Enteric Coating of Mycophenolate Reduces Dosage Adjustments

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ABSTRACT

Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS) are bioequivalent. However, the effectiveness of MMF may be limited by gastrointestinal (GI) side effects. This study assessed the relationship between the number of medication dosage adjustments and posttransplantation side effects. In a review of 109 kidney transplant patients, 65 initially received MMF and 44 initially received EC-MPS. The incidences of patient-reported GI complications were significantly different: MMF 45.5% vs EC-MPS 35.3% ($P = .0194$). The proportions of patients requiring dosage adjustment due to GI complications were MMF 5.9% and EC-MPS 2.3% ($P < .0001$). Patients receiving MMF were more likely to experience GI complications resulting in dosage adjustment (odds ratio = 9.9; $P = .0306$). The incidences of acute rejection, cytomegalovirus (CMV), and leukopenia resulting in dosage adjustment were not significantly different. Patients receiving MMF required more immunosuppressive medication adjustments, which may complicate care and decrease overall compliance.

MYCOPHENOLATE MOFETIL (MMF; CellCept) and enteric-coated mycophenolate sodium (EC-MPS; Myfortic) are bioequivalent immunosuppressive drugs that provide similar maximal plasma concentrations of mycophenolic acid, the active component.[1] Conversion from MMF to EC-MPS has been shown to be safe with no adverse outcomes.[2–4] Mycophenolic acid is a reversible inhibitor of inosine monophosphate dehydrogenase which is required for the conversion of inosine into guanine. T and B cells use this enzyme for de novo synthesis of guanine and are thus inhibited by mycophenolic acid.[5]

Unfortunately, the effectiveness of MMF is limited by significant gastrointestinal (GI) side effects, such as diarrhea and vomiting.[5] EC-MPS was developed with the goal to reduce GI side effects through the use of an enteric coating. This coating delays absorption until it reaches the small intestine.[2] However, there are conflicting reports as to whether EC-MPS actually reduces GI side effects such as nausea, vomiting, and diarrhea compared with MMF.[6–8] GI side effects are a common reason for dosage adjustments. The cumulative time that patients receive MMF at levels below full dosage correlates with the incidence of acute rejection.[9] Acute rejection, in turn, portends future graft survival.[10] It has been found that changing MMF dosages within the first year posttransplantation adversly impacts rejection rates and graft survival.[11]

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0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.02.071

Our program made a complete protocol change in February 2006. Prior to this date, de novo and maintenance immunosuppression consisted of tacrolimus, MMF, and prednisone. After the change, EC-MPS replaced MMF. Patients were followed prospectively, and this study was conducted to assess the relationship between the number of dosage adjustments of MMF and EC-MPS and posttransplantation side effects and complications.

MATERIALS AND METHODS

We used the medical records of all adult patients who underwent kidney transplantations at our transplant center between December 2005 and April 2006. Routine protocols for patient care and follow-up were the same for all patients in both groups. The following exclusion criteria were implemented: patients who did not receive MMF or EC-MPS (due to other ongoing trials), those who did not have at least 1 year posttransplantation follow-up data, those who were HIV positive at the time of transplantation, those who had received previous nonrenal transplants, pediatric patients, and those whose grafts were lost due to extensive medication noncompliance. Applying these criteria, 109 patients were included in this study: 65 initially received MMF and 44 initially received EC-MPS. The starting dose for MMF was 1000 mg po twice a day; for EC-MPS, 720 mg po twice a day. All patients received tacrolimus and steroids, tapering to 5 mg/d by week 8. We performed a comprehensive review of the medical records for the first year posttransplantation and recorded the demographic details. The clinical details analyzed were: incidence of posttransplant cytomegalovirus (CMV) infection, incidence of acute rejection episodes, transplant failure, incidence of GI complications (nausea, vomiting, diarrhea), incidence of leukopenia ($\leq$3000/mm^3) resulting in adjustment of immunosuppression, number of MMF or EC-MPS dosage adjustments, and creatinine levels at days 3 and 7 and months 3, 6, and 12 posttransplantation. Using SAS software, we calculated P values and odds ratios (OR) and performed a logistic regression analysis.

RESULTS

Demographic data are shown in Table 1. The groups were similar. The incidence of diabetes, both types 1 and 2, was not different. Serum creatinine levels between the groups were similar (Fig 1). The incidences of one or more GI complication (defined as nausea, vomiting, or diarrhea) were significantly different between groups: MMF 45.5% vs EC-MPS 35.3% (P = .0194). The proportions of patients requiring dosage adjustment due to GI complications were also significantly different: MMF 5.9% vs EC-MPS 2.3% (P < .0001). Patients who continued MMF for the duration of their treatment were more likely to experience GI complications resulting in dosage adjustment than those in the EC-MPS group (OR = 9.9; P = .0306). The proportions of patients requiring 4 or more dosage adjustments were significantly different between groups (MMF 9.8% vs EC-MPS 4.5%; P = .01), whereas those experiencing at least 1 acute rejection episode were not (MMF 9.8% vs EC-MPS 6.8%). The incidences of CMV infections and leukopenia resulting in dosage adjustment were not significantly different between groups.

Table 1. Patient Demographics

Characteristic	Group	
	MMF (n = 65)	EC-MPS (n = 44)
Gender		
Male	40	25
Female	25	19
Age (y)	49.45 ± 12.95	49.39 ± 13.43
Ethnicity		
African American	32	19
Asian	1	2
Hispanic	0	1
Caucasian	32	22
Diabetes	21	19

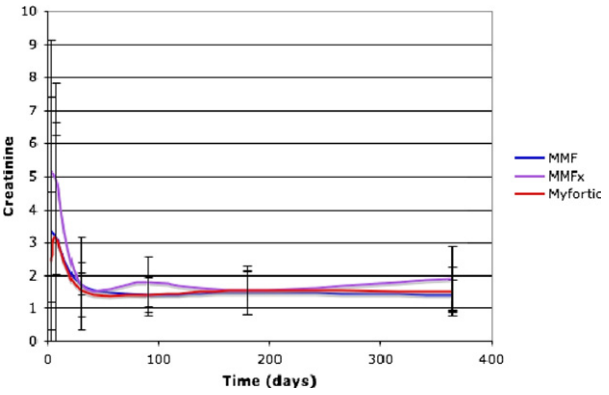

Fig 1. Serum creatinine.

DISCUSSION

The results of this study showed a significantly greater number of dose adjustments for patients receiving MMF compared with EC-MPS. This is a new way of considering the importance of immunosuppressive medication side effects and their potential impact on patient compliance and outcomes. The incidences of one or more GI complication were determined from patients self-reporting to transplant coordinators, and were significantly different between the MMF and EC-MPS groups: 35.3% vs 45.5%, respectively. While this may not be as strictly accurate as data collected using a defined questionnaire and a trained examiner, these data reflect what transplant coordinators and physicians contend with treating patients on a daily basis. When interpreting observational data, there is always a concern about unintentional bias, but in this case, we think this risk is minimized for 2 reasons: first, the patients and coordinators were not told the data were being reviewed, so they were in effect blinded, and second, the transplant center has 6 post-kidney transplant coordinators and data patients were distributed randomly among them.

Our center does not measure mycophenolic acid serum levels, so those data were not available. One would postulate that overall drug exposure was less in patients experiencing more frequent dose adjustments, however, we did not observe any differences in short-term (1 year) out-

comes. The long-term consequences of more frequent dose adjustments in the MMF group are unknown.

Dose adjustments, including reducing the total daily dose and dividing the doses (to 3 times a day or 4 times a day), were performed by both physicians and posttransplant coordinators, although most were done by coordinators responding to patient phones calls without direct physician involvement. Our center has standardized protocols for adjusting immunosuppressive medications, which base adjustment strategies on time from transplantation, serum drug levels, or presumed medication side effects.

Handling patient concerns is time consuming for posttransplant coordinators and requires increased staffing. The need to address presumed medication side effects could increase the risk of transplant complications or failure due to changes in exposure to immunosuppression where monitoring may not be adequate to detect subtle changes in organ function. In addition, there is the possibility that medications may not be returned to prescribed doses when the acute symptoms have resolved.

Two other concerns were identified in our review. First, some patients who had been told to reduce their medication dose in response to GI symptoms began to self-adjust dosing when symptoms recurred. These patients did not feel it was necessary to let their coordinator know because they came to believe that these dose adjustments were "routine" and without consequence. Self-directing dose adjustments could be considered a form of noncompliance, though not with the traditional negative personal implications given to noncompliant patients. The second concern we identified was that referring physicians were adjusting the medications without informing the transplant center. While these physician-directed dose adjustments were most often appropriate, if the transplant center is not aware, then posttransplant monitoring loses some of its effectiveness and outcome analysis becomes less certain.

As this study was retrospective and involved a relatively small number of patients, it may have missed other reasons for dose adjustments, especially because all data about side effects were culled from nurses' notes, not patient questionnaires. Sometimes dosages were changed without indicating reasons. Nonetheless, there is no question that patients had doses of important medications adjusted, usually reduced for some period of time, and that the frequency of dose adjustments was significantly more common with MMF. In conclusion, patients receiving MMF required more immunosuppressive medication adjustments than those receiving EC-MPS, however, this did not affect the incidences of acute rejection episodes or graft survival in this patient cohort. Medications requiring frequent dosage adjustments may complicate care, increase staffing needs and costs, and decrease overall patient compliance.

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