Mycophenolate Mofetil Dose Reductions and Discontinuations after Gastrointestinal Complications Are Associated with Renal Transplant Graft Failure

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Background. Mycophenolate mofetil (MMF) use in renal transplantation has steadily increased since 1995 because of its ability to lower the risks of rejection and chronic allograft nephropathy. However, significant gastrointestinal (GI) complications may lead to MMF dose reductions and discontinuations. Little is known of the association between MMF dose reductions and discontinuations following GI complications and graft survival.

Methods. Using the United States Renal Data System, we identified 3,675 adult recipients (age ≥18) with a diagnosed GI complication who were prescribed MMF at the time of first GI diagnosis and had Medicare as their primary insurer. MMF doses were ascertained from Medicare payment records. We estimated risk of graft loss associated with MMF dose adjustments after GI diagnosis: dosage unchanged (reference), reduced <50%, reduced ≥50%, and MMF discontinued. Patients were followed until graft loss, death, last recorded immunosuppression prescription, or 3 years posttransplant.

Results. Compared to those with no MMF dose reductions or discontinuations, the risk of graft failure increased with MMF doses reduction ≥50% (HR=2.36, 95% CI 1.23–4.54) and those with MMF discontinuation (2.72, CI 1.60–4.64).

Conclusion. Renal transplant recipients who underwent MMF dose reduction or withdrawal following GI diagnosis are associated with increased risk of graft failure.

Keywords: Complications of immunosuppression, USRDS, Pharmacoepidemiology, Maintenance immunosuppression.

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Mycophenolate mofetil (MMF) has been used increasingly since 1995 as an adjunct immunosuppressive agent to calcineurin inhibitor (CNI) containing regimens for the prevention of acute rejection in renal transplantation (*1*). In addition, experimental and clinical studies suggest that MMF may prevent chronic allograft nephropathy (*2*). A registry analysis of US data collected between 1988 and 1997 from 66,774 renal transplant recipients revealed that patients who received MMF experienced 27% decrease in the relative risk of developing chronic rejection compared with those who received azathioprine ($P<0.001$) (*3*). The rate of death-censored graft survival at four years was significantly higher in the MMF-treated group as opposed to the azathioprine-treated group (85.6% v. 81.9%, $P<0.0001$) and this effect was independent of acute rejection (*4*). With this result, MMF has become the standard adjunct immunosuppressant in most transplant centers the United States (*4*).

Despite its excellent efficacy, the use of MMF is associated with a high incidence of gastrointestinal (GI), hematological and other adverse events (*5*, *6*). In clinical trials, a high proportion of patients require MMF dose reductions, interruptions, or discontinuation due to such complications (*1*, *6*, *7*). Consequently, dose reduction or discontinuation of MMF is often undertaken to ameliorate GI symptoms (*8*, *9*). However, MMF dose reduction or discontinuation may result in increased risk of acute rejection (*9*) and poorer long-term graft survival (*8*, *10*).

Using the United States Renal Data System (USRDS) database, we have shown that GI complications and/or MMF discontinuation during the first year following renal transplantation are associated with an increased risk of subsequent graft failure (*10*). Patients with GI complications and MMF discontinuation experienced significantly lower four-year graft survival compared to patients without GI complication and MMF discontinuation (70% versus 87%; $P=0.0001$). GI complications in the first year posttransplant were associated with a 33% increase in the risk of MMF discontinuation. However, it was not possible in that study to determine if MMF discontinuation occurred after GI complications nor were we able to determine if MMF dose reduction impacted graft survival. Concentration-controlled studies have demonstrated that the plasma concentration of mycophenolic

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acid, the active metabolite of MMF, correlates inversely with the incidence of acute rejection, whereas tolerability is related to the dose of MMF (*11*, *12*).

Here, we examined whether MMF dose reduction or discontinuation following a GI complication was associated with an increased risk of subsequent graft failure. The availability of immunosuppressant prescription data for patients with Medicare as their primary insurer has allowed us to study prescribed dose reduction or discontinuation of immunosuppressants as time-dependent variables in this subgroup. Pharmacy prescription fill records were used to identify the timing and degree of MMF dose changes. Coded diagnosis data allowed the identification of the date of first posttransplant GI diagnosis. Identification of MMF dose reductions or discontinuations following GI diagnosis permitted estimates of the association of these dose changes with subsequent graft survival. The association of MMF dose reduction and discontinuation was assessed simultaneously with changes of other immunosuppressants following GI complications.

PATIENTS AND METHODS

We included adult (age ≥18 years) renal allograft recipients transplanted between 1995 and 2001 and reported to the OPTN Registry and to the USRDS who met all of the following criteria: 1) received a first single organ kidney transplant; 2) had a diagnosis of a GI complication recorded within Medicare part A or B billing records after transplantation; 3) had prescription records indicating Medicare payment for MMF at the time of the first GI diagnosis. This ensured that Medicare was the primary payer for the patient's medical care at the time of GI diagnosis and selected a uniform set of patients for study. To identify transplant recipients with posttransplant GI diagnoses or procedures, we required that International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for any of the following appeared in Medicare billing records of the USRDS: abdominal pain (ICD9-CM 789.xx), anorexia (783.xx), inflammation, functional disorder, ulcer, hemorrhage, and/or perforation (including duodenum (532.xx), gastrojejunal (534.xx), intestine (562.xx, 569.8×, 564.1×) ischemic, peptic (533.xx), colon (556.xx), appendix (540.xx, 541.xx), stomach (531.xx, 536.xx), gastritis (535.xx), and other gastroduodenal disorders (537.xx, 578.xx, 558.xx)), nausea, vomiting, and other GI symptoms (787.xx), diarrhea (787.91), constipation (564.0×), and abdominal pain (789.xx).

MMF Dose Reductions and Discontinuations

MMF doses were drawn from Medicare claims data which contain pill composition, size and count for immunosuppression prescriptions when medications are filled in outpatient pharmacies. We calculated daily doses assuming 30-day prescription fills. A 30-day interval is the standard fill duration and the maximum covered by Medicare. Prescribed daily dose was calculated by multiplying the pill or capsule strength by the number of pills in the fill and dividing by 30 days. We assumed no dose change occurred until a prescription record was observed indicating a new dose. This record was used to calculate a new daily dose, and to indicate the first date of known dose change. The same methods were used to identify immunosuppression regimen used at the time of GI diagnosis including cyclosporine, tacrolimus, azathioprine, sirolimus and prednisone, and to identify doses and dose changes of these drugs.

The actual date of dose change could occur between prescriptions. Thus we assessed alternatives to dating dose changes to the day of the prescription indicating a change including: 1) assigning a prescribed dose change to the day of the prescription fill just prior to the prescribed dose change; and 2) averaging a prescribed dose change between prescriptions (e.g., if the MMF dose record after the new prescription was 1.5 g/day and before it was 2 g/day, a dose of 1.75 g/day was assumed between prescriptions).

MMF dose reduction or discontinuation were modeled as time-varying variables, as at any point in time a patient could be: 1) continued on initial MMF dose at time of GI complications; 2) dose-reduced to <50% of initial MMF dose; 3) dose-reduced to ≥50% of the initial MMF dose; or 4) discontinued from MMF, defined as at least one episode of MMF dose recorded as zero lasting at least 31 days. A given patient could use different doses of MMF at different points in time. A cumulative analysis until graft failure or last follow-up for each patient post-GI complication was performed to assess the percentage of patients who experienced: 1) no discontinuation or dose reduction, 2) discontinued but not dose reduced, 3) dose reduction with or without discontinuation.

Statistical Analysis

The study interval began with first GI diagnosis and ended at graft failure, censoring at 3 years posttransplant, last follow-up, 30 days following the last immunosuppressant prescription record, or December 31, 2001. The primary outcome was graft failure as identified by graft loss, return to dialysis or death. We used multivariate Cox's hazards analysis to obtain estimates of the risk of graft loss (hazard ratio, HR; 95% confidence interval, CI) associated with MMF dose reduction or discontinuation, adjusted for important covariates and for the propensity to receive specific immunosuppressive prescriptions at the time of GI complications.

We considered the following covariates as predictors in the model of graft loss: year of transplant, donor source (living versus deceased), donor and recipient demographics (age, race, ethnicity, gender, and obesity), cause of end-stage renal disease, number of HLA mismatches, number of HLA DR mismatches, donor and recipient cytomegalovirus (CMV) status, recipient hepatitis C seropositivity, GI diagnosis in hospital, more severe GI diagnoses (any GI hemorrhage, perforation, vomiting blood or fecal matter), diagnosis of posttransplant comorbidities (diabetes mellitus, malignancy, CMV disease), MMF withdrawal, MMF reduction >50%, MMF reduction <50%, conversion from MMF to azathioprine, cyclosporine dose reduction or discontinuation, tacrolimus dose reduction or discontinuation, prednisone dose reduction or discontinuation, calcineurin inhibitor prescription at the time of GI diagnosis, and prednisone prescription at the time of GI diagnosis. The validity of the proportional hazards assumption was tested with time interactions and violations of the proportionality assumption were corrected by retaining significant time interactions in the final model. We used a step-wise approach to limit final models to include

only those covariates with *P* values <0.15, an inclusion level for variable selection that protects against negative confounding.

A propensity score is the estimated probability of being assigned to one treatment over another given the observed subject's characteristics. Propensity score adjustments are effective methods for condensing the information from many covariates into a single variable (*13–15*). It has been demonstrated that observed characteristics are balanced between treatment groups conditional on each level of the propensity score (*13–15*). We estimated four stepwise logistic regression models to calculate the propensities of: 1) tacrolimus prescription at the time of GI diagnosis; 2) any reduction (<50%) of initial MMF dose; 3) any reduction (≥50%) of the initial MMF dose; or 4) any discontinuation of MMF. We used each propensity score to partition the data into two groups of equal size, those with low and high estimated propensities. These groups were then combined into 16 groups (all possible combinations of the pair wise partitions) and used to stratify the Cox regression for graft survival. This generated a statistically randomized analysis with respect to tacrolimus prescription and degree of MMF dose reduction.

We considered a *P* value <0.05 to be statistically significant. SAS for windows version 9 was used for all statistical analyses.

RESULTS

During the study period, 19,128 renal transplant recipients age 18 or older, at transplant had a GI diagnosis recorded at some time following transplant. Of these, 9,337 received a first single organ kidney transplant, used Medicare as the payer for their immunosuppression at some time following transplant, and had their first posttransplant GI complication diagnosed while their graft was functioning. Of these, 6,425 were prescribed one or more immunosuppressants and 3,675 (57.2%) had an MMF prescription at the time of their first GI diagnosis, the index diagnosis. These 3,675 patients with a Medicare paid and recorded MMF prescription and functioning graft at the time of their first diagnosed posttransplant GI complication were included in the study, as the primary goal was to assess affects associated with MMF prescription reductions following posttransplant GI diagnosis in patients who had experienced a GI complication.

Sixty-nine percent had a GI diagnosis in the first year and the median time to GI diagnosis after transplantation was 166 days. The median prescribed MMF dose at the time of GI diagnosis was 2000 mg/day. More than 50% of recipients had dose reductions or discontinuations following GI complications during the study (Table 1). The average number of days of dose reduction postGI complication was 85 days and the number of days of discontinuation was 36 days. Baseline characteristics of the sample, stratified according to maximum MMF dose reduction during the study period are shown in Table 1.

Prescribed MMF dose reductions were associated with increased risk of graft failure compared to no prescribed dose reduction (Table 2). The observed rate of graft failure in the reference group for multi-variate analysis (i.e. patients never experiencing an observed MMF dose change following GI complication diagnosis) was 4.1% per year. Intervals of MMF dose reduction <50% were associated with an adjusted HR of graft loss of 1.64 (CI 0.74–3.62; $P=0.22$), reflecting an annual graft loss rate of 6.8%. Intervals of MMF dose reduction ≥50% were associated with approximately 2-fold increased risk of graft loss (HR 2.36, CI 1.23–4.53; $P=0.010$), reflecting an annual graft loss rate of 9.8% per year. Finally, the risk of graft loss increased approximately threefold (HR 2.7; CI 1.59–4.64; $P=0.0002$) during intervals of MMF discontinuation, indicating an annual graft loss rate of 11.3%. Modeling alternatives for the estimation of dose change dates did not alter the results.

The impact of concurrent immunosuppressant medications and dose changes were also examined. Patients not treated with a calcineurin inhibitor at the time of GI diagnosis

TABLE 1. Baseline characteristics and significant differences by maximal degree of mycophenolate mofetil (MMF) dose reduction during the study

Characteristic	Full sample	MMF maintained	MMF reduced <50%	MMF reduced >50%	MMF withdrawn	*P* value
N (%)	3,675 (100%)	1,681 (45.7%)	299 (8.1%)	455 (12.40%)	1,240 (33.70%)	
Recipient						
Age >60 years	776 (21.1%)	341 (43.9%)	52 (6.7%)	117 (15.1%)	266 (34.3%)	0.029
Pretransplant blood transfusion	1,241 (33.8%)	584 (47.1%)	79 (6.4%)	156 (12.6%)	422 (34.0%)	0.046
Preemptive transplant	665 (18.1%)	338 (50.8%)	60 (9.0%)	78 (11.7%)	189 (28.4%)	0.006
African American	1,129 (30.7%)	468 (41.5%)	105 (9.3%)	146 (12.9%)	410 (36.3%)	0.005
Hispanic	528 (14.4%)	229 (43.4%)	32 (6.1%)	54 (10.3%)	213 (40.3%)	0.003
Donor						
Age >55 years	551 (15.0%)	233 (42.3%)	54 (9.8%)	86 (15.6%)	178 (32.3%)	
GI class during study						
In-hospital diagnosis	1,167 (31.8%)	420 (36.0%)	109 (9.3%)	179 (39.3%)	459 (39.3%)	<0.0001
Mild diagnoses	3,347 (91.1%)	1,514 (45.2%)	270 (8.1%)	425 (12.7%)	1,138 (34.0%)	0.106
More severe diagnoses	1,213 (33.0%)	493 (40.6%)	109 (9.0%)	158 (13.0%)	453 (37.4%)	0.021
Treatment						
Tacrolimus at GI diagnosis	1,296 (35.3%)	565 (43.6%)	87 (6.7%)	173 (13.4%)	471 (36.3%)	0.006

TABLE 2. Multivariate Cox graft survival analysis

Variable	Hazard ratio	Confidence limits		*P* value>chi square
		Lower	Upper	
MMF withdrawn[a]	2.722	1.598	4.638	0.0002
MMF reduced by 50% or more from the time of GI diagnosis[a]	2.364	1.231	4.538	0.010
MMF reduced by less than 50% from the time of GI diagnosis[a]	1.637	0.739	3.625	0.225
Tacrolimus prescribed at the time of index GI diagnosis	4.717	2.305	9.654	<0.0001
Neither tacrolimus or CSA prescribed at time of GI diagnosis	3.319	1.041	10.580	0.043
CSA discontinued	3.056	1.298	7.196	0.011
Dose of CSA decreased	2.789	1.243	6.255	0.013
Dose of prednisone decreased	0.638	0.377	1.082	0.096
More severe GI diagnoses	1.449	0.930	2.256	0.101
GI diagnosis in hospital	2.272	1.394	3.703	0.001
Recipient hepatitis C positive	0.348	0.084	1.432	0.144
Recipient CMV seropositive	1.624	0.996	2.646	0.052
Diabetes type II cause of ESRD	0.459	0.198	1.064	0.070
Unknown cause of ESRD with a time interaction[a,b]	2.225	1.404	3.527	0.001
Diagnosis of malignancy[a]	3.112	1.409	6.875	0.005
Donor HLA mismatch	1.366	0.999	1.869	0.051
Donor with CVA	1.901	1.234	2.928	0.004
Recipient obese	1.049	1.013	1.087	0.007
Recipient Hispanic	0.267	0.095	0.751	0.012
Transplant year 1996	1.725	1.040	2.862	0.035
Transplant year 1999	0.607	0.320	1.150	0.126

[a] Time varying covariate indicating periods when the indicated dose or condition was present.
[b] The graft survival relationship associated with unknown cause of ESRD was found not to be constant over time relative to other causes of ESRD. This violation of the proportionality assumption was accounted for by including the time varying time interaction between the duration from the GI diagnosis and unknown cause of ESRD. This correction had a minimal effect on the remaining estimates.

had an increased risk of graft failure (HR 3.32; CI 1.04–10.58; $p=0.043$) compared to cyclosporine-treated patients. Among patients treated with a calcineurin inhibitor, treatment with tacrolimus at the time of GI diagnosis (1,296, 35.3%) was also associated with increased risk of graft failure (HR 4.72; CI 2.31–9.65; $P<0.0001$) compared to cyclosporine. After GI diagnosis, cyclosporine dose reduction (HR 2.79, CI 1.24–6.26; $P=0.013$) and cyclosporine withdrawal (HR 3.06, CI 1.30–7.30; $P=0.011$) were significantly associated with increased risk of graft loss, whereas tacrolimus dose changes were not.

DISCUSSION

With newer immunosuppressive agents outcomes are greatly improved over previous eras, renal allograft survival now routinely exceeds 90% at 1 year posttransplant (*16*, *17*). However, these agents have known side effects and safety concerns leading to a high rate of treatment interruptions or withdrawal. Such adverse effects include GI complications, especially diarrhea, which are common in the first year after renal transplantation (*18*). The reported incidence of GI complications is variable according to immunosuppressive regimen and may exceed 50% in patients who receive a combination of tacrolimus-MMF (*19*), the most commonly used regimen in the United States (*4*). These complications often prompt MMF dose reductions, interruptions or discontinuation, which in turn may lead to subtherapeutic dosing and suboptimal clinical outcomes (*9*). In a single center retrospective study of 213 transplant recipients, MMF dose reduction below 2000 mg/day after kidney transplantation was associated with an increased risk of acute rejection (*9*).

In our previous study, we demonstrated an association of both GI complications and MMF withdrawal that occurred in the first posttransplant year with significantly reduced subsequent graft survival (*10*). In that study, it was not possible to determine whether MMF withdrawal occurred before or after GI complications, and indications or measures of dose changes were unavailable. This current study was designed specifically to overcome these two important limitations of our previous work. Here we ascertained the timing of GI events in relation to MMF dose modifications, examined the impact of MMF dose reduction, and did not limit our study to MMF discontinuation. We were able to study a larger cohorts of patients (n=3,675), as opposed to 1,934 in the previous study. We used a new dosing data which included information on the timing of dose changes. An algorithm estimating doses and dose changes from Medicare pharmacy billing data was developed, allowing the estimation of time-varying covariate incidence models, more appropriately describing the hypothesized causality between an MMF dose reduction and subsequent graft loss.

In this study, we found that more than half of renal transplant recipients who developed posttransplant GI side effects underwent MMF dose reduction or discontinuation. The majority of GI complications occurred in the first year

after transplant, although late diagnoses were noted throughout the observation period. MMF dose changes after GI complications were associated with a marked increase in the risk of subsequent graft loss. The increased risk was observed even after adjustment for the presence and changes of other immunosuppressants concurrent with and following diagnosed GI complications. We observed a gradient effect in that MMF discontinuation was associated with the highest risk estimate of subsequent graft loss. There also was a trend towards increased risk of graft loss in those managed with MMF dose reductions <50%; the lack of statistical significance was likely due to the small number of participants in this group.

In an attempt to control for treatment bias and other unaccounted confounders, we used propensity score methods to balance patient characteristics associated with MMF dose reductions and tacrolimus prescriptions after GI complications. Observing similar risks of graft loss with and without propensity score stratification suggest that our multivariate analysis model effectively controlled for confounding factors (*15–17*). Although such methods do not provide perfect corrections for bias, they lend credibility to the results.

In addition to MMF dose changes, other factors were also associated with poor graft outcome after GI complications (Table 2). We found that the risk of graft loss was increased by fourfold if tacrolimus was prescribed compared to cyclosporine at the time of GI complications. It may be that this finding is due to more severe or longer lasting GI complications in patients treated with tacrolimus. However, we can neither prove nor disprove this conjecture, as the methodologies to determine either severity or duration with claims are not well developed. It is important to note that factors such as tacrolimus trough levels and the rational behind the choice of tacrolimus and tacrolimus dose adjustment strategies were not measurable in our data. We also confirmed previous findings that recipients who received neither Tac or CSA had a higher risk of graft loss (*20*). We also found that a reduction in CsA dose but not tacrolimus dose at the time of GI complications was associated with an increased risk of graft loss. It is known that persistent diarrhea in MMF-treated renal transplant recipients is associated with increased trough levels of tacrolimus; however, the level of CSA remained stable (*21*). Therefore, a reduction in CsA dose but not Tacrolimus may result in inadequate immunosuppression. Based on this finding, one may hypothesize that a reduction in tacrolimus dose may be a feasible alternative to a dose reduction in MMF after GI complications. However, we observed a small but significant pattern of greater MMF dose reduction with tacrolimus. Ultimately, a clinical trial would be necessary to evaluate hypotheses about optimal immunosuppressive adjustment following GI diagnosis. The finding presented here can suggest the design of such studies, but due to limitations such as lack of recorded drug levels, cannot prove best practice.

Our study has several limitations. We analyzed effects associated with the relative dose reduction compared to initial dose. It is possible that the impact of the same percentage dose reduction may differentially impact on outcome depending on the starting dose. For example, the consequences of a 50% reduction of MMF dose from 3000 mg per day to 1500 mg per day may be different than the impact of a 50% reduction of MMF dose from 1000 mg to 500 mg per day. The cumulative time of dose reduction or discontinuation may also influence outcomes. While we did not observe these relationships in our data, we can not rule them out with this study. Our algorithm for determining dosing from prescription records is prone to underestimate the occurrence of dose changes, as a dose reduction may have occurred before the new fill was captured. Another limitation includes those intrinsic to the use of claims data, including patient and data miscoding, missing data elements, and misclassification. However, a recent study of pharmaceutical claims data suggests pharmacy claims to be among the most accurate data in medicine with coding error rates in less than 1% of cases (*22*). Another concern related to use of billing claims is that patients with more medical complications are more likely to have complications coded, such that the presence of any set or sets of codes may simply indicate a sicker patient with expectations of worse outcomes. We attempted in our previous paper to account for this by including coded CMV infection, hyperlipidemia, posttransplant diabetes and the frequency of hospitalization in the analysis. It was interesting and supported the main hypothesis that the combination of a GI complication and MMF discontinuation outweighed any of theses factors when predicting graft failure. In this analysis we included a richer list of complications and comorbid conditions. Further, we attempted to remove bias related to the frequency of hospitalizations from the analysis, a variable strongly impacted by the complications and comorbid conditions. In an attempt to control for treatment bias and other unaccounted confounders, we used propensity score methods to balance patient characteristics associated with MMF dose reductions and tacrolimus prescriptions after GI complications. The fact that the hazard ratio of graft loss were similar with and without propensity score included as covariates suggest that our multivariate analysis model were able to control for confounding factors. Although such methods do not provide perfect corrections for these biases, they lend credibility to the results. Finally, an important limitation of the clinical data elements is the coarse follow-up. Claims data following transplant is recorded in near continuous time in units of days, whereas clinical follow-up is on units of 6 months to 1 year. This prevented us for incorporating potentially important measured on course intervals into the analysis, such as serum creatinine.

To our knowledge, this is the first reported study that examines the association of varying doses of immunosuppressive medication and renal allograft outcomes using Medicare claims data. Most registry analyses use the initial immunosuppressive regimens indicated in UNOS recipient registration form in an intention-to-treat approach and do not adjust for posttransplant events known to influence outcomes (*20*, *23*, *24*). Our findings suggest that medical claims data may be used to examine these changes which may impact allograft survival.

In conclusion, MMF dose reduction and withdrawal following the diagnosis of a GI complication are associated with considerably higher risk of subsequent graft failure in renal transplant recipients, even when use and changes of other immunosuppressants are taken into account. Although this analysis cannot establish a causal relationship between MMF dose changes and graft failure, it demonstrated a temporal relationship and identified considerable risk among pa-

tients with MMF dose reductions and discontinuations following GI complications. These patients should be managed with great care to minimize the risk of graft failure. New strategies to prevent and treat GI complications are needed.

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