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Long-term outcome of gastrointestinal complications in renal transplant patients treated with mycophenolate mofetil

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Abstract This study examined consequences of gastrointestinal (GI) complications and mycophenolate mofetil (MMF) discontinuation on long-term outcomes in patients who received MMF at transplantation and had graft function 12 months post-transplantation. Data were obtained from the United States Renal Data System for cadaveric renal transplant recipients between 1995 and 1998. GI complications or MMF discontinuation occurred in 27.4% and 17.5% of patients, respectively. MMF was discontinued in 21.3% of patients with GI complications and 16.0% of patients without ($P < 0.00001$). Four-year graft survival was reduced from 87.1% to 82.3% ($P = 0.091$) with MMF discontinuation, to 83.0% ($P = 0.001$) with GI complications, and to 70.2% ($P < 0.0001$) with GI complications and MMF discontinuation. While the retrospective nature of this work cannot prove causality, which will require future prospective studies, both GI complications and MMF withdrawal are associated with increased risk of graft loss and may warrant further study in the management of transplant recipients.

Keywords Kidney transplantation · Graft survival · Cost · Gastrointestinal complications · Immunosuppression · Post-transplant complications

Introduction

Gastrointestinal (GI) complications are a common side effect of transplantation and range from less severe illnesses such as intermittent diarrhea or nausea to life-threatening complications such as colonic necrosis or perforation [1]. Mechanical injury during surgery, metabolic changes associated with transplantation, infectious agents, endogenous GI dysfunction, and organ toxicity of immunosuppressive agents may contribute to

GI disturbances. Immunosuppressive agents can cause GI complications through direct action in the gut or by increasing vulnerability to infectious agents [2, 3].

Mycophenolate mofetil (MMF) has been used successfully since 1995 as an adjunct immunosuppressive agent for the prevention of acute rejection in renal transplantation [4]. However, hematologic and GI side effects are a concern with MMF-containing immunosuppressive regimens [5]. Diarrhea, abdominal pain, nausea, vomiting, intestinal bleeding, and perforation occurred more frequently in the MMF-treated group than in placebo or azathioprine (AZA)-treated groups in phase III clinical trials [6, 7, 8]. A general trend of GI side effects toward dose dependence was also noted in those studies. Consequently, in practice, dose reduction or elimination of MMF is often undertaken to ameliorate GI symptoms [9, 10]. However, inappropriate dose reduction of MMF may result in an unnecessarily increased risk of acute rejection [10].

The long-term consequences of GI complications in MMF-treated patients are not known. Moreover, the frequency of GI manifestations in patients treated with MMF has been difficult to determine. There is considerable variability in the reported incidence from the estimates derived from the three multicenter clinical trials—the incidence of diarrhea, for example, ranged from 15.6% in the European trial [7] to 37.3% in the US trial [6]. Also, safety data from short-term, protocol-driven clinical trials may not accurately reflect the incidence of GI complications in clinical practice.

We used a large national cohort of cadaveric renal transplant recipients drawn from the United States Renal Data System (USRDS) to examine the long-term consequences of GI complications or MMF discontinuation in renal transplant recipients treated with an MMF-containing regimen. Specifically, we wished to determine whether GI complications are associated with increased likelihood of MMF discontinuation and whether MMF discontinuation in the presence of GI complications is associated with poorer clinical and economic outcomes.

Methods

Patient population

The data used in the study were derived from the USRDS [11]. The USRDS is a joint effort of the National Institutes of Diabetes and Digestive and Kidney Diseases and the Center for Medicare and Medicaid Services (CMS). The collaboration was designed to collect, analyze, and distribute data describing end-stage renal disease in the United States of America, including prevalence, treatment modality, survival, and cost of care. We used the USRDS transplant and outcome data on all kidney transplants recorded by the United Network for Organ Sharing renal transplant registry.

The USRDS database was analyzed for single-organ, adult cadaver kidney transplant recipients between 1995 and 1998 with Medicare as the primary payer. Patients treated with MMF at transplant discharge, with functioning grafts at 12 months post-transplantation and with records of their immunosuppression regimen at 12 months post-transplantation were included in the analysis. To identify patients using Medicare as their primary insurer, we excluded patients from economic analyses if (1) no Medicare payment for their transplant hospitalization was listed or (2) a Medicare payment for transplant hospitalization was less than $15,000, following methods designed by the USRDS to identify primary Medicare coverage in the dialysis population [11]. Four main groups of patients were analyzed: (1) patients with GI complications in whom MMF was discontinued; (2) patients without GI complications in whom MMF was discontinued; (3) patients with GI complications in whom MMF was not discontinued; (4) patients without GI complications in whom MMF was not discontinued.

This study was reviewed and approved by the Washington University Human Studies Committee. The blind, retrospective nature of the data made it impossible for us to obtain informed consent from study subjects; therefore an informed consent exemption was obtained.

Post-transplantation GI complications

The presence of GI complications during the first transplantation year was identified from data from Medicare claims and a method that has been validated for post-transplantation diabetes mellitus [12]. A GI complication was considered to have occurred if ICD-9 codes for one of the following diagnoses or procedures were reported on Medicare billing records of the USRDS: abdominal pain, anorexia, constipation, diarrhea (including ulcerative or toxic), ulcer (including abdomen, bowel, duodenum, gastrojejunal, ileum, ischemic, peptic, sigmoid, stomach), vomiting (functional, habit, allergic, or with nausea), severe vomiting (blood, causing asphyxia, fecal matter), nausea, hemorrhage (duodenum, gastric/intestines), perforation (bowel, cecum, diverticulum, small intestine), biopsy (stomach, small intestine, cecum, ileum, intestine), endoscopy (small, colon, ileum, intestine, or stomach), or colonoscopy.

Outcome measures

Graft loss in each of the four groups of patients was determined by date of indicated graft loss, return to dialysis, or death.

Costs were calculated from the perspective of Medicare for patients believed to have used Medicare as

the primary payer for their transplant. Primary Medicare insurance cannot be determined directly from the database. Reported costs are Medicare payments for all medical equipment, supplies and services covered by Medicare and provided to a patient during the second year post-transplantation. Medicare covers the large majority of all medical equipment, supplies and services, ranging from inpatient hospitalizations to physician office visits to home health to immunosuppressive drugs, etc. Outpatient oral medications are an important exclusion from Medicare coverage, with the exception of immunosuppressive medications. All costs are reported in US dollars adjusted for inflation to the year 2000.

Analysis of risk factors for GI complications and MMF discontinuation

We used multivariate models to understand further the determinants of GI complications and MMF discontinuation. We examined the following clinical and demographic variables available in the clinical information in the USRDS registry: *in the donor*—body mass index, female gender, presence of diabetes, expanded criteria donor [13]; *in the recipient*—age, female gender, African–American ethnicity, body mass index, previous pregnancy, cytomegalovirus (CMV) serology, insulin dependency, peak panel reactive antibody level, previous renal transplant, pretransplant dialysis, peritoneal dialysis, delayed graft function, number of HLA and HLA-DR mismatches, positive T- or B-cell cross match, year of transplantation, calcineurin inhibitor, cyclosporine or tacrolimus, for maintenance immunosuppression, conversion between calcineurin inhibitors or calcineurin inhibitor withdrawal by 12 months post-transplantation, acute rejection episode through 12 month post-transplantation follow-up, cause of end-stage renal disease, limited activities of daily living, employment-limiting disability, and median educational and income level of the recipient's zip code. In a multivariate analysis we used the incidence, during the first-year post-transplantation, of post-transplant diabetes mellitus (PTDM) [12, 14], CMV-infection [15], and hyperlipidemia, using the same technique that was used to derive the incidence of GI complications from ICD-9 codes. The number of post-transplant hospitalizations was also used in multivariate models to account for the possibility that GI complications and/or MMF withdrawal are markers for patients that require more intense medical services.

Statistical analysis

Differences in graft survival were compared by the Kaplan–Meier method, and statistical significance was determined with the log-rank test. Multivariate graft survival analysis was performed with Cox regression. Differences in costs were compared by two-tailed Student's *t*-test. Multivariate cost analysis was performed with linear regression. Differences in MMF discontinuation rates in the presence or absence of GI complications were compared with Fisher's exact two-tailed test. Multivariate analysis of the incidence of MMF discontinuation was performed with logistic regression. Results of multivariate analyses were adjusted for significant variables from the list above.

Results

Incidence of GI complications and MMF discontinuation

USRDS records identified 46,564 kidney transplantations performed between 1995 and 1998. From these 6,400 renal graft recipients were identified that had received post-transplant immunosuppression with MMF, had an intact graft and immunosuppression records at the 12-month follow-up, and used Medicare as their primary insurance coverage. The characteristics of these patients are shown in Table 1.

Table 2 shows the frequencies of GI complications and MMF discontinuation in this cohort. In the first post-transplantation year, GI complications were diagnosed in 1,753 patients (27.3%), and MMF was discontinued in 1,117 patients (17.5%). The frequency of MMF discontinuation was significantly higher in patients with GI complications (21.3%) than in those without such complications (16.0%) (odds ratio 1.33; $P < 0.0001$).

Risk factors for MMF discontinuation

In a multivariate analysis using stepwise logistic regression, GI complications in the first 12 months were associated with a 19% increased risk of MMF discontinuation [odds ratio (OR) 1.19; $P = 0.01$] (Table 3). The greatest risk factor associated with MMF discontinuation was CMV infection (OR 1.60; $P < 0.0001$). De novo tacrolimus immunosuppression (OR 1.51; $P < 0.0001$) and the number of hospitalizations during the first year post-transplantation (OR 1.14; $P < 0.0001$) were also strongly associated with MMF discontinuation. Significant associations with greater risk of MMF discontinuation were also observed for unknown cause or hypertension as the cause of end-stage renal disease (ESRD), peak panel reactive antibody (PRA) level greater than 10%, recipient age greater than 60 years, and no pre-transplant dialysis.

Table 1 Characteristics of study population. Results are expressed as the percentage of patients with the characteristic, except as otherwise noted (*ADL* activities of daily living)

Characteristics	
Donor	
Body mass index	25.3 ± 7.3
Female gender	40.7%
Presence of diabetes	3.3%
Expanded-criteria donor	12.3%
Recipient	
Age (years) (mean ± SD)	47.3 ± 13.5
< 20	1.8%
20 to < 40	28.1%
40 to < 60	50.7%
> 60	19.4%
Female gender	38.9%
African–American	32.7%
Previous pregnancy	24.5%
Body mass index	26.0 ± 3.2
Insulin dependency	16.0%
Peritoneal dialysis	19.1%
Duration of pretransplantation dialysis (y) (mean ± SD)	3.0 ± 2.0
Previous renal transplant	8.2%
Peak panel reactive antibodies	12.6 ± 22.8
< 10%	66.1%
10% to < 50%	25.5%
50% to < 80%	3.8%
> 80%	4.6%
HLA mismatches (mean ± SD)	3.6 ± 1.7
HLA-DR mismatches (mean ± SD)	1.1 ± 0.7
CMV sero-status (donor/recipient)	
+/+	37.8%
−/+	22.4%
+/−	18.4%
−/−	21.4%
Positive T cell crossmatch	1.7%
Positive B cell crossmatch	3.9%
Year of transplantation	
1995	6.2%
1996	25.0%
1997	36.7%
1998	32.0%
Limitation in ADL	8.0%
Employment-limiting disability	38.7%
Median education in recipient's zip code	
Completed high school	72.2% ± 12.8%
College degree	18.1% ± 11.6%
Median income of recipient's zip code($)	29,305 ± 11,181
Calcineurin inhibitor	
Neoral	66.3%
Tacrolimus	20.7%
Other or none	13.0%
Cause of disease	
Type 1 diabetes mellitus	9.0%
Type 2 diabetes mellitus	12.7%
Hypertension	23.9%
Glomerulonephritis	14.7%
Other	28.0%
Unknown	11.7%
First-year post-transplantation complications	
GI complications	27.3%
Delayed graft function	24.0%
Acute rejection in first 6 months	15.4%
PTDM	21.0%
CMV infection	12.5%
Hyperlipidemia	14.6%

Risk factors for GI complications

We used a stepwise Cox regression procedure to determine significant predictors of GI complication incidence (Table 4). The greatest risk associated with GI complications was in patients with CMV infection [risk ratio (RR) 1.85; $P < 0.0001$]. The influence of CMV was also seen in an additionally higher risk in patients known to be at greatest risk of CMV disease, the CMV sero-pairing D^+/R^- (RR 1.16; $P = 0.01$). Other factors associated with a heightened risk of GI complications were hyperlipidemia (RR 1.29; $P < 0.0001$), PTDM (RR 1.20; $P = 0.0002$), the number of post-transplant hospitalizations (RR 1.20; $P < 0.0001$), pre-transplant maintenance peritoneal dialysis (RR 1.21; $P = 0.002$), pre-transplant maintenance hemodialysis (RR 1.39; $P < 0.0001$), and hypertension as the cause of ESRD (RR 1.19; $P = 0.002$), Peak PRA level between 10% and 50% was associated with a significantly decreased risk of GI complications compared with peak PRA level less than 10% (RR 0.84; $P = 0.005$).

Graft survival

Figure 1 shows graft survival between 1 and 4 years post-transplantation in the four patient groups. Four-year graft survival was highest (87.1%) in patients who did not develop GI complications or discontinue MMF. The occurrence of GI complications in the first year was associated with significantly reduced graft survival after 12 months post-transplantation, the reduction being most pronounced when MMF was also discontinued (70.2%; $P < 0.0001$); however, even when MMF was continued, GI complications were associated with lowered survival, to 83.0% ($P = 0.0010$). Similarly, MMF discontinuation was associated with reduced 4-year graft survival, to 82.3%, in patients who had suffered no GI complications. However, graft survival after 12 months post-transplantation in these patients did not differ significantly from that of patients without GI complications who continued MMF ($P = 0.091$). This may be due to type II error caused by the smaller sample size in the group that discontinued MMF but had no GI complications (see Table 2).

The results of a stepwise multivariate analysis of graft survival after 12 months post-transplantation is presented in Table 5. Patients with both GI complications and MMF withdrawal were at significantly increased risk of graft failure compared with the other groups [hazard ratio (HR) 1.51; $P = 0.0007$]. However, there were no significant differences observed between the other groups: GI complications without MMF withdrawal, MMF withdrawal without GI complications, or neither. We found it interesting that CMV infection was a strong predictor of both GI complications and MMF

Table 2 Incidence of GI complications and MMF discontinuation

Parameter	Incidence	
Total number of patients	6,400	
With GI complications	1,753	(27.4%)
Without GI complications	4,647	(72.6%)
Discontinued MMF	1,117	(17.5%)
Continued MMF	5,283	(82.6%)
Patients with GI complications who discontinued MMF	373/1,753	(21.3%)
Patients with GI complications who continued MMF	1,380/1,753	(78.7%)
Patients without GI complications who discontinued MMF	744/4,647	(16.0%)
Patients without GI complications who continued MMF	3,903/4,647	(84.0%)

Table 3 Risk factors associated with MMF discontinuation

Characteristic	Odds ratio	*P*
Post-transplantation complications		
CMV infection	1.60	< 0.0001
GI complications	1.19	0.01
Tacrolimus immunosuppression	1.51	< 0.0001
Cause of ESRD unknown	1.24	0.03
Peak PRA greater than 10%	1.23	0.006
Recipient age greater than 60 years	1.23	0.01
Cause of ESRD: hypertension	1.21	0.01
No pretransplantation dialysis	1.17	0.03
Number of post-transplantation hospitalizations	1.14	< 0.0001

discontinuation, but not a significant predictor of graft survival after 12 months post-transplantation. Therefore, we examined this further in additional multivariate models, considering interactions between CMV infection, GI complications and MMF discontinuation. In no case was CMV infection or a CMV–infection interaction found to be significant, but the combination of GI complications and MMF discontinuation was always found to be a significant predictor of increased risk of graft failure after 12 months post-transplantation.

Table 4 Risk factors associated with GI complications

Characteristic	Relative risk	*P*
Post-transplantation complications		
CMV infection	1.85	< 0.0001
Hyperlipidemia	1.29	< 0.0001
Post-transplant diabetes mellitus	1.20	0.0002
Number of post-transplantation hospitalizations	1.20	< 0.0001
Pretransplantation maintenance peritoneal dialysis	1.21	0.002
Pretransplantation maintenance hemodialysis	1.39	< 0.0001
Pregnancy pretransplantation	1.20	0.0006
Cause of ESRD: hypertension	1.19	0.002
CMV sero-pairing D^+/R^-	1.16	0.01
Peak PRA 10–< 50%	0.85	0.005

Analysis of costs

Average second-year Medicare payments for patients remaining on MMF at 12 months post-transplantation and free of GI complications were $14,799. By contrast, second-year average Medicare payments were 53.3% higher in patients who had GI complications and who also discontinued MMF ($22,694; $P = 0.0042$). Second-year payments were also significantly higher, by 31.1%, for patients with GI complications but continuing MMF ($19,400; $P < 0.0001$). However, patients who discontinued MMF but were free of GI complications were associated with only a trend toward higher Medicare payments, a 9.3% increase ($16,178; $P = 0.18$).

Examination of costs by graft survival revealed a difference between GI complications and MMF

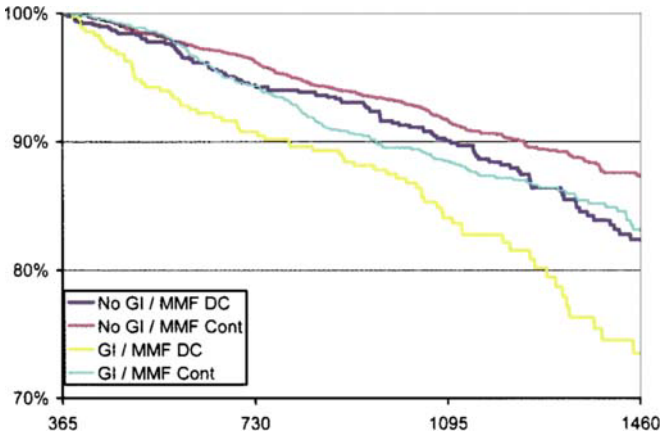

Fig. 1 Four-year graft survival was highest (87.1%) in patients who did not develop GI complications or discontinue MMF. The occurrence of GI complications in the first year was associated with significantly reduced graft survival, the reduction being most pronounced when MMF was also discontinued (70.2%; $P < 0.0001$); however, even when MMF was continued, GI complications were associated with lowered survival, to 83.0% ($P = 0.0010$), compared with patients with neither GI complications nor MMF discontinuation. Similarly, MMF discontinuation was associated with reduced 4-year graft survival, to 82.3%, in patients who had no GI complications. However, graft survival in these patients did not differ significantly from that of patients without GI complications who continued MMF ($P = 0.091$)

Table 5 Risk factors associated with graft failure

Characteristic	Hazard ratio	*P*
Previous kidney transplant	1.85	<0.0001
Acute rejection during first-year post-transplantation	1.73	<0.0001
Recipient age over 60 years	1.58	<0.0001
GI complications and MMF withdrawal	1.51	0.0007
African–American recipient	1.49	<0.0001
Expanded-criteria donor	1.47	<0.0001
Cause of ESRD type II diabetes mellitus	1.33	0.03
Pretransplantation dialysis	1.25	0.008
Male recipient	1.23	0.01
Number of post-transplantation hospitalizations	1.19	<0.0001

discontinuation in their association with costs. Graft failure was associated with a tripling of costs, from an average of $13,423 for patients with a surviving graft to $39,022 for patients with a graft that had failed during the study ($P<0.0001$). In patients with graft failure, neither GI complication nor MMF withdrawal was associated with a significant effect on costs. However, in patients with an intact graft, GI complications increased costs by 33%, from $12,321 to $16,414 ($P<0.0001$). However, MMF withdrawal had no significant association with second-year Medicare payments in patients surviving to the end of the study—second-year payments were $13,107 in patients who continued MMF and $13,699 in those who discontinued MMF. In a multivariate analysis that included the number of first-year hospitalizations there were no significant differences in second-year costs associated with either GI complications or MMF withdrawal. The number of hospitalizations, one measure of resource utilization, in the first-year had a powerful association with first-year costs, another measure of resource utilization. Therefore, this analysis is a regression of second year costs on proxy for first-year costs and may be subject to colinearity problems, increasing the likelihood of type II error. The multivariate results, excluding the number of first-year hospitalizations, were entirely consistent with the univariate results described above. However, given the results, including the number of hospitalizations, we must interpret this with caution.

Discussion

The present study documents the incidence of GI complications and MMF discontinuation in MMF-treated renal transplant recipients with a functioning graft after 1 year and analyzes the associations of these events with long-term transplant outcomes. GI complications occur in almost one-third of the MMF-treated population in the first year after renal transplantation, which broadly reflects the incidence in standard clinical practice outside the constraints of a clinical trial. Although the frequency of GI complications reported in clinical trials varies considerably, the incidence documented in this study is similar to that of GI complications reported in the USA [6] and tri-continental [8] double-blind randomized studies. Ours is the first study to associate GI complications that occur in the first post-transplant year with a significant negative impact on graft outcomes in the following years. This raises the importance of GI complications, from that of an inconvenient or uncomfortable complication to that of a threat to graft and, possibly, patient survival in renal transplantation.

We observed MMF discontinuation in 17.5% of the patients. The rate was significantly higher in patients with GI complications than in those without GI complications. Multivariate analyses showed that GI complications that occurred in the first 12 months post-transplantation were associated with MMF withdrawal during that same period. Relationships between GI adverse events, MMF dose, and MMF discontinuation have been examined in studies of pharmacokinetic and pharmacodynamic predictors of clinical effectiveness and side effects of MMF [16, 17]. A concentration-controlled study demonstrated that the plasma concentration of mycophenolic acid (MPA), the active metabolite of MMF, correlates inversely with the incidence of acute rejection, whereas tolerability is related to the dose of MMF [18]. In this study, adverse events led to MMF withdrawal in 25.3% of patients; GI side effects accounted for 39% of these withdrawals, and 80% of these patients were in the group with high exposure to MPA. Furthermore, MMF withdrawal due to GI events was dose related, whereas withdrawal for other adverse events was not. Another similar pharmacokinetic study showed that the risks of both GI complications and premature withdrawal were related to the dose of MMF [19]. There was also a relationship between GI complications and MMF withdrawal, because 46% of patients who withdrew prematurely had experienced GI complications at some point, whereas only 20% of continuing patients experienced GI complications.

The adverse GI effects associated with MMF may be attributed to a number of factors including an enhanced immunosuppressive milieu, which promotes the emergence of GI infection [20]. MMF increases the severity of CMV invasive disease in renal transplant recipients [21], and CMV enteropathy may account for some GI symptoms [22]. Not surprisingly, we have found CMV infection to be associated both with the incidence of GI complications and with MMF discontinuation. Further, we observed additional risk of GI complications in the CMV sero-pairing D^+/R^-, patients at the greatest risk of severe CMV infection. Interestingly, CMV infection is not a predictor of graft failure after the first-year

post-transplantation, despite the CMV's strength as a predictor of GI complications and MMF discontinuation. In an additional analysis neither CMV infection, or its interaction with GI complications or MMF discontinuation, nor the triple interaction of all three factors significantly predicted graft failure after the first-year post-transplantation. However, the combination of GI complications and MMF withdrawal was a strong predictor of graft failure in each of these additional analyses. This may suggest that the complications of CMV infection lead to adverse outcomes more than the simple fact of infection.

There were several potential limitations to this study. These limitations stem primarily from the use of registry data. Therefore, our analysis was limited to information available in the registry, the data were collected retrospectively, and the patients were not randomly allocated to treatment groups. On the other hand, these data are relatively free of investigator bias and reflect standard clinical practice in a large population. Because of its retrospective design the study does not explain the causalities between MMF treatment or any other immunosuppressive drug used in this population and the occurrence of GI complications. Hence, our results suggest that further study should be conducted to verify these findings. We must consider the possibility that there are explanations other than causal relationships between GI complications, MMF discontinuation, and outcomes, causing some, and perhaps all, of the effects observed here.

It is important to note that the results of any retrospective analysis be seen as evidence of effects, but never considered as proof without corroboration. Therefore, this and other retrospective analyses are best used as starting points for further studies and guidance for the thoughtful management of patients. It should also be noted that, although the use of ICD-9 codes has been validated for other diagnoses, it has not been validated for the various manifestations of GI disease [12]. Another drawback was that we could not identify patients who continued with MMF but at reduced doses. Based on the report by Pelletier et al. [10], the incidence of these patients is approximately 50%. Hence, the group continuing with MMF is likely diluted with those who continued on a reduced dose, leading to an underestimation of the survival difference when compared with the group that discontinued MMF.

There were additional limitations of this study, due to the reporting structure of MMF discontinuation. There was no specific date indicated for MMF discontinuation, only that it had occurred at some time between transplantation and 1 year after. Therefore, multivariate models that estimated the risk of MMF discontinuation, and models that estimated the risk of graft failure, must be interpreted with caution. While the results presented here are evidence of a causal effect of the combination of GI complications and MMF withdrawal, we cannot be certain that GI complications and MMF withdrawal are causally linked.

We were also limited because both GI complications and MMF discontinuation are intermediate outcomes preceding graft failure. Estimated effects of characteristics with possible causal relationships with GI complications or MMF discontinuation, patient age for example, may not be directly interpretable in graft survival models including these intermediate outcomes [23]. It is important to understand that these analyses were performed to examine the robustness of the relationships between GI complications and MMF discontinuation and their combined effect on graft survival. These analyses should be considered consistent with the hypothesis that GI complications leading to MMF discontinuation lead to increased risk of graft failure, but the results of this study cannot be considered definitive proof of this hypothesis.

However, our findings do provide evidence of a rationale for strategies that reduce the GI complications occurring with MMF-containing immunosuppressive regimens without compromising immunosuppressive efficacy. Current practice is to administer MMF at a dose of 2,000 mg per day, but a more flexible regimen that permits dosage adjustment according to clinical status may enable the dose to be tailored to individual needs [3]. Because the GI effects of MMF are dose related, dose splitting (spreading the dose of MMF over the day) may reduce local toxicity.

In summary, this study shows that there is a high incidence of GI complications during the first post-transplantation year in renal transplant patients treated with MMF and that patients with GI complications are more likely to discontinue MMF. GI complications are associated with increased risk of graft failure in combination with MMF discontinuation. These are important considerations in the management of transplant patients, and efforts directed at minimizing the risk of GI complications and maintaining optimal exposure of MPA should be studied further.

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