

Comparing Outcomes Associated With Dose Manipulations of Enteric-Coated Mycophenolate Sodium Versus Mycophenolate Mofetil in Renal Transplant Recipients

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Background. This study assessed the incidence of reported gastrointestinal (GI) complications in patients treated with enteric-coated mycophenolate sodium (EC-MPS) versus mycophenolate mofetil (MMF) and to examine the impact of dose manipulations on biopsy-proven acute rejection (BPAR).

Methods. A retrospective study was conducted in 379 renal transplant recipients initiated on EC-MPS or MMF through 3-months posttransplant between the years of 2001 to 2007. Descriptive univariate analyses were used for comparisons of baseline characteristics and outcome measures between the cohorts. A Cox proportional hazards model was used to evaluate the time to a first BPAR event.

Results. GI complications occurred at an incidence of 52.8% and 48.9% in the EC-MPS and MMF cohorts, respectively (NS). Patients requiring dose manipulations due to GI complications were 19.7% with EC-MPS and 25.3% with MMF (NS). The mean equimolar dose reduction below 2000 mg was 930 ± 292.13 mg with EC-MPS and 933 ± 173.95 mg with MMF (NS). Patients treated with EC-MPS experienced significantly fewer BPAR episodes than those treated with MMF (14% EC-MPS vs. 23.1% MMF; $P=0.0221$).

Conclusions. In this study, EC-MPS had a similar incidence of GI complications and dose manipulations compared with MMF. Despite similar GI complication rates and dose manipulations, treatment with EC-MPS seemed to result in a lower incidence of BPAR. Based on these observations, more studies need to be conducted to evaluate risks for BPAR relating to mycophenolic acid product.

Keywords: Gastrointestinal adverse events, Mycophenolate sodium, Mycophenolate mofetil, Renal transplant, Rejection-risk.

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Over the past decade, outcomes in renal transplantation have improved dramatically in part due to the introduction of novel immunosuppressive induction and maintenance agents. One such class, the inosine monophosphate

dehydrogenase inhibitors have improved graft survival significantly by inhibiting the de novo guanosine nucleotide synthesis, which in turn halts guanosine incorporation into DNA in both T and B cells (1). The first Food and Drug Administration -approved medication in this class, mycophenolate mofetil (MMF; CellCept, Roche) requires hydrolysis to form mycophenolic acid (MPA), the active inhibitory compound. Although acute cellular rejection rates are significantly reduced when used in combination with a calcineurin

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inhibitor and steroids, hematological and gastrointestinal (GI) adverse events (AE) have been found to be dose limiting (2).

Enteric-coated mycophenolate sodium (EC-MPS; Myfortic, Novartis Pharmaceuticals Corporation), a recent addition into this class, is the activated component formulated into delayed release tablets. The development was designed to delay the release of MPA, thereby improving the GI tolerability (3). Therapeutic equivalency has been established between EC-MPS 720 mg two times per day and MMF 1000 mg two times per day (4). While long-term graft survival and GI tolerability have been shown to be similar between the two products, the question regarding how to alleviate GI tolerability still remains unanswered (5).

Dose manipulations to limit MPA exposure have been commonly used in the MMF population (6, 7). Studies have shown that by decreasing MPA exposure, by decreasing the dose or extending the dosing interval, GI tolerability may be gained at the expense of an increased risk for acute cellular rejection (6, 8). The primary objective of this cohort study is to describe the incidence of reported GI complications in patients treated with EC-MPS versus MMF and to examine the impact of dose manipulations on biopsy-proven acute rejection episodes (BPAR).

MATERIALS AND METHODS

A retrospective cohort study was conducted by abstracting medical records from two teaching hospitals. A primary investigator and study coordinators were recruited from each site and were responsible for submitting the study protocol to their institution's Institutional Review Board. The study protocol was approved by both institutions' Institutional Review Board.

Each site selected approximately 200 EC-MPS cases that met inclusion/exclusion criteria and an equivalent sample of MMF patients who met the criteria. Data were collected from the transplant hospitalization through 3-month posttransplant. The inclusion criterion was more than or equal to 18 years of age and receiving a single organ de novo renal transplant. Patients were excluded if they met any of the following criteria: had a previous transplant, lost to follow-up within 3 months posttransplant, or were participating in a clinical trial with protocol driven EC-MPS or MMF dosing.

Immunosuppression

Both institutions maintenance immunosuppression included an MPA formulation plus tacrolimus and steroids. Patients initiated on MMF were from years 2001 to 2005, and those initiated on EC-MPS were between the years of 2006 and 2007. Both institutions had a steroid weaning protocol and specific indications for induction therapy. The first institution's practice for steroids weaning was to decrease to 5 mg by 3 months. Their indications for basiliximab induction were for patients with a panel reactive antibody (PRA) more than 20% or a prior transplant. The second institution withdrew steroids after 21 days in low-risk patients (e.g., whites with low PRA, living donor, >60 years of age, and no rejections within the first 21 days). This second institution used basiliximab from 2001 to 2005 then switched to using more rabbit antithymocyte globulin with basiliximab reserved for the living donor population.

Definitions

GI complications were classified as gastroesophageal reflux disease, dyspepsia, indigestion, nausea, vomiting, diarrhea, constipation, abdominal pain, ulcers, and other GI events. Dose manipulations were defined as dose reductions, dose splitting, drug stop, drug hold, and drug switching. Equimolar dose was produced by adjusting EC-MPS doses to the equivalent MMF dose (e.g., 1440 mg EC-MPS=2000 mg MMF; 720 mg EC-MPS=1000 mg MMF). MPA-related events were defined as infection, hematologic, and GI events that resulted in a dose manipulation. Acute rejection episodes were determined by both BPAR and empirically treated elevated serum creatinine (i.e., methylprednisolone \times 3 doses). Infections were only recorded if confirmed by microbiologic or virologic lab report. The time periods reported are baseline (days 0–22), 1 month (days 23–74), and 3 months (days 75–120) from MPA therapy initiation, unless otherwise noted.

Statistical Analysis

Before study initiation, a sample size calculation was performed. The sample size calculation indicated that a minimum of 174 patients in each cohort would allow 80% power to detect a 15% difference of reported GI complications between the EC-MPS and MMF cohorts, based on a 0.05 significance level (paired *t* test). This assumed the incidence of GI complications in patients treated with EC-MPS was 40%.

All study variables, including baseline and outcome measures, were analyzed descriptively between the two cohorts (EC-MPS vs. MMF). Univariate analysis of patient characteristics and outcome measures between the two treatment cohorts were conducted. Numbers and percents were provided for dichotomous and polychotomous variables. Means and standard deviations, and median and range were provided for continuous variables. Student's *t* test or Wilcoxon rank sum test was used for all continuous variables and chi-square test was used for all categorical variables. Subgroup analysis focused on African American (AA) patients.

Variables were tested for multicollinearity before and during multiple regression analysis and Cox's hazard analysis. Variables with a *P* value less than or equal to 0.10 or variables that were important from published literature were used for statistical modeling to determine GI complications, dose manipulations, and time to acute rejection. Control variables considered for the models included: year of transplantation, donor source (living vs. deceased), donor and recipient demographics (age, race, and gender), recipient pretransplant comorbid conditions, cause of end-stage renal disease, pretransplant dialysis, delayed graft function (DGF), calcineurin inhibitors treatment and levels, glucocorticoid treatment and withdrawal, induction therapy (rabbit antithymocyte globulin vs. basiliximab), and posttransplant complications.

Logistic regression analysis was used to predict the probability of a dose manipulation and GI complication to occur between the two drug cohorts (odds ratio [OR]; 95% confidence interval [CI]). Cox proportional hazards regression model was used to examine the time to first GI complication and risk of BPAR associated with MMF dose adjustment (hazards ratio [HR]; 95% CI). The Cox's hazard analysis adjusted for predictor variables of the treatment cohorts and relevant explanatory variables as covariates. In ad-

dition, Kaplan-Meier survival curves of time to acute rejection were evaluated.

A two-sided *P* value of less than 0.05 was considered statistically significant. All analysis were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL) and SAS version 9.0 (SAS, Chicago, IL).

RESULTS

Three hundred and seventy-nine renal transplant recipients, from two teaching hospitals, initiated on EC-MPS or MMF between 2001 and 2007 were included. Of these patients, 193 received EC-MPS and 186 received MMF immediately posttransplant. The overall results did not vary between the two institutions.

Table 1 describes the baseline patient demographics and transplant characteristics of the two cohorts. Patients receiving EC-MPS had a greater prevalence of female patients, alcohol abuse, prior GI surgery, and hypertension causing renal disease. The median time on dialysis before transplant was also significantly higher in the EC-MPS cohort. Transplant characteristics differing significantly between the EC-MPS and MMF cohorts were the proportion of deceased donor renal transplants and DGF. Compared with MMF, the EC-MPS cohort had an increase incidence of deceased donor renal transplants (82.4% vs. 71.9%; *P*=0.0292) and DGF (38.3% vs. 23.7%; *P*=0.0028).

Immunosuppressive characteristics and use at baseline, 1-month, and 3-month time periods are described in Table 2. More than 80% of patients were on a regimen of MPA, tacrolimus, and steroids at baseline. Tacrolimus levels were similar between the two cohorts at discharge, 1 month, and 3 months (data not shown). Use of induction therapy was similar in both cohorts, however, significantly more MMF patients received basiliximab (20% EC-MPS vs. 55.4% MMF; *P*=0.0001). At 90 days, steroid use was reported at 69.6% in the EC-MPS cohort compared with 88.9% in MMF cohort.

GI Complications/Dose Manipulations

The incidence of GI complications and dose manipulations were similar between the EC-MPS and MMF cohorts (Table 3). GI complications occurred at an incidence of 52.8% and 48.9% in the EC-MPS and MMF cohorts, respectively (NS). Diarrhea, the most frequent GI complication reported, was significantly higher in the EC-MPS cohort (33.7% EC-MPS vs. 22.6% MMF; *P*=0.0164). The total proportion of patients experiencing a dose manipulation due to GI complications was 19.7% with EC-MPS and 25.3% with MMF (NS). Dose splitting and reductions were the most common types of dose manipulations due to GI complications. The mean equimolar dose reduction below 2000 mg was 930 ± 292.13 mg in the MPS cohort and 933 ± 173.95 mg in the MMF cohort (data not shown). Two patients (1%) in the EC-MPS cohort required the drug be discontinued due to a GI event compared with five patients (2.7%) in the MMF cohort (NS).

As expected, patients with one or more GI complication were more likely (63%) to have a dose manipulation compared with patients with no GI complications, holding other factors constant (OR 1.632, CI 1.333–1.997; *P*<0.01; data not shown). There was no statistically significant differ-

TABLE 1. Recipient and donor characteristics

	EC-MPS (N=193)	MMF (N=186)	<i>P</i>
Baseline demographics			
Age (yr)	52.2±13.46	51.5±12.60	0.6342
Patients>60 yr	60 (31.1)	51 (27.4)	0.4327
BMI (kg/m ²)	28.6±5.88	28.8±6.00	0.7919
Female	93 (48.2)	73 (39.3)	0.0795
White	68 (35.2)	75 (38.7)	0.7414
African American	116 (60.1)	107 (57.5)	—
Other ^a	9 (4.7)	7 (3.8)	—
Clinical history			
Alcohol abuse ^b	21 (11.0)	7 (3.8)	0.0074
Previous pregnancy ^c	61 (78.2)	53 (84.1)	0.3743
GI disease	60 (31.1)	48 (25.8)	0.2548
GI surgery	65 (33.7)	26 (14.0)	0.0001
Malignancy	20 (10.4)	12 (6.5)	0.1710
Hyperlipidemia	79 (40.9)	59 (31.7)	0.0624
Dialysis	173 (89.6)	169 (90.9)	0.6884
Length of dialysis pretransplant (mo)	37 (0–187)	34 (1–120)	0.0086
Causes of disease			
Diabetes	62 (32.1)	63 (33.9)	—
Hypertension	154 (79.8)	89 (47.9)	0.0001
Glomerulonephritis	13 (6.7)	13 (7.0)	0.9222
Polycystic kidney disease	15 (7.8)	16 (8.6)	0.7681
Other	57 (29.5)	67 (36.0)	0.1784
Cytomegalovirus (CMV) sero-status			
Donor+/recipient+	61 (31.6)	56 (30.1)	0.7522
Donor–/recipient+	21 (10.9)	28 (15.1)	0.2261
Donor+/recipient–	29 (15.0)	20 (10.8)	0.2152
Donor–/recipient–	23 (11.9)	20 (10.8)	0.7209
Transplant characteristics ^d			
Transplant length of stay (d)	6 (2–30)	5 (3–42)	0.5592
Living related	20 (10.4)	36 (19.5)	0.0137
Living unrelated	13 (6.7)	16 (8.7)	0.4944
Deceased donor	159 (82.4)	133 (71.9)	0.0292

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

^a MMF has 1 patient with missing data.

^b EC-MPS has 2 patients with missing data.

^c EC-MPS has 15 patients with missing data; MMF has 10 patients with missing data.

^d Both cohorts have 1 patient with missing data.

BMI, body mass index; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; GI, gastrointestinal; BPCR, biopsy-proven chronic rejection; HTN, hypertension.

ence between MMF and EC-MPS on predicting GI complications when adjusting for all other factors (OR 0.798, CI 0.470–1.355; NS; data not shown).

Other MPA-related events that resulted in dose manipulations are infection and hematologic complications (Table

TABLE 2. Immunosuppression characteristics

	EC-MPS	MMF
MPA equimolar dose ^a	N=193	N=186
Start dose (mg)	2054±365.71	2153±492.56
Discharge dose (mg)	1645±542.77	1694±508.58
1-mo dose (mg)	1973±405.22	1979±401.80
3-mo dose (mg)	1845±410.25	1861±398.09
Induction		
Total	119 (61.7)	113 (60.8)
Alemtuzumab	5 (2.6)	0 (0)
Basiliximab	56 (29.0)	103 (55.4)
Rabbit ATG	56 (29.0)	8 (4.3)
Other	2 (1.0)	2 (1.1)
Frequency of use at baseline		
Cyclosporine	4 (2.1)	5 (2.7)
Sirolimus	4 (2.1)	5 (2.7)
Tacrolimus	173 (89.6)	167 (89.8)
Steroids	176 (91.2)	173 (93.0)
Antibodies	106 (54.9)	121 (65.1)
Frequency of use at 1 mo	N=191	N=183
Cyclosporine	8 (4.2)	8 (4.4)
Sirolimus	18 (9.4)	7 (3.8)
Tacrolimus	174 (91.1)	162 (88.5)
Steroids	134 (70.2)	161 (88.0)
Antibodies	9 (4.7)	9 (4.9)
Frequency of use at 3 mo	N=184	N=180
Cyclosporine	8 (4.3)	8 (4.4)
Sirolimus	21 (11.4)	8 (4.4)
Tacrolimus	157 (85.3)	160 (88.9)
Steroids	128 (69.6)	157 (87.2)
Antibodies	4 (2.2)	7 (3.9)

Continuous variables are shown as mean values (±SD) and binary variables are shown as n (%) of patients.

^a Weighted daily mean doses. EC-MPS dose was converted to equimolar dose of MMF.

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; MPA, mycophenolic acid; ATG, antithymocyte globulin.

3). Infection-related reasons for dose manipulations were more common in the EC-MPS cohort (10.9% EC-MPS vs. 5.9% MMF; $P=0.0821$) whereas hematologic-related reasons were slightly less than the MMF cohort (17.6% EC-MPS vs. 19.4% MMF; NS).

Graft Outcomes

Patients treated with EC-MPS experienced significantly fewer BPAR episodes than those treated with MMF (14% EC-MPS vs. 23.1% MMF; $P=0.0221$; Table 4). Table 5 illustrates the adjusted risk of experiencing a BPAR episode at 3 months in the MMF cohort was 1.8 times higher than the EC-MPS cohort (HR 1.824, CI 1.017–3.269; $P<0.05$). Patients having a drug manipulation were 4.4 times more likely to have BPAR compared with those who did not holding all factors equal (HR 4.366, CI 2.222–8.578; $P<0.01$). The confounding variables incorporated in the multivariate analysis are reported in Table 5. These include variables to account for

TABLE 3. Primary and secondary outcomes (unadjusted)

	EC-MPS (N=193)	MMF (N=186)	P
Primary outcome			
Incidence of GI complications	102 (52.8)	91 (48.9)	0.4448
Incidence of diarrhea	65 (33.7)	42 (22.6)	0.0164
Dose Manipulations due to GI complications			
Total proportion of patients with a drug manipulation ^a	38 (19.7)	47 (25.3)	0.1929
Dose reductions	14 (7.3)	21 (11.3)	0.1748
Dose splittings	22 (11.4)	30 (16.1)	0.1809
Dose stops	2 (1.0)	5 (2.7)	0.2325
Dose holds	9 (4.7)	6 (3.2)	0.4730
Dose switching	1 (0.5)	3 (1.6)	0.2971
Drug discontinuations ^b	2 (1.0)	5 (2.7)	0.2325
Reasons for dose manipulations			
GI complications	43 (22.3)	54 (29.0)	0.1321
Infection	21 (10.9)	11 (5.9)	0.0821
Hematologic	34 (17.6)	36 (19.4)	0.6629

Variables are shown as n (%) of patients.

^a Total drug manipulation is defined as patient having a dose reduction, dose splitting, drug stop, drug hold, or drug switch.

^b Drug discontinuation is defined as patient has drug stop or drug switch. EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; GI, gastrointestinal.

TABLE 4. Graft outcomes (unadjusted)

	EC-MPS	MMF
1 mo ^a	N=191	N=183
BPAR	28 (14.7)	46 (25.1)
BPCR	3 (1.6)	0
Graft failure	0	1 (0.5)
3 mo	N=184	N=180
BPAR	1 (0.5)	5 (2.8)
BPCR	0	0
Graft failure	0	0

Variables are shown as n (%) of patients.

^a 1 mo is defined as 0–74 d after MPA therapy initiation.

EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; BPAR, biopsy-proven acute rejection.

immunosuppressant regimen differences between the two cohorts such as steroid use, mean calcineurin inhibitor levels, and induction therapy.

Safety

Patient survival at 3 months was 100% in both cohorts (data not shown). The most common AEs reported were GI, infections, and hematologic (Table 6). GI events occurred at a frequency of 87% in the EC-MPS cohort and 76.9% in the

TABLE 5. Cox proportional hazards model of BPAR at 3 mo

Variable	95% Confidence interval			P
	Hazard ratio	Lower	Upper	
MMF	1.824	1.017	3.269	0.044
Age	0.998	0.976	1.021	0.873
Female	0.774	0.435	1.376	0.383
African American	1.028	0.574	1.842	0.927
History of alcohol abuse	1.141	0.320	4.072	0.839
History of hyperlipidemia	1.045	0.595	1.835	0.879
History of GI surgery	0.886	0.454	1.730	0.722
HTN-cause of ESRD	0.994	0.565	1.749	0.984
Length of dialysis pretransplant	1.010	0.994	1.026	0.234
Deceased donor renal transplants	0.640	0.278	1.474	0.295
Living-related donor	0.567	0.170	1.891	0.356
Delayed graft function	0.946	0.447	2.002	0.885
Dialysis required posttransplant	1.884	0.889	3.995	0.099
Infection	1.677	0.887	3.171	0.112
Having a GI complication	1.182	0.686	2.038	0.547
Having a dose manipulation	4.366	2.222	8.578	0.000
Mean equimolar MPA dose ^a	1.001	1.000	1.001	0.141
Basiliximab induction	0.899	0.498	1.624	0.725
Rabbit ATG induction	0.656	0.292	1.470	0.306
Tacrolimus use	0.868	0.201	3.745	0.850
Mean CNI level	0.948	0.833	1.078	0.414
Steroid use	2.314	0.492	9.247	0.311

Weighted daily mean dose. EC-MPS dose was converted to equimolar dose of MMF.

MMF, mycophenolate mofetil; GI, gastrointestinal; MPA, mycophenolic acid; ATG, antithymocyte globulin; ESRD, end-stage renal disease; CNI, calcineurin inhibitors.

MMF cohort. The frequency of infection episodes was 62.7% and 37.6% in the EC-MPS and MMF cohorts, respectively. The EC-MPS cohort reported a 6.7% frequency of hematologic complications and the MMF cohort reported 11.3%.

AA Subgroup

Subgroup analyses were planned a priori due to the large AA population at both institutions. Table 1 illustrates AA race accounted for the just over half of the population (60.1% EC-MPS and 57.5% MMF). The AA group had higher mean equimolar doses of both EC-MPS and MMF at 3 months compared with the non-AA group (data not shown). Total manipulations due to MPA-related events in the AA population were similar between EC-MPS and MMF (63.8% vs. 58.9%; NS) (data not shown). In the EC-MPS cohort, non-AA had significantly higher dose manipulations due to GI complications than the AA group (28.6% vs. 13.8%; $P=0.0115$; data not shown). The difference between the non-AA group and the AA group in the MMF cohort was

TABLE 6. Adverse events (unadjusted)

	EC-MPS (N=193)	MMF (N=186)
Adverse event frequencies		
Hematologic	13 (6.7)	21 (11.3)
Infection	121 (62.7)	70 (37.6)
GI	168 (87.0)	143 (76.9)
Nephrotoxicity	19 (9.8)	12 (6.5)
Other	19 (9.8)	11 (5.9)
Incidence of infection type		
BK virus	6 (3.1)	0
Clostridium difficile	6 (3.1)	7 (3.8)
CMV	13 (6.7)	7 (3.8)
Fungal	1 (0.5)	0
UTI	33 (17.1)	13 (7.0)
Other	44 (22.8)	31 (16.7)

Variables are shown as n (%) of patients.

CMV, cytomegalovirus; UTI, urinary tract infection; EC-MPS, enteric-coated mycophenolate sodium; MMF, mycophenolate mofetil; GI, gastrointestinal.

nonsignificant (20.5% non-AA group vs. 29.0% AA group; NS) (data not shown).

DISCUSSION

MMF approved by the Food and Drug Administration in 1995 quickly became a standard component in the immunosuppressive regimens for renal transplants. The restrictive factors for patients taking MMF are the AEs associated with it. The most common AEs that result in dose reductions, interruptions, and discontinuation of therapy are GI complications and cytopenias (9). EC-MPS was developed in an effort to reduce the GI complications associated with MMF and was approved in February of 2004 by showing equal efficacy and safety to MMF through two large, multicenter, Phase III clinical studies (4, 10). Like MMF, the most common AEs are GI complications and in these noninferiority trials no significant difference was reported (4, 10). Open-label trials with endpoints regarding GI-specific health status and GI-associated quality of life have provided evidence that GI AEs differ between these two agents. In MMF to EC-MPS conversion studies, these differences have been detected even in patients greater than 4 years posttransplant and remained evident several months following conversion (11–13). In the present study, no significant difference in the incidence of GI complications was seen between EC-MPS and MMF cohorts.

The large phase III clinical studies in de novo renal transplant recipients were not designed to detect differences in GIAEs. Therefore, this study was designed and powered to evaluate the incidence of GI complications in de novo renal transplant recipients treated with EC-MPS compared with MMF. Second, we looked at the effect of dose manipulations and GI complications on BPAR events at 3 months. The incidence of GI complications in both cohorts of our study were similar to what has been reported in the literature (30%–50%) (6, 7, 14). For sample sizing, we assumed the incidence of GI complications would be ~40% to detect a 15% difference between the two cohorts and no difference was found.

Diarrhea was significantly higher in the EC-MPS cohort compared with the MMF cohort; however, in a retrospective study it is hard to attribute any AE to a medication.

GI AEs can be associated with a variety of factors in renal transplant recipients, such as surgical anesthetics, infections, pretransplant patient comorbidities (i.e., diabetes mellitus), and side effects of all immunosuppressants and other concomitant medications (15). A major strength of our study was the detail of data we were able to collect from chart review. We were able to assess documented reasons for dose manipulations unlike the use of claims data. In a study using the United States Renal Data System analysis, claims data were used to determine associations between GI complications and dose manipulations (16). Based on our chart review, we determined that GI complications were a reason for dose manipulations in nearly a quarter of the patients.

Two recent retrospective cohort analyses showed EC-MPS having less dose manipulations due to AEs compared with MMF (17, 18). Several studies examining the effects of dose reductions and discontinuations due to GI complications of MMF have shown negative clinical outcomes. These studies indicate that patients experiencing GI side effects and requiring dose reductions or discontinuations are at increased risk for acute rejection and decreased long-term graft survival (6–8, 16, 19). The United States Renal Data System study by Hardinger et al. (16), reported MMF dose adjustments following GI AEs were associated with a significant increase in graft loss. In a multivariate Cox regression analysis, the increase in risk among patients with MMF discontinuation was almost threefold ($P=0.0002$). Our results show approximately a fourfold increase of risk with BPAR in patients who had a dose manipulation holding all factors equal. There was also a significant association with EC-MPS treatment, despite similar GI complication rates and dose manipulations to MMF, and a lower incidence of BPAR at 3 months. We adjusted for all significant confounding variables and tested for multicollinearity and there are no indicators that multicollinearity is present in the model.

Evidence supporting increased dosing has not been demonstrated following improvement in GI AEs. The present study reported a frequency of GI complications with EC-MPS 14.1% lower at baseline, 31.2% higher at 1 month, and 5.7% higher at 3 months. The mean equimolar dose was equivalent with EC-MPS and MMF throughout these time periods. In the recent retrospective cohort analysis of 200 patients, EC-MPS had less dose manipulations due to AEs compared with MMF at 3 months (4% EC-MPS vs. 17% MMF; $P<0.001$) yet all allograft outcomes were similar between the two cohorts (17). The mean MPA doses in this study at 3 months were 752 ± 220 mg in the EC-MPS cohort and 1026 ± 177 mg in the MMF cohort (17). Based on our observations, it remains to be seen if a relationship exists between GI AEs, optimal MPA dose and clinical outcomes.

Limitations

This study has several potential limitations. The data were collected retrospectively and patients were not randomized. Patients were collected based on meeting predefined inclusion/exclusion criteria with selection of the most current until the sample size was fulfilled thus relatively free of investigator bias and reflect the most up to date practice for each

treatment cohort. Additionally, the overall results were similar between the two institutions.

To reduce potential confounders, we excluded any previous or concomitant transplants because there would be small patient numbers in these groups, potential for higher BPAR risk, and differences in baseline risk factors for GI complications. Both institutions stopped using MMF in 2005 so the treatment patterns and clinical practice may contribute to confounding the results. In this study, we tried to control for the variables relating to practice changes within the Cox proportional hazards regression model; however there is the possibility of undetected confounders.

Because of the limitations of chart review, we were limited to collection of only what was documented in the outpatient and inpatient charts. The follow-up period post-transplantation was limited to 3 months due to significant loss of follow-up data. In addition, not all risk factors for rejection were consistently documented and therefore not reported such as PRA values, human leukocyte antigen mismatches, donor and recipient ABO blood type, or HIV status. Retrospective studies cannot explain the causality between MPA treatment, GI complications, dose manipulations, and BPAR. Effects not observed must be considered as possible explanations for the causal relationships between MPA treatment, GI complications, dose manipulations, and BPAR.

CONCLUSIONS

There are limited comparative effectiveness studies using real-world practice data to evaluate differences between EC-MPS and MMF. In this retrospective study of 379 patients, EC-MPS had a similar reported incidence of GI complications and dose manipulations compared with MMF. Despite similar GI complication rates and dose manipulations, treatment with EC-MPS appeared to result in a lower incidence of BPAR episodes. More studies are warranted to evaluate the risks for BPAR relating to the use of MPA products.

REFERENCES

1. Kitchin JE, Pomeranz MK, Pak G, et al. Rediscovering mycophenolic acid: A review of its mechanism, side effects, and potential uses. *J Am Acad Dermatol* 1997; 37: 445.
2. Mycophenolate mofetil in cadaveric renal transplantation. US Renal Transplant Mycophenolate Mofetil Study Group. *Am J Kidney Dis* 1999; 34: 296.
3. Arns W. Noninfectious gastrointestinal (GI) complications of mycophenolic acid therapy: A consequence of local GI toxicity? *Transplant Proc* 2007; 39: 88.
4. Salvadori M, Holzer H, de Mattos A, et al; The ERL B301 Study Groups. Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in *de novo* renal transplant patients. *Am J Transplant* 2004; 4: 231.
5. Ciancio G, Burke GW, Gaynor JJ, et al. Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplant recipients given tacrolimus and daclizumab/thymoglobulin: One year follow-up. *Transplantation* 2008; 86: 67.
6. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. *Transplantation* 2006; 82: 102.
7. Tierce JC, Petrilla AA, Kilburg A, et al. Impact of mycophenolate mofetil (MMF)-related gastrointestinal complications and MMF dose alterations on transplant outcomes and healthcare costs in renal transplant recipients. *Clin Transplant* 2005; 19: 779.

8. Knoll GA, MacDonald I, Khan A, et al. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. *J Am Soc Nephrol* 2003; 14: 2381.
9. Budde K, Knoll G, Curtis J, et al. Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, myfortic). *Clin Nephrol* 2006; 66: 103.
10. Behrend M. Adverse gastrointestinal effects of mycophenolate mofetil: Aetiology, incidence and management. *Drug Saf* 2001; 24: 645.
11. Budde K, Knoll G, Chan L, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: Results of a 1-year study. *Am J Transplant* 2004; 4: 237.
12. Bolin P, Tanriover B, Zibari GB, et al. Improvement in 3-month patient-reported gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients. *Transplantation* 2007; 84: 1443.
13. Chan L, Mulgaonkar S, Walker R, et al. Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. *Transplantation* 2006; 81: 1290.
14. Pietruck F, Abbud-Filho M, Vathsala A, et al. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in stable maintenance renal transplant patients: Pooled results from three international, multicenter studies. *Transplant Proc* 2007; 39: 103.
15. Davies NM, Grinyo J, Heading R, et al. Gastrointestinal side effects of mycophenolic acid in renal transplant patients: A reappraisal. *Nephrol Dial Transplant* 2007; 22: 2440.
16. Hardinger KL, Lowell J, Schnitzler MA. Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil. *Transpl Int* 2004; 17: 609.
17. Hardinger KL, Bloomer T, Murillo D. Adverse drug reaction driven immunosuppressive drug manipulations: A single-center comparison of enteric-coated mycophenolate sodium vs. mycophenolate mofetil. *Clin Transplant* 2008; 22: 555.
18. Pelletier RP, Henry ML, Rajab A, et al. Clinical outcomes of renal transplant recipients treated with enteric-coated mycophenolic acid vs. mycophenolate mofetil as a switch agent using a primary steroid-free rapamune and micro-emulsion cyclosporine protocol. *Clin Transplant* 2007; 21: 532.
19. Pelletier RP, Henry ML, Bumgardner GL, et al. The impact of mycophenolate mofetil dosing patterns on clinical outcome after renal transplantation. *Clin Transplant* 2003; 17: 200.