patients were screened, of whom 134 were randomized (one patient experienced a severe adverse event prior to randomization). The study was conducted between the period September 2005 and March 2008. Recruitment was terminated early because enrollment became progressively slower over time. An unplanned, group-blinded analysis was therefore

performed when 134 patients had been recruited, at which point a 20% difference in the primary endpoint between groups was observed and the investigators decided to terminate recruitment.

In total, 135 patients were screened, of whom 134 were randomized (EC-MPS 69, MMF 65) (Fig. 1). The remaining patient was not randomized because of a serious adverse event prior to the randomization visit. Five patients were excluded from the ITT and safety populations because they did not provide at least one postbaseline assessment, a requirement for inclusion (none of these patients received any study drug). The ITT and safety populations thus comprised 129 patients (EC-MPS 68, MMF 61). The study was completed by 110 patients (82.1%). The most frequent reasons for premature discontinuation from the study were adverse events (6 patients in each group) and withdrawal of consent (3 EC-MPS, 4 MMF).

Patient characteristics are summarized in Table 1. A significantly higher proportion of patients randomized to EC-MPS were <65 years old, but otherwise the two groups were well matched at study entry. Approximately half the patients (54%) were receiving concomitant tacrolimus, and approximately 25% were on ciclosporin (Table 1). There were 28 CNI-free patients who were receiving neither ciclosporin nor tacrolimus. The majority were also receiving corticosteroids.

Table 1. Patient characteristics and concomitant maintenance immunosuppression

	EC-MPS (n = 68)	MMF (n = 61)
Age (years)		
Mean ± SD	46.1 ± 11.02	49.0 ± 13.26
<65	65 (95.6%)*	51 (83.6%)*
≥65	3 (4.4%)*	10 (16.4%)*
Male gender	37 (54.4%)	36 (59.0%)
White race	65 (95.6%)	56 (91.8%)
Body mass index, mean ± SD (kg/m^2)	26.0 ± 5.1	25.7 ± 4.8
Deceased donor	39 (57.4%)	46 (75.4%)
Time post-transplant		
Median (range) (weeks)	138.1 (1–953)	179.9 (13–1030)
0–3 months	3 (4.4%)	1 (1.6%)
3–6 months	8 (11.8%)	9 (14.8%)
6–12 months	10 (14.7%)	3 (4.9%)
1–2 years	9 (13.2%)	12 (19.7%)
2–5 years	13 (19.1%)	12 (19.7%)
>5 years	25 (36.8%)	24 (39.3%)
Maintenance immunosuppression†		
Tacrolimus	37 (54.4%)	33 (54.1%)
Ciclosporin	16 (23.5%)	15 (24.6%)
Sirolimus	7 (10.3%)	4 (6.6%)
Prednisolone	47 (69.1%)	44 (72.1%)

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

*P = 0.038, Fisher's exact test.

†In addition, one patient received basiliximab and one patient received methylprednisolone during the study.

MPA dosing

At study entry, the mean MMF dose was 1283 ± 461 mg/day in the EC-MPS group and 1279 ± 485 mg/day in the MMF group. The proportion of patients in each dosage group was similar in both groups at Visit 2, with 16.2% of EC-MPS patients and 21.3% of MMF patients on the maximum recommended dose (Fig. 2). Changes in MPA

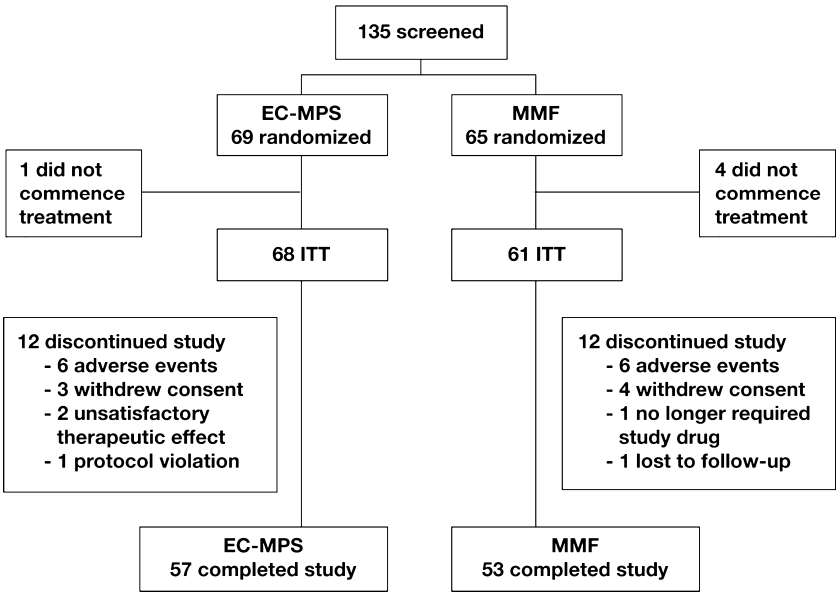

Figure 1 Patient disposition

dose are summarized in Table 2. The proportion of patients at Visit 4 who were maintained on an EC-MPS or MMF dose at least one dose step higher than at baseline (Visit 2) was significantly greater in the EC-MPS arm as compared with the MMF arm: 32/68 vs. 10/61 patients, respectively (47.1% vs. 16.4%, $P < 0.001$, Fisher's exact test), a difference of 30.7% (95% CI 15.6, 45.7). The proportion of patients receiving the maximum recommended dose at Visit 4 was 50.0% (34/68) in the EC-MPS arm as compared with 26.2% (16/61) in the MMF arm ($P = 0.007$), a difference of 23.8% (95% CI 7.6–40.0) (Fig. 3). In total, 16/36 EC-MPS patients (44.4%) increased from a dose of ≤1000 mg/day MMF at baseline to an EC-MPS dose equivalent to >1000 mg/day at Visit 4, as compared with 5/31 patients (16.1%) in the MMF arm who moved from ≤1000 mg/day to >1000 mg MMF. Following randomization, there was a mean increase of 1.3 dose steps from baseline (Visit 2) to Visit 4 in the EC-MPS group compared to 0.2 dose steps in the MMF cohort ($P < 0.001$). In the MMF group, 75.4% of patients had no increase in dose between Visit 2 and Visit 4 (21.3% were already on the maximum dose). The dose remained unaltered in 50.0% of EC-MPS patients but 16.2% of all patients in the EC-MPS group were already on the maximum recommended dose at the point of conversion. Two EC-MPS patients (2.9%) and five MMF patients (8.2%) required a dose reduction.

Concerning the dosing schedule, 18 patients in the EC-MPS arm (26.5%) and 23 in the MMF arm (37.7%) were receiving t.i.d. or q.d. MMF dosing prior to randomization. The protocol specified that EC-MPS was to be initiated as b.i.d. dosing in all patients randomized to receive EC-MPS. All but one patient (17/18) who was changed to b.i.d. dosing after conversion to EC-MPS successfully remained on a b.i.d. regimen until Visit 4 (one patient converted from b.i.d. to q.d. dosing).

Changes in MPA dose were analysed *post hoc* according to whether patients were receiving concomitant CNI therapy. As expected, the mean MMF dose at baseline was higher in CNI-free patients [EC-MPS group 1450 ± 380 mg/day ($n = 15$), MMF group 1550 ± 478 mg/day ($n = 13$)] versus those receiving CNI [EC-MPS group 1200 ± 453 mg/day ($n = 53$), MMF group 1200 ± 468 mg/day ($n = 48$)]. However, the mean increase in MPA dose from baseline to Visit 4 following conversion to EC-MPS was unaffected, increasing by 1.3 dose steps (i.e. EC-MPS 234 mg/day, equivalent to MMF 325 mg/day) in patients with or without concomitant CNI.

A *post hoc* analysis was conducted in patients receiving tacrolimus-based immunosuppression (EC-MPS 37, MMF 33). At randomization, the distribution of MMF doses in tacrolimus-treated patients was similar in each randomized group, with four EC-MPS patients (10.8%) and five MMF patients (15.2%) receiving the maximum recommended dose. Among these tacrolimus-treated patients, significantly more EC-MPS patients were receiving a

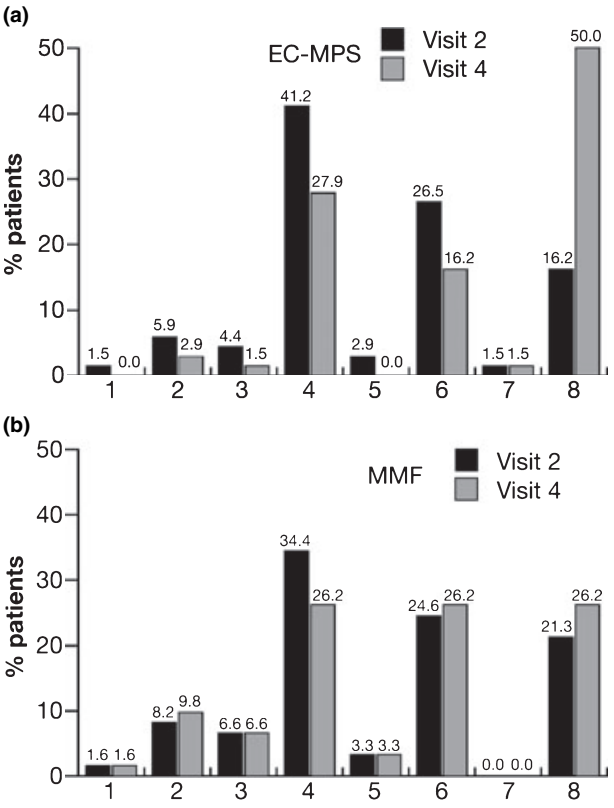

Figure 2 (a) EC-MPS dose category and (b) MMF dose category at time of randomization (Visit 2) and end of study (Visit 4). Dose categories were defined as 1, EC-MPS 180 mg/day or MMF 250 mg/day; 2, EC-MPS 360 mg/day or MMF 500 mg/day, etc. Dose category 8 was the maximum recommended dose (EC-MPS 1440 mg/day, MMF 2000 mg/day).

Table 2. Change in MMF or EC-MPS dose from time of randomization (Visit 2) to end of study (Visit 4). A dose step of '1' equates to EC-MPS 180 mg/day or MMF 250 mg/day, a dose step of '2' equates to EC-MPS 360 mg/day or MMF 500 mg/day, etc.

Change in dose (number of dose steps)	EC-MPS ($n = 68$)	MMF ($n = 61$)
5	1 (1.5%)	0
4	12 (17.6%)	2 (3.3%)
3	2 (2.9%)	0
2	15 (22.1%)	6 (9.8%)
1	2 (2.9%)	2 (3.3%)
0	34 (50.0%)	46 (75.4%)
−1	0	2 (3.3%)
−2	1 (1.5%)	2 (3.3%)
−4	1 (1.5%)	1 (1.6%)

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.

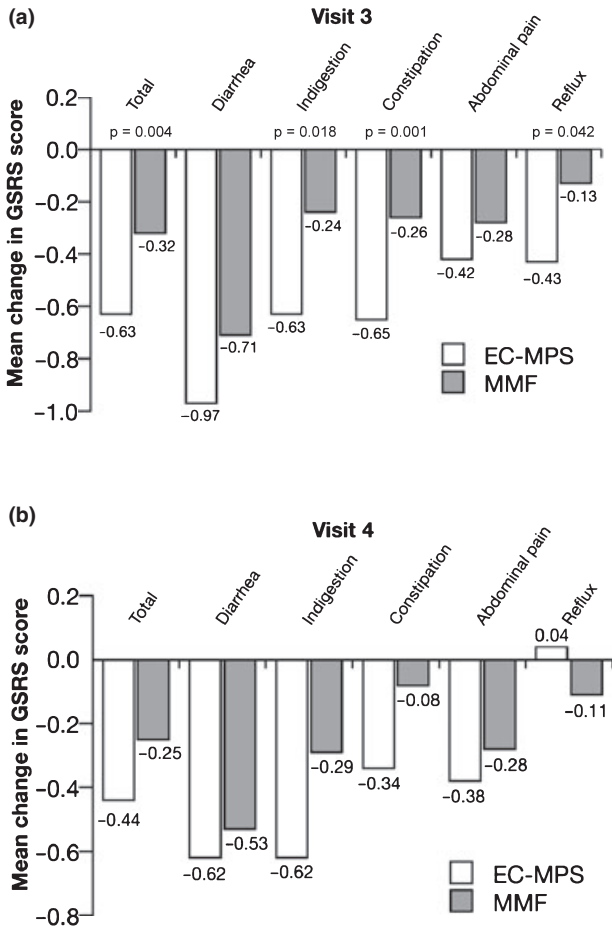

Figure 3 Change in GSRS total score and subscale scores from Visit 2 to (a) Visit 3 and (b) Visit 4. Values shown are mean LSM change. Higher scores represent greater symptom burden. *P*-values calculated by ANCOVA

higher maintenance dose at Visit 4 as compared with patients in the MMF group [18/37 (48.6%) vs. 6/33 (18.2%), $P = 0.011$] and the mean dose increase from Visit 2 to Visit 4 was 1.3 dose steps in the EC-MPS group versus 0.2 dose steps in MMF group ($P = 0.003$).

In terms of time duration post-transplant, patients who were more than 5 years post-transplant achieved a smaller increase in MPA dose following conversion to EC-MPS [EC-MPS 144 mg/day, equivalent to MMF 200 mg/day ($n = 25$)] in relation to those who were ≤5 years post-transplant [EC-MPS 270 mg/day, equivalent to MMF 375 mg/day ($n = 43$)].

Gastrointestinal symptoms

The most frequent GI symptoms reported prior to randomization were flatulence (72.6% of patients), diarrhea (72.6%) and abdominal pain (65.9%), with dyspepsia, nausea and constipation occurring in 46.8%, 43.2% and 21.3% of patients respectively. The incidence and severity of GI symptoms at the point of randomization (Visit 2) were similar between treatment groups (data not shown). Mean severity score for flatulence improved to a significantly greater extent in the EC-MPS group versus the MMF group between Visit 2 and Visit 4. Other between-group differences did not reach statistical significance (Table 3).

Table 3. Change in mean severity score for GI symptoms between Visit 2 and Visit 4 according to treatment group. Severity was graded as none (0), mild (1), moderate (2) or severe (3).

	EC-MPS ($n = 68$)	MMF ($n = 61$)	*P*-value*
Abdominal pain	−0.49 ± 1.00	−0.28 ± 0.93	0.319
Dyspepsia	−0.30 ± 1.16	0.07 ± 1.01	0.055
Nausea	−0.18 ± 0.97	−0.19 ± 0.91	0.959
Flatulence	−0.52 ± 1.04	−0.06 ± 1.02	0.023
Constipation	−0.09 ± 0.61	0.13 ± 0.73	0.231
Diarrhea	−0.88 ± 1.27	−0.52 ± 1.06	0.081

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil.
*Wilcoxon two-sample test.

Patient-reported outcomes

Mean GSRS total score at Visit 2 was 2.49 ± 0.97 and 2.29 ± 0.79 in the EC-MPS and MMF groups respectively. An improvement in GSRS total score was observed in both treatment groups between Visits 2 and 3, but the improvement was significantly greater in the EC-MPS cohort [−0.63 ± 0.14 vs. −0.32 ± 0.14 with MMF; difference −0.31 ± 0.11, 95% CI −0.52 to 0.10; $P = 0.004$ (LSM ± SEM values)] (Fig. 3a). By Visit 4, the difference was no longer significant. Between Visits 2 and 3, the between-group improvement in mean scores was significant for the indigestion, constipation and reflux subscales in EC-MPS patients (Fig. 3a), but no significant differences between the two cohorts remained by Visit 4 (Fig. 3b). At Visit 2, mean GIQLI score was similar in the EC-MPS and MMF cohorts (97.0 ± 25.3 and 100.6 ± 18.8 respectively). As observed with GSRS, the improvement in GIQLI total score was significantly greater in the EC-MPS cohort in relation to the MMF group at Visit 3 [11.7 ± 3.5 vs. 6.1 ± 3.5; difference 5.6 ± 2.6, 95% CI 0.35 to 10.8; $P = 0.037$ (LSM ± SEM values)] but not at Visit 4 (4.8 ± 4.3 vs. 1.8 ± 4.5; difference 3.1 ± 3.3, 95% CI −3.4 to 9.6; $P = 0.350$). On the SF-36 scale, the improvement in the physical composite score from Visit 2 was significantly greater in the EC-MPS group versus the MMF group at Visit 3 [3.1 ± 1.8 vs. 0.1 ± 1.9; difference 3.0 ± 1.4, 95% CI 0.1 to 5.8; $P = 0.045$ (LSM ± SEM values)] but

not at Visit 4 (2.7 ± 1.9 vs. 0.1 ± 1.9; difference 2.6 ± 1.5; 95% CI −0.40 to 5.6; $P = 0.089$). The change in mental composite score did not differ significantly between groups at either visit.

Regarding overall treatment effect, a significantly higher proportion of patients reported an improvement at Visit 4 on the OTE scale for GI symptoms in the EC-MPS group than in the MMF arm (65.0% vs. 39.3%). Results were similar when physicians completed the OTE scale for symptoms (67.2% vs. 29.8%). On the OTE scale for HRQoL, the proportion of EC-MPS patients reporting an improvement was also higher than in the MMF cohort (53.3% vs. 26.8%).

The mean daily number of bowel movements recorded by patients on the Bristol Stool Chart decreased by 0.42 ± 0.17 and 0.16 ± 0.18 from Visit 2 to Visit 3 in the EC-MPS and MMF groups respectively (difference 0.26 ± 0.13, 95% CI −0.52 to 0.00; $P = 0.051$ [LEM ± SEM values]), and by 0.36 ± 0.23 and 0.03 ± 0.24 from Visit 2 to Visit 4 (difference −0.40 ± 0.18, 95% CI −0.75 to −0.04; $P = 0.029$). The mean change in form score did not differ significantly between treatment groups at either time point (data not shown).

Adverse events

There were no graft losses or deaths. One patient in the EC-MPS group experienced biopsy-confirmed acute rejection at week 20 post-transplant (12 weeks after study entry). Immunosuppression at study entry in this patient comprised tacrolimus, MMF 500 mg b.i.d. and 20 mg prednisolone; the MPA dose was not increased following conversion to EC-MPS, but the steroid dose was progressively reduced, reaching 5 mg/day 1 week before rejection was diagnosed.

Adverse events were reported in 66.2% of EC-MPS patients and 54.1% of MMF patients during the study. The incidence of GI events was similar in both groups (EC-MPS 39.7%, MMF 39.3%). Serious adverse events occurred in seven EC-MPS patients (10.3%), including one patient with serious GI adverse events (diarrhea, nausea and vomiting), and in five MMF patients (8.2%) of whom two experienced serious GI events (upper abdominal pain/gastritis and nausea). Neutropenia was reported in one EC-MPS patient, and anemia was reported in two MMF patients, with one case being graded a serious adverse event. In total, adverse events considered by the investigator to be related to study drug were reported in 22/68 EC-MPS patients (32.4%) and 15/61 MMF patients (24.6%). Six patients in each cohort discontinued the study drug because of adverse events (8.8% EC-MPS patients, 9.8% MMF patients). Adverse events leading to EC-MPS discontinuation were gastrointestinal [$n = 5$; abdominal discomfort (1), abdominal pain (1), diarrhea (1), gingival pain (1), nausea (2) and vomiting (2)], decreased appetite ($n = 1$), headache ($n = 1$) and acute renal failure ($n = 1$). Adverse events leading to MMF discontinuation were anemia ($n = 1$), gastrointestinal [$n = 2$; diarrhea (1), gastric disorder (1) and vomiting (1)], increased blood creatinine ($n = 1$), dehydration ($n = 1$) and dypsnea ($n = 1$).

Discussion

This is the first randomized study to assess whether conversion from MMF to EC-MPS permits MPA dosing to be increased in kidney transplant patients with significant GI symptoms. The proportion of patients at the end of the study who were maintained on a higher MPA dose than at baseline was approximately 30% higher in the EC-MPS cohort than the MMF group. This difference was significant, such that the primary endpoint was met. Encouragingly, by the end of the study, 50% of EC-MPS-treated patients were on the recommended dose of MPA as compared with 26% of MMF patients, despite similar proportions at baseline (20.6 and 21.3% respectively). Conversion to EC-MPS therapy was associated with significant improvements in GI symptom burden and HRQoL as compared with MMF, as assessed by validated patient-reported outcomes instruments. The improvement in patient-reported outcomes from baseline were sustained following increases in EC-MPS dose, but differences in improvement between treatment groups became nonsignificant at the end of the study largely because of gains in the MMF cohort.

It was notable that almost half (44%) of the patients on a low dose of MMF (≤1000 mg/day MMF) at baseline achieved a dose equivalent to MMF >1000 mg/day after conversion to EC-MPS. In a large-scale analysis of data from the United States Renal Data System, Bunnapradist *et al.* demonstrated that while even MMF dose reductions of <50% are associated with an increased risk of graft loss of approximately 1.6, reductions of ≥50% (which could be assumed to result in doses of 1000 mg/day or less) led to a greater increase in risk of graft loss – approximately twofold higher than in patients who had no MMF dose reduction [6]. Subsequently, Opelz *et al.* analysed data from the Collaborative Transplant Study and observed similar findings even when the MMF dose reduction took place beyond 1 year post-transplant [23]. This is of particular concern as MMF dose reductions of >50% in patients with GI side-effects are more frequent than smaller reductions [6]. Furthermore, we observed that the increase in MPA dose after conversion to EC-MPS was sustained even in patients without concomitant CNI

therapy who were receiving a higher mean dose of MMF at baseline. While this study was not designed to assess the effect on rejection, CNI-free patients may be particularly vulnerable to breakthrough acute or subclinical rejection following CNI discontinuation [24] so it is encouraging that MPA dose could be increased. In terms of dosing schedule, all patients who had been receiving three- or four-times daily MMF (presumably in an attempt to ameliorate side-effects) and were converted to the recommended twice-daily EC-MPS successfully continued on the new dosing regimen, a point that has not been assessed previously.

Other studies using patient-reported outcomes have also observed consistent improvements in patient-reported outcomes following conversion to equimolar EC-MPS [10,11]. The extent of improvement in GI symptom burden, as assessed by the GSRS scale, was greater in previous trials than in our population, possibly because of higher MMF doses (1400–1600 mg/day vs. approximately 1280 mg/day in our trial) and shorter times post-transplant (ca 2.5 years vs. ca 4.5 years here). The pattern of change was similar, however, with other researchers observing the greatest improvements to be on the diarrhea and indigestion scales, as seen in our population. Results from the Bristol Stool Chart in this study confirmed there to be fewer bowel movements per day in EC-MPS patients even after dose increases, although stools were of a similar consistency in both cohorts.

Certain aspects of the study design must be taken into account. First, we recognize that the open-label nature of the study may have partly influenced the results. A placebo effect may have played a role in the improved patient-reported outcomes following conversion, and indeed it is possible that the higher MPA dosing may have been tolerated partly because of the placebo effect. This issue was partially addressed in the *my*TIME study described by Bolin *et al.*, [11] in which 728 patients with GI symptoms were converted from MMF to EC-MPS. The authors noted that improvements in GSRS scoring at month 1 after conversion were sustained to month 3, even though a placebo effect would be expected to have diminished over a period of time postconversion. Second, the follow-up period was relatively short (12 weeks following randomization), and it is possible that EC-MPS dose reductions could become necessary in some patients over longer follow-up. We recognize that longer follow-up would have been desirable. It is relevant, however, that in a large single-arm trial in which patients were followed for 6 months, Massari *et al.* [25] converted 237 kidney transplant recipients from any dose of MMF to the standard dose of EC-MPS (720 mg b.i.d.). In 47 patients, this represented an increase in MPA dose, of whom 40 (85%) maintained the new higher dose to month 6 follow-up, suggesting that dose increases after conversion to EC-MPS can be sustained for longer than the duration of this study. Third, it would have been of interest to compare MPA blood concentrations in the two cohorts to determine the degree to which MPA exposure increased in the EC-MPS arm following conversion, despite similar patient-reported outcomes, but these data were not recorded. Last, the study population was smaller than that intended, to a large extent because of patients' reluctance to enroll lest they be assigned to remain on MMF. However, the population size was adequate to meet the pre-defined criteria of detecting ≥20% difference between groups in the proportion of patients maintained on at least one dose step higher at the end of the study in relation to randomization.

In conclusion, results from this randomized, multicenter study demonstrate that kidney transplant patients experiencing troublesome GI symptoms while under MMF therapy (many of whom had required dose reduction) can tolerate a significant increase in MPA dose following conversion to EC-MPS. The conversion was associated with improved GI symptom burden and HRQoL as compared with MMF-treated patients; differences diminished after EC-MPS dose increases but patient-reported outcomes with higher doses of EC-MPS remained at least as good as in the MMF control group. At equivalent doses, EC-MPS was associated with fewer GI side-effects than MMF, and where the side-effects were equivalent, EC-MPS permitted higher MPA dosing than MMF. EC-MPS appears to offer a useful therapeutic option either when seeking to avoid GI-related MMF dose reductions or when attempting to increase MPA dose in patients with previous MMF-related GI side-effects.

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