Reduction of Gastrointestinal Complications in Renal Graft Recipients after Conversion from Mycophenolate Mofetil to Enteric-coated Mycophenolate Sodium

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ABSTRACT

Gastrointestinal (GI) complications such as diarrhea or indigestion frequently occur in renal graft recipients treated with mycophenolate mofetil (MMF), requiring dose reductions to reduce side effects, thereby increasing the risk of rejection episodes and graft loss. In a prospective clinical trial, the immunosuppressive therapy of renal graft recipients was converted from MMF to enteric-coated mycophenolate sodium (EC-MPS) to identify a strategy to reduce GI symptoms without dose reduction. At baseline and 6–8 weeks later patients filled in 4 questionnaires related to GI symptoms and general and health-related quality of life. In 15 German study centers, 196 renal graft recipients (mean age 49.5 ± 13.5 years; male/female, 120/76) were included; 51.0% of patients suffered from GI complications at baseline. The Gastrointestinal Symptom Rating Scale score decreased significantly ($P < .001$) in patients with GI complications from 2.61 ± 0.86 at baseline to 2.14 ± 0.86 at visit 2. Health-related and general quality of life improved significantly. Fifty percent of patients with GI symptoms and 34% of the total per protocol population reported an improvement of their physical condition after converting the medication. In conclusion, conversion from MMF to EC-MPS reduces GI complications in renal graft recipients, reduces the patients' physical discomfort, and maintains their quality of life.

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IMPROVEMENT of surgical techniques and introduction of new immunosuppressive drugs in organ transplantation have led to excellent clinical results with a 1-year kidney graft survival rate of more than 90%.[1] Successful organ transplantation improves quality of life as has been shown in several surveys including renal transplant recipients and/or patients on dialysis. However, the score values for graft recipients are still lower than those found in the general population.[2–9] Symptom distress resulting from side effects of the immunosuppressive therapy is a major cause for reduced quality of life in graft recipients.[7,9]

In transplant recipients, dose reduction, a common policy to reduce side effects of drug treatment, causes increased risk of graft rejection. Because modern post-transplantation immunosuppressive schedules offer several alternatives in terms of chemical moieties or pharmaceutical preparations, it should be possible to identify better strategies to reduce side effects in transplant recipients on the one hand and to maintain full efficacy on the other hand.

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The inosine monophosphate dehydrogenase (IMPDH) inhibitor mycophenolic acid (MPA) is used routinely as adjunct immunosuppressant after renal transplantation. A high proportion of MPA-treated graft recipients suffer from gastrointestinal (GI) complications such as diarrhea or abdominal pain. As demonstrated by Ekberg et al,[10] GI symptoms contribute considerably to deterioration of health-related quality of life (HRQoL) in transplant recipients. As for other immunosuppressive agents, MPA dose reduction has been shown to be associated with an increased risk of rejection episodes and graft loss.[11–13] MPA is available in 2 different formulations, both providing MPA as the active principle: the prodrug mycophenolate mofetil (MMF, CellCept, Roche Pharma, Basel, Switzerland) and the gastric- acid resistant enteric-coated mycophenolate sodium (EC-MPS, myfortic, Novartis Pharma, Basel, Switzerland).

Two pivotal trials and their extension trials have demonstrated the therapeutic equivalence of 1440 mg/d EC-MPS and 2 g/d MMF in adult renal transplant recipients with respect to clinical efficacy.[14–17]

Because previous reports observed a better GI tolerability of EC-MPS as compared with MMF,[18] prospective clinical trials were initiated to investigate the influence of an exchange of MMF for EC-MPS on GI symptoms and quality of life of renal graft recipients.[19,20] To our knowledge, no validated data are available including both patients with and without GI complications before conversion. The present study evaluated if conversion from MMF to EC-MPS leads to a reduction of GI symptoms and has an impact on general and GI-specific HRQoL in a study population comprising both patient groups.

MATERIALS AND METHODS

Study Design

The study was designed to investigate GI symptom severity and HRQoL after conversion from MMF to EC-MPS. It was a multicenter, nonrandomized, open-label, prospective trial in adult renal transplant recipients receiving EC-MPS in combination with other immunosuppressives. 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 Harmonization harmonized Tripartite Guidelines for Good Clinical Practice and the ethical principles in the Declaration of Helsinki.

Patient Population

Patients 18 years of age or older were eligible if they had received a renal transplant at least 3 months previously and if they received a stable immunosuppressive regimen including MMF for at least 1 month prior to study enrollment. Patients were to be excluded if they had GI symptoms assumed or known not to be caused by MMF, if they had experienced an acute rejection episode <1 week prior to study enrollment, and in presence of a medical condition not related to GI symptoms that required immediate medical intervention.

Patients who met all inclusion/exclusion criteria and who had given informed consent were enrolled in the study and converted from MMF to an equimolar daily dose of EC-MPS; 720 mg EC-MPS correspond to 1000 mg MMF. The patients were evaluated at baseline (visit 1) and after 6–8 weeks on EC-MPS treatment (visit 2).

Quality of Life Assessments

The following 4 questionnaires were used to examine the patients' condition:

(1) Gastrointestinal Symptom Rating Scale (GSRS),
(2) Gastrointestinal Quality of Life Index (GIQLI),
(3) Psychological General Well-Being Index (PGWB), and
(4) Overall Treatment Effect (OTE) scales.

The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders.[21,22] The GSRS consists of 5 subscales (reflux, diarrhea, constipation, abdominal pain, and indigestion) producing a mean subscale score ranging from 1 (no discomfort) to 7 (very severe discomfort). The GSRS has been validated in renal transplant recipients.[23]

The GIQLI is a 36-item questionnaire to assess the impact of GI disease on daily life.[24] The GIQLI has 5 subscales (GI symptoms, emotional status, physical functions, social functions, and stress of medical treatment), producing a total score of the 36 items. Lower scores represent more dysfunction. It has been validated in renal graft recipients.[23]

The PGWB is a self- or interviewer-administered 22-item measure designed to assess affective or emotional states reflecting a sense of subjective well-being or distress.[25] It has 6 subscales (anxiety, depressed mood, positive well-being, self-control, general health, and vitality).

The OTE is an assessment of change in symptoms or HRQoL since the previous visit.[26,27] The respondents indicate the degree of improvement or worsening on a 7-point scale.

Patients completed the GSRS, GIQLI, and PGWB at visits 1 (baseline) and 2 (after 6–8 weeks on EC-MPS treatment). The OTE was administered only at visit 2. The patients completed an OTE questionnaire for symptoms and one for HRQoL, the physicians completed an OTE questionnaire for symptoms.

Study Objectives/Statistical Analysis

Descriptive statistics, including mean, standard deviation, and range, for each of the patient-reported outcome questionnaires were calculated at each time point. The working hypothesis was that, after the conversion, patients with GI complications would experience a reduced symptom severity more similar to patients without GI complications. The main objective was to determine the changes in GI symptom severity after patients were converted from MMF to EC-MPS. The corresponding primary variable was the change of GSRS total score at visit 2 compared with visit 1.

Assuming a minimal clinically important difference (MID) of the GSRS total score of 0.33, a standard deviation of GSRS total score of 1.3, an alpha level of .05, and a power of 90%, a minimum of 165 evaluable patients was determined in the sample size calculation. One hundred ninety-four patients were to be enrolled, taking into account an over-recruitment rate of 15% to compensate potential drop-outs or major protocol violations. The intent-to-treat (ITT)/safety population included all enrolled patients; the per protocol (PP) population included all patients without major protocol violations with entries for at least 4 subscales of the GSRS at visit 1 and visit 2. As predefined by the protocol, the analysis of the primary objective was based on the PP population.

Changes from visit 1 to visit 2 were tested by means of a paired *t* test (significance level .05, 2-sided). A 2-way ANOVA model was used to analyze the additional influence of gender on the primary variable.

Secondary objectives were to determine the proportion of renal transplant recipients experiencing at least minor GI symptoms under MMF-based immunosuppressive therapy, GIQLI, PGWB, and GI symptom severity changes measured by GSRS subscales, and OTE at visit 2. Subgroup analyses were performed for patients with and without GI complications at baseline and for patients treated with cyclosporine, tacrolimus, sirolimus, everolimus, or other immunosuppressives.

RESULTS

In 15 German study centers, a total of 196 patients (mean age, 49.5 ± 13.5 years; male/female, 120/76) were screened and enrolled. The median time since renal transplantation was 3.0 years. Also, 78.4% of patients had received a kidney from a deceased donor and 21.6% from a living donor. Also, 56.1% of patients (n = 110) were treated with tacrolimus as concomitant immunosuppressive therapy, 31.1% (n = 61) with cyclosporine, 10.7% (n = 21) with sirolimus, and 1.5% (n = 3) with everolimus. One hundred eighty patients fulfilled the criteria for inclusion in the PP analysis, whereas 16 patients showed at least 1 major deviation to the protocol including missing GSRS total score for 1 visit (n = 7), time schedule failure occurrence (n = 7), or a not equimolar dose of EC-MPS to the dose of MMF (n = 2). Premature discontinuation of the study drug was observed 15 times, mostly because of adverse events such as diarrhea or abdominal pain.

At baseline 51.0% (100/196) of patients suffered from GI complications. In this regard the most frequently reported events were diarrhea and abdominal pain/bloating/fullness (Table 1). Seventy-three patients (37.2%) took medications for treatment of GI symptoms and 93 patients (47.4%) for prophylaxis of GI symptoms.

Severity of GI complications was rated mostly mild to moderate (Fig 1). Mean duration of exposure to EC-MPS was 51.2 ± 8.2 days (range, 27–76 days) in the PP population; the median daily dose was 720 mg (range, 180–1440 mg).

Table 1. GI Complications at Baseline

	Safety/ITT n (%)	PP n (%)
n	196	180
Any complication	100 (51.0)	91 (50.6)
Diarrhea	56 (28.6)	50 (27.8)
Dyspepsia	20 (10.2)	17 (9.4)
Nausea	16 (8.2)	15 (8.3)
Vomiting	7 (3.6)	6 (3.3)
Abdominal pain/bloating/ fullness	44 (22.4)	41 (22.8)
GI bleeding	4 (2.0)	4 (2.2)
Other	14 (7.1)	14 (7.8)

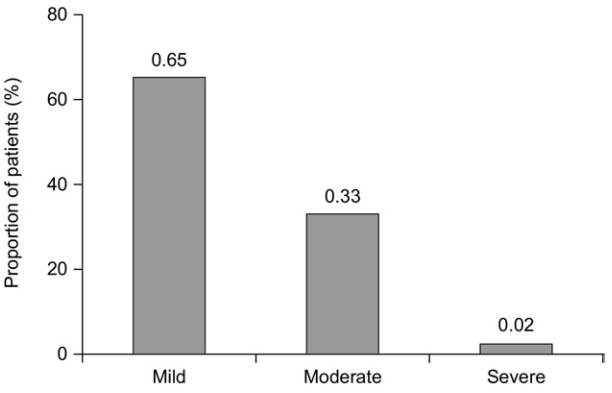

Fig 1. Severity of GI complications in patients suffering from GI complications at baseline (n = 100).

In patients with GI complications (n = 100), the GSRS total score decreased significantly from 2.61 ± 0.86 at baseline (visit 1) to 2.14 ± 0.86 at visit 2 ($P < .001$). Mean improvement of 0.43 exceeded the assumed MID of 0.33. For the whole patient population (n = 196), a significant decrease was observed too (visit 1, 2.18 ± 0.89; visit 2, 2.01 ± 0.90; $P = .021$), whereas no changes were stated for the subgroup of patients free from GI symptoms (n = 96; Fig 2). No differences in GSRS response were seen for male and female patients or for patients with different concomitant immunosuppressive treatment. Figure 3 shows the responses of patients with GI symptoms at baseline in the 5 GSRS subscales; in 4/5 subscales a significant response was seen ($P < .05$).

In accordance with the analysis of the GSRS, a statistically significant improvement of GI-related quality of life in the GIQLI score was observed (mean total score visit 1, 84.6 ± 15.8; visit 2, 89.3 ± 14.4; $P < .001$), which was distinctly more pronounced in the subgroup of patients with GI symptoms at baseline (mean total score visit 1, 77.56 ± 15.2; visit 2, 87.1 ± 14.6; $P < .001$). In patients with GI symptoms at baseline changes in the GIQLI subscales gastrointestinal symptoms, emotional status, and physical

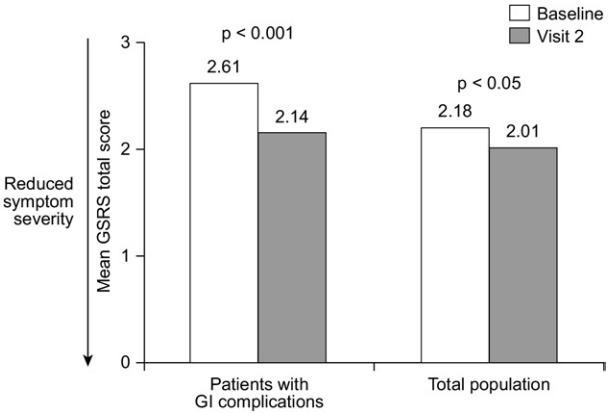

Fig 2. Responses of patients in total GSRS score.

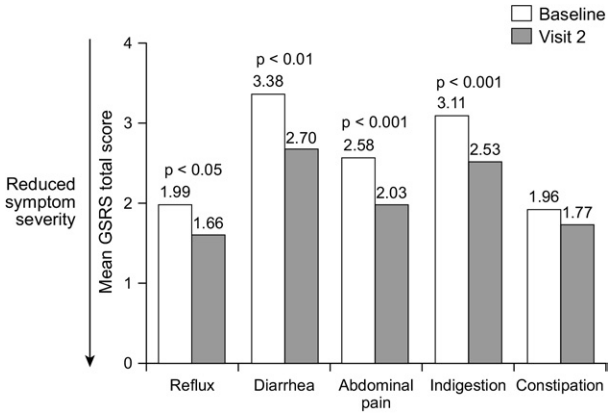

Fig 3. Responses of patients with GI symptoms in GSRS subscales.

function were significant ($P < .05$); social function and stress by medical treatment tended to improve.

The PGWB improved significantly for patients with GI complications at baseline (mean visit 1, 65.6 ± 15.6; visit 2, 69.8 ± 15.6; $P = .006$) with the most marked change in the subscale general health (mean visit 1, 59.9 ± 18.1; visit 2, 69.1 ± 16.3; $P < .001$).

The rating of the OTE revealed that 50% of patients with GI symptoms and 34% of the total PP population felt an improvement of their physical condition after the switch from MMF to EC-MPS (Figs 4 and 5). Also, 41% of patients with GI complication and 26% of the total population had an improvement of their HRQoL. In the perception of the investigators 61% of patients with GI complications and 38% of the total population had an improvement of their GI symptoms.

DISCUSSION

In this exploratory study we evaluated the impact of converting the immunosuppressive therapy of renal transplant recipients from MMF to EC-MPS on occurrence and severity of GI complications as well as on HRQoL. This is the first study that we are aware of providing validated data regarding patients either with or without GI complications prior to conversion of MMF to EC-MPS.

In our study 51% of enrolled patients suffered from GI-related MPA side effects such as diarrhea or abdominal pain at baseline. This finding is quite important because unrecognized and untreated side effects can be associated with impaired compliance and thus set patients at a higher risk of rejection episodes or even graft loss. Takemoto et al demonstrated that patients with poor, low, and medium compliance developed a 43%–46% increased risk of graft failure as compared with highly compliant patients. Furthermore, dose reductions >50% were observed in 7.7% of all cases 2 years posttransplantation, increasing the hazard of graft loss.[28] In a large survey in 3675 MMF-treated renal graft recipients, Bunnapradist et al found that 54.3% of patients underwent MMF dose reduction or discontinuation following GI complications. Intervals of MMF dose reduction <50% were associated with a 1.64-fold increased risk of graft loss; intervals of MMF discontinuation were associated with an approximately 3-fold risk.[12]

These data unequivocally point out the importance of low rates of side effects for renal transplant recipients with an immunosuppressive therapy based on MPA.

To improve occurrence and severity of GI side effects, kidney graft recipients were switched from MMF to EC-MPS. Our results demonstrated that patients presented with GI complications at baseline benefited significantly from a conversion. The GSRS total score decreased from 2.61 ± 0.86 at baseline (visit 1) to 2.14 ± 0.86 at visit 2 ($P < .001$) and mean improvement of 0.43 exceeded the assumed MID of 0.33. Regarding GSRS subscales, significant improvements were observed concerning reflux, diarrhea, abdominal pain, and indigestion. The subscale constipation improved only marginally, however, constipation is not a typical side effect of MPA. Chan et al found similar results. In this study patients suffering from GI complaints were converted from MMF to EC-MPS (cohort A), whereas patients without GI symptom burden remained on MMF treatment (cohort B). Mean improvements on GSRS subscales of cohort A after conversion all exceeded the corresponding estimated MID except for the subscale constipation.[20]

Our data have shown similar significant improvements regarding GIQLI, the greatest benefit being observed on the subscales gastrointestinal symptoms and emotional status, which are strongly connected with GI-related symptom burden. The PGWB scores provided comparable findings. Furthermore, 50% of patients who were experiencing GI side effects at baseline reported an improvement of their physical condition and 41% of their HRQoL. Interestingly, investigators rated the improvements of HRQoL even higher. Our results confirmed an obvious correlation between GI complications and overall well-being, which was previously reported by Ekberg et al. They found that all dimensions of general HRQoL documented by means of

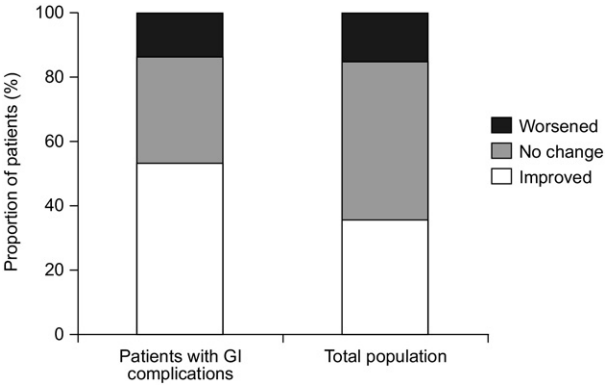

Fig 4. Patient-rated change of GI symptoms after switch from MMF to EC-MPS.

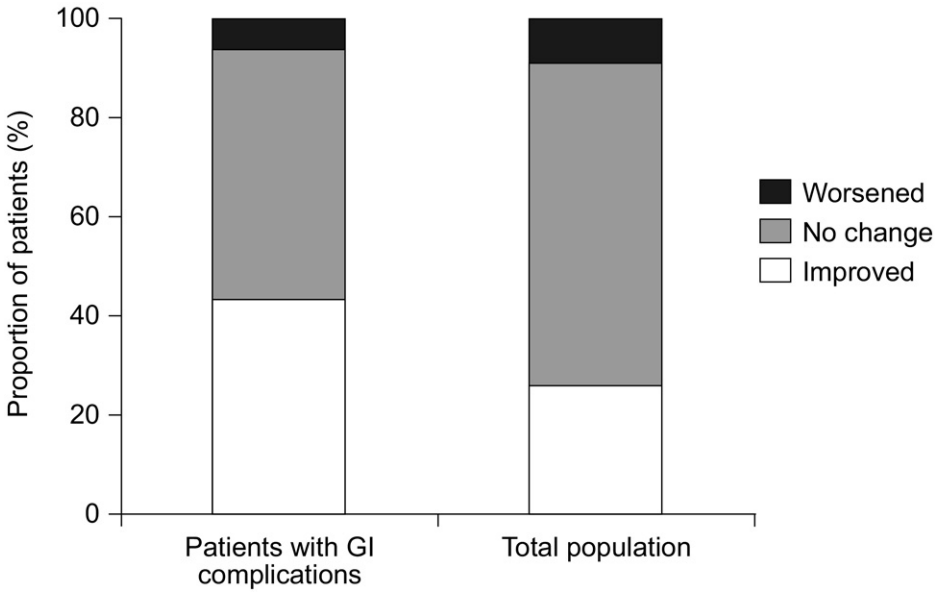

Fig 5. Patient-rated change of HRQoL after switch from MMF to EC-MPS.

the Short-Form 36 general health questionnaire (SF-36) were significantly impaired in patients with GI symptoms.[10]

Patients without GI complaints at baseline showed only slight changes in any of the mentioned questionnaires. Neither GSRS nor GIQLI nor PGWB scores varied significantly. Furthermore, the OTE concerning GI complications and HRQoL evaluated by physicians and patients remained stable. These findings are not surprising. Because patients free from GI complaints reported a considerably better overall well-being at baseline with regard to all used questionnaires, it was to be expected that changes in this group were not as pronounced as in patients suffering from GI-related MPA side effects. Thus we conclude that conversion from MMF to EC-MPS is safe and well-tolerated by patients without GI complaints.

Although our study was not performed in a controlled and randomized fashion, the results cannot be reduced solely to the placebo effect or regression to the mean. Remarkably, changes in the GSRS score or the HRQoL were significant regarding statistics as well as clinical relevance. The results of all different questionnaires were comparable, indicating that the chosen scales were applicable in this setting. Nevertheless, further research is necessary to confirm our findings and to further estimate the benefit of converting immunosuppressive therapy from MMF to EC-MPS.

In view of our data we conclude that conversion from MMF to EC-MPS is a safe and effective means to reduce GI complications in renal graft recipients. Thus we are in line with the results of several studies, finding a decrease in GI symptom burden in patients converted from MMF to EC-MPS.[19,20,29,30] Because dose reductions or discontinuations of MPA are associated with higher incidence of rejection episodes and graft loss, the conversion to equimolar doses of EC-MPS is the preferable strategy to reduce patient physical discomfort, to maintain quality of life, and to keep patients compliant.

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