Gastrointestinal Disorders After Renal Transplantation

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ABSTRACT

Background. Gastrointestinal disorders (GDs) are common in renal transplant recipients. The main cause of GDs seems to be the use of immunosuppressive medications, especially mycophenolic acid in the form of mycophenolate mofetil (MMF).

Objective. The aim of this study was to estimate the frequency and severity of GDs in renal allograft recipients with the use of the Gastrointestinal Symptom Rating Scale (GSRS).

Methods. Eighty-five renal allograft recipients, 50 ± 12 years old, treated with methylprednisolone, calcineurin inhibitor (cyclosporine [CsA], $n = 42$; tacrolimus (TAC), $n = 43$), and MMF were studied.

Results. At the time of completion of the GSRS questionnaire, 38 of the 85 patients (45%) already had their MMF dose reduced because of GDs. Only 15 patients (18%) were totally free from GDs. The most frequent and severe GDs recorded were indigestion and diarrhea who were significantly more frequent in women ($P = .045$). GDs were recorded in patients receiving both standard and reduced dose of MMF. MMF dose was significantly associated only with diarrhea. Although TAC-treated patients had the highest mean GSRS scores, no statistically significant differences were observed compared with CsA-treated patients. In 31 patients, MMF was replaced by enteric-coated mycophenolate sodium (EC-MPS) and new questionnaires were completed 1 month later. Significant improvement in total and all subscores of GSRS was demonstrated ($P < .001$). Although EC-MPS dose tolerated by the patients was higher than MMF dose, the difference was not statistically significant.

Conclusions. Female sex and the use of MMF, especially in combination with TAC, are related to the occurrence of severe gastrointestinal symptoms. Substitution of MMF with EC-MPS significantly reduces the severity of symptoms and permits the use of higher doses.

GASTROINTESTINAL DISORDERS (GDs) occur frequently after renal transplantation, affecting 20%–40% of recipients. Severity of GDs varies widely. Symptoms may be relatively mild, such as intermittent episodes of nausea or diarrhea, or extremely rigorous, such as colonic necrosis or perforation in rare cases, and may lead to graft loss and/or the patient's death. These disorders may be related to surgical stress, infections, exacerbation of preexisting gastrointestinal disease, and medications such as antibiotics, glucose-lowering agents, proton-pump inhibitors, and immunosuppressants [1,2].

Apart from infections and preexisting gastrointestinal disease, the main cause of GDs after renal transplantation seems to be the use of immunosuppressive drugs, especially mycophenolic acid (MPA) in the form of mycophenolate mofetil (MMF), affecting up to 45% of patients in a dose-dependent manner [3]. Various strategies have been tried to ameliorate symptoms, including dose reduction or drug discontinuation. However, reduction of MMF dose has been shown to significantly increase the risk of acute graft rejection and to decrease long-term graft survival [4].

Enteric-coated mycophenolate sodium (EC-MPS) has been developed in an attempt to reduce the incidence of GDs caused by MMF while maintaining its safety and efficacy profile. Indeed, EC-MPS has demonstrated safety and

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efficacy equivalent to MMF in renal transplant recipients in a number of controlled trials [5,6]. In MMF-treated patients with GDs, switching from MMF to EC-MPS seems to improve both gastrointestinal symptoms and quality of life [7,8].

There are few available data regarding the prevalence of GDs in stable renal transplant patients. A possible explanation may be that symptoms are often trivial and therefore not mentioned to physicians [9]. We used the Gastrointestinal Symptom Rating Scale (GSRS) [10] to assess the frequency and severity of GDs after renal transplantation, correlate them with potential noninfectious predisposing factors (sex, age, immunosuppressive drugs) and estimate the possible impact of switching MMF to EC-MPS.

PATIENTS AND METHODS

Patients

Eighty-five renal allograft recipients, 50 men and 35 women, overall mean age 50 ± 12 years, were included in the study. Patients had undergone renal transplantation 6 months to 10 years before the study and all remained in a stable general condition. All patients were receiving a triple immunosuppressive regimen including methyl-prednisolone, MMF, and calcineurin inhibitor (CNI; cyclosporine [CsA], $n = 42$; tacrolimus [TAC], $n = 43$). None of these patients had a history of gastrointestinal disease, neither symptoms nor signs of active infection during the completion of the questionnaire.

Methods

Severity of GDs was assessed with the use of the GSRS. This questionnaire consists of 15 questions addressing the most frequent gastrointestinal symptoms. Questions are grouped into 5 main categories of symptoms (reflux, abdominal pain/discomfort, indigestion, diarrhea, and constipation), each containing 3 questions. Answers are rated from 1 to 7 on a scale of increasing severity. The mean rating of all 15 questions represents the total score of the questionnaire, and the mean rating of the 3 questions of each group represents each group's subscore.

All patients completed the questionnaire at a random time, at least 6 months after transplantation. Patients who suffered the most severe GDs switched from MMF to EC-MPS and completed a second questionnaire, one month later.

Statistical analysis was performed with the use of IBM SPSS Statistics 17.0 software (Armonk, New York). Paired t test and Mann-Whitney test were used to compare means, and Spearman correlation test was used to check for correlations between continuous variables.

RESULTS

In 38 out of 85 patients (45%), MMF dose had been reduced before the study because of gastrointestinal symptoms. In 18 out of 42 CsA-treated patients (42%), MMF dose had been reduced to 1,222 ± 256 mg, and in 20 out of 43 TAC-treated patients (47%) to 962 ± 122 mg. An MMF dose <2,000 mg/d for CsA- and <1,500 mg/d for TAC-treated patients was considered to be a reduced dose.

Fifteen patients (18%) did not mention any gastrointestinal symptoms (CsA, $n = 8$; TAC, $n = 7$). Out of these, 7 patients (CsA, $n = 5$; TAC, $n = 2$) were treated with a reduced dose of MMF (1,300 mg/d and 1,000 mg/d, respectively) and 8 were treated with full dose of MMF (2,000 mg/d and 1,500 mg/d, respectively).

Indigestion and diarrhea were the most frequent (48.4% and 35.1%), and severe (GSRS scores, 2.21 and 2.02) GDs recorded in both CsA- and TAC-treated patients. Age did not correlate with the occurrence of GDs. Women demonstrated a higher total score than men (2.15 vs 1.7; $P = .046$), and this was particularly evident for the occurrence of diarrhea (2.37 vs 1.8; $P = .043$). No statistically significant difference in MMF dose was recorded between men and women (1,600 ± 473 mg vs 1,421 ± 464 mg, respectively; $P = .09$).

MMF dose was correlated only with the occurrence of diarrhea, independently from CNI use ($r = 0.216$, $P = .047$). In addition, there was no statistically significant difference in scores between patients receiving full ($n = 47$) versus reduced ($n = 38$) MMF dose, in both CsA- and TAC-treated patients.

Patients treated with TAC demonstrated higher mean scores (total and subscores) and max values compared with CsA, however this difference was not statistically significant. In addition, patients treated with TAC were receiving a significantly lower MMF dose compared with CsA (1,350 ± 400 mg vs 1,700 ± 455 mg; $P = .018$).

Changes in GSRS Score After Replacement of MMF With EC-MPS

Out of 85 patients, 31 (36%; CsA, $n = 11$; TAC, $n = 20$) who suffered the most severe GDs (mean total GSRS score, 2.71), switched from MMF to EC-MPS. Statistically significant improvement in the total score (2.71 to 1.81; $P < .001$) as well as in all subscores ($P < .001$) was demonstrated 1 month later (Fig 1). Compared with the previously administered MMF dose (1,280 ± 360 mg), all patients tolerated a

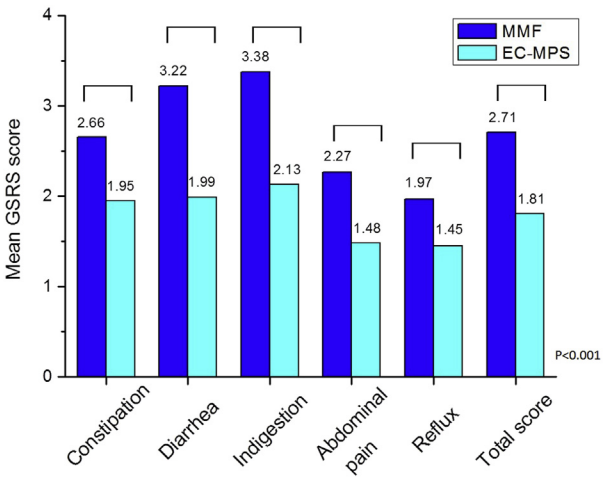

Fig 1. Gastrointestinal Symptom Rating Scale (GSRS) score before and after switch of mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS) ($n = 31$).

higher equivalent dose of EC-MPS (1,000 ± 250 mg EC-MPS, equivalent to 1,380 ± 350 mg MMF). However this difference was not statistically significant.

DISCUSSION

This study has shown that up to 90% of stable renal transplant recipients experienced gastrointestinal symptoms, even when they received a reduced dose of MMF. Similar results have been reported in other studies [9,10], although reported frequencies were generally lower. This variation may be related to the methodology used for the assessment of gastrointestinal symptoms in different studies, because such symptoms are often underestimated by both patients and physicians. Use of the GSRS scale may have helped to reveal the existence of silent GDs and to quantify their severity among renal transplant recipients [9,10].

MMF dose reduction is one of the first interventions undertaken to relieve gastrointestinal symptoms. Mourad et al have shown that the occurrence of gastrointestinal adverse events in MMF-treated patients is related to MPA concentration in blood [11]. However, reducing MMF dose is followed by an increased incidence of acute rejection and graft loss [4]. Although 45% of our patients were already receiving reduced MMF dose, the use of the GSRS scale showed that the majority of them (82%) were still suffering from gastrointestinal symptoms and that their overall scores did not differ from those of patients receiving full MMF dose. Unfortunately, the GSRS scale had not been used before MMF dose reduction in these patients, so the impact of this intervention could not be estimated. Further reduction of MMF dose was not attempted, either because of the risk of acute rejection or because GDs had been underestimated.

Age was not found to correlate to the occurrence of GDs. Female sex demonstrated more severe symptoms, particularly evident in the occurrence of diarrhea. Moreover, there was no difference in MMF dose between men and women and there was no correlation with the age of patients. This is consistent with findings from other studies. MMF seems to cause diarrhea in a dose-dependent manner, independently from the administered CNI.

Although TAC+MMF–treated patients demonstrated higher mean subscores in all categories except for reflux compared with CsA+MMF patients, these differences were not statistically significant. Possibly, MMF dose reduction that had been already undertaken confounded these results. We can be certain, though, that both combinations (TAC+MMF and CsA+MMF) are related to GDs. Measurement of MPA exposure by measurement of blood levels may be the only way to estimate the contribution of each of these agents separately. In the literature, MMF seems to contribute in a dose-dependent manner, whereas for TAC there are only sporadic reports [12,13].

Substitution of MMF with EC-MPS was followed by a significant improvement in GDs. Similar results have been reported by others using equivalent doses of the 2 agents [7,8]. In our study, a higher EC-MPS dose was well tolerated, but this difference was not statistically significant. In addition, 1 month was not a sufficient interval to undertake further interventions and evaluate their possible effects. The results from other studies further support our findings [14,15].

It is becoming clearer that GI toxicity of this class of agents is related to events surrounding drug absorption and metabolism. Two possible molecular targets that may cause GI toxicity are N-(2-hydroxyethyl)morpholine and acyl-MPAG. Both molecules are metabolites of mycophenolic acid. N-(2-Hydroxyethyl)morpholine is a metabolic product of MMF and has been shown to manifest local irritating properties. Acyl-MPAG is an active metabolite of both MMF and EC-MPS, and in situ production and exposure of this metabolite in the intestinal wall may induce toxic damage via protein adduct formation. If local intestinal toxicity is important in determining tolerance of MPA treatment, then strategies that alter the location of MPA delivery to the intestines may be beneficial. These strategies may include the use of formulations such as EC-MPS that stagger MPA release in the gut [16,17].

In conclusion, GDs occur very frequently after kidney transplantation. Although >80% of patients experience gastrointestinal symptoms, this is often underestimated. Female sex and use of MMF, especially in combination with TAC, are related to the occurrence of severe gastrointestinal symptoms, leading to a significant reduction of MMF dose. Switching MMF to EC-MPS seems to improve gastrointestinal symptoms.

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