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A Retrospective Analysis of Immunosuppression Compliance, Dose Reduction and Discontinuation in Kidney Transplant Recipients

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We describe factors associated with poor compliance and dose reductions and examine the relative impact of compliance, dose reduction and discontinuation on graft outcome.

Medicare claims for MMF in 7062 deceased donor renal recipients with at least 1 year of graft function were used to calculate compliance and dose reductions. Compliance was modeled using medication possession ratio to define quartiles for poor, low, medium and high compliance. The relative impact of compliance, dose reduction and discontinuation on graft outcome was assessed with Cox proportional hazards.

Pediatric (Age 0–18, Odds ratio = 1.71, 95% CI 1.11–2.63, $p = 0.014$) and adolescent recipients (19–24, 1.57, 1.23–2.00, $p < 0.001$) were more likely poorly compliant compared to adults age 25–44. Poor compliance was also associated with physical limitations, hypertension, delayed graft function, rejection, infection and GI conditions. Poor (1.43, 1.11–1.84, $p = 0.005$) and low (1.46, 1.13–1.88, $p = 0.004$) compliance was associated with an increased hazard of graft loss as was >50% dose reduction (1.69, 1.15–2.50, $p = 0.008$) and discontinuation (8.34, 6.85–10.2, $p < 0.001$).

Medication possession ratios lower than the 3-year mean were associated with an increased risk of graft loss. These results may indicate that interventions to improve compliance among kidney transplant recipients should strive for high rather than discourage low compliance.

Key words: Compliance, diabetes, graft survival, infections, kidney transplantation, medication possession ratio, mycophenolate mofetil, rejection

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Introduction

Recent literature reviews combining the results from over 300 articles estimated the prevalence of poor immunosuppression compliance among kidney transplant recipients to be between 22 and 28% (1,2). Twenty percent of late acute rejections and 16% of graft losses were attributed in part to poor compliance (2). Other literature reviews have suggested that the impact of compliance on graft loss may be even greater in children (3–5).

Compliance has been measured in many ways. The measurement of immunosuppressant drug levels is performed routinely in kidney transplant recipients and can be used to directly measure of drug compliance. The drawback is that these assays are dependent on the half-life of the metabolite and provide information only on days when the patient visits the clinic (6). Electronic monitoring has become the gold standard for measuring compliance in prospective studies and clinical trials (7–9) but monitoring the opening of pill dispensers is intrusive and not commonly done at most transplant centers. The majority of studies have used surveys to obtain a patient self-report of compliance (1,2,10). Unfortunately, this methodology may overestimate compliance rates because most patients are hesitant to reveal their pill taking behavior (2,11). Previous studies on immunosuppression compliance have been limited to clinical trials or single centers studies and the number of cases ranged from less than 100 to approximately 1500 (2). Here we present an unobtrusive method for assessing compliance using existing data contributed by all transplant centers in the United States.

A recent review outlines three approaches for examining compliance using insurance claims electronically submitted to obtain reimbursement for dispensed medications: fixed time point, gaps in prescription filling and medication possession ratio (MPR) (12). Different results that might occur using the 3 approaches are illustrated in Figure 1. Using a fixed 1-year time point, a patient would be noncompliant if there was no prescription filled between days 330 and 400. Case 1 would be considered noncompliant even

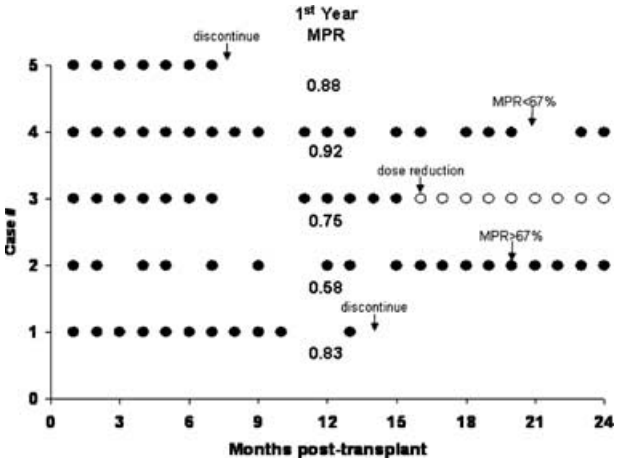

Figure 1: Five example cases indicating months posttransplant with filled prescriptions with a filled circle and dose reduction with an empty circle. The MPR is calculated at month 12, and dates of discontinuation and dose reduction are indicated.

though there was consistent prescription filling prior to the 12-month time point. Case 2, on the other hand, would be considered compliant even though previous prescriptions were sporadically filled. If compliance were instead defined in terms of a 3-month gap, case 2 would be considered noncompliant. MPR is defined as the number of days medication is supplied over a 1-year time interval (13). The first year MPR for five case examples is noted above the 12-month time point in Figure 1. Case 5 illustrates how discontinuation of prescription filling might affect the MPR calculation. If the denominator is limited to 1 month after the last prescription fill, the MPR is 88%; without this adjustment, the MPR would be 58%.

Unfortunately, detailed information about immunosuppressive medications is not collected on Organ Procurement Transplant Network (OPTN) survey forms. Pill composition, size and count for prescriptions filled by outpatient pharmacies are indicated on Medicare Part-B records. A 30-day interval is the standard fill duration and also the maximum covered by Medicare. The diagnosis codes associated with emergency department incidents, hospitalizations and outpatient visits is also included in administrative claims and is useful for outcomes research. These diagnosis codes have been used to show that posttransplant complications including diabetes (14,15), gastrointestinal (GI) conditions (16,17), myocardial infarction (18) and congestive heart failure (19) are associated with poor graft outcome.

The importance of strict compliance to treatment regimens for optimizing graft outcome has been well documented (1,2,20). Calcineurin inhibitors have a narrow therapeutic window, and therefore warrant frequent drug monitoring and adjustment (21). As a result, therapeutic drug monitoring may help to identify noncompliant patients. In contrast, mycophenolate mofetil (MMF) is usually given at fixed doses since therapeutic drug monitoring was deemed unnecessary due to its favorable safety profile (22). Therefore, MMF dose changes are usually in response to side effects such as gastrointestinal intolerability. In previous studies, we used Medicare billing records to show that discontinuation or changes in prescriptions to reduce MMF doses, were associated with poor graft survival when associated with GI complications (16,17). The inclusion criterion is expanded beyond patients with GI complications in the current study. Furthermore, we consider the possibility that patients reduced their MMF dosages with poor compliance to their dispensed prescription. The first aim of the study is to examine patient characteristics and transplant factors associated with patient-directed (poor compliance) and physician-directed (prescription changes) dose reductions. The second aim is to examine whether three competing factors: poor compliance, dose reductions and discontinuation are independently associated with increased risk of graft loss.

Methods

The study population was drawn from kidney recipients transplanted between 1995 and 2002 and included in the analytic files obtained from the United States Renal Data System (USRDS). We excluded patients with inpatient transplant charges less than $15 000 to avoid patients with dual insurance coverage since those patients might have incomplete Medicare prescription records (16). Patients receiving multi-organ transplants and those with a prior kidney transplant were excluded because of differing risk profiles. In order to study compliance to MMF regimens, we included only those patients with at least one Medicare claim for MMF during the first posttransplant year. To simplify the analysis, we excluded patients filling prescriptions for azathioprine or rapamycin. Patients were followed until either the last date of Medicare eligibility, graft failure, death or 3-year posttransplant.

Outcomes and measurements

Compliance was defined in terms of MMF MPR assuming each prescription was for 30 days, and multiplying the number of prescription fills during the previous 360 days by 30 and then dividing the product by 360. A total of 6825 patients filled prescriptions at month 12 and 2996 in month 36 posttransplant. During this period, the mean MPR was 81%. We modeled compliance as a time-varying variable by splitting patients into quartiles based on overall 1–3 year MPR values: poor compliance when MPR fell below 69%, low for MPR between 69 and 81%, medium for MPR 81 and 98% and high when the MPR exceeded 98%. Case 2 would be considered poorly compliant at month 12, but would move to the 'low' group at month 20. Case 4 on the other hand would move into the 'poor' group at month 21. Dose reductions and discontinuation dates were defined as previously described (16,17). MMF doses were calculated assuming 30-day prescription fills, multiplying the pill or capsule strength by the number of pills in the prescription and dividing the product by 30 to determine milligrams of MMF per day. To be consistent with previous studies, and to distinguish dose reductions associated with intolerability from those associated with tapering, the mode first-year dose was considered baseline. Dose reductions were defined as a percentage decrease from the first-year dose on subsequent prescriptions. Case 3 from Figure 1 shows how a dose

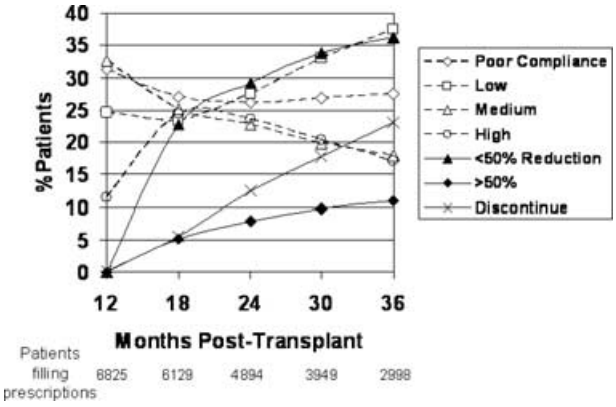

Figure 2: The percentage of patients included in the compliance, dose reduction and discontinuation cohorts from months 12–36. The number of patients with filled prescriptions are indicated below the graph.

reduction could occur in a compliant patient. We defined the discontinuation date 30 days after the last prescription fill.

The percentages of patients in the compliance, dose reduction and discontinuation cohorts at time points from months 12 to 36 are illustrated in Figure 2. The fraction in the medium and high compliance cohorts decreased from 33% at month 12 to 17% at month 36. The percentage of patients with >50% dose reduction increased from 0% at 1 year to 11% at month 36. Twenty-three percent of patients discontinued MMF by month 36.

Rejection was defined based on the OPTN discharge, 6-month or first-year follow-up responses indicating a rejection episode, steroid or antibody rejection therapy. Diabetic (15) and GI complications (16,17) were defined as previously described using International Classification of Disease 9th edition clinical modification (ICD-9-CM) diagnosis codes. Infections were defined with ICD-9-CM codes 001–139 and malignancies with the range of codes spanning 140–165, 170–176 and 179–208.

Parameters included in the multivariate models included donor and recipient age, gender, race, cytomegalovirus serology, recipient comorbid conditions, physical limitations (as defined by New York Heart Association performance of daily activities), panel reactive antibody, level of human leukocyte antigen match, cold and warm ischemia time, delayed graft function, calcineurin inhibitor and first-year complications including rejection, infection, diabetes, gastrointestinal disturbances and malignancies. Pretransplant comorbidities were defined as a composite cause of end-stage renal disease and other OPTN survey variables, which indicated the presence of cardiovascular disease, diabetes and hypertension. This approach is similar to that taken by others to define comorbidities in other fields of medicine (23–26).

Statistical analysis

Covariate associations between poor compliance and >50% dose reductions were examined at the time point where a year of data could be evaluated. Covariates associated with MPR were evaluated at the 1-year time point. Since dose reductions could only occur starting in month 13, covariates associated with dose reductions were evaluated at month 24 posttransplant. Adjusted clinical correlates of poor compliance and dose reductions were identified using multivariate logistic regression.

Relative hazards of graft failure were estimated using Cox Proportional Hazards where death was considered both as failure and censored when graft function was indicated. Compliance, dose reductions and discontinuation were defined as competing time-varying covariates. Periods of high compliance were the reference group for poor, low and medium compliance. No dose reduction was the reference for <50 and >50% dose reductions. No discontinuation was the reference for discontinuation. Sensitivity analyses were performed to test the impact of competing risks such as complications and alternative methods for defining discontinuation in the MPR calculation. 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 stepwise approach to limit final models to include only covariate factors with p-values < 0.05. Windows Version 9 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results

Demographics for the overall study population are shown in Table 1. Patients included in the study represented 7.8% of the 90234 primary kidneys transplanted from 1995 to 2002 and reported to the OPTN (as of June 23, 2007, www.unos.org). The percentage of overall recipients included in the study was 4.5% in years 1995–1997, 12.7% from 1998 to 2000 and 5.2% in 2001–2002. The percentage of recipients' age 0–18 years (1.3 vs. 6.5%) and those with living donors (13.8 vs. 38.2%) were lower than reports to the OPTN.

At month 12, 33% of patients were in the poor compliance cohort (Table 1). The percentage with poor compliance decreased with increasing recipient age, was lower in patients given cyclosporine and higher in patients with physical limitations and complications including delayed graft function, rejection, infection and GI conditions. At month 24, 7.7% of patients experienced a dose reduction greater than 50%. Non-white recipients, those transplanted in the earlier years of the study, with pretransplant hypertension, delayed graft function and first-year rejections more often received a dose reduction.

Multivariate logistic regression indicates recipients less than 25 years of age, those receiving tacrolimus, with physical limitations, delayed graft function, rejection, GI conditions and infections had increased odds of being poorly compliant (Table 2). Non-white recipients and those without pretransplant hypertension and those with first-year infections or malignancies had increased odds of dose reductions.

Results from time-varying Cox proportional Hazards models are shown in Table 3. Patients in the three lower compliance quartiles (poor, low and medium) had increased risk of graft failure compared to those in the top quartile. Dose reductions greater than 50% were also associated with an increased hazard of graft loss. Discontinuation was associated with an 8-fold increase in the hazard of graft loss. Other factors associated with graft loss included younger

Table 1: Demographics for the overall study population, and the percentage of poorly compliant and dose-reduced patients stratified by various covariates

	Total population		Poor compliance at month 12		50% dose reduction at month 24	
	N	%[†]	N	%[‡]	N	%[‡]
Overall	7046		2343	33.3	544	7.7
Recipient age				*		
0–18	91	1.3	40	44.0	8	8.8
19–24	305	4.3	126	41.3	24	7.9
25–60	5098	72.4	1687	33.1	406	8.0
Over 60	1552	22.0	490	31.6	106	6.8
Recipient ethnicity						*
Caucasian	4544	64.5	1501	33.0	320	7.0
African American	2066	29.3	704	34.1	180	8.7
Other	436	6.2	138	31.7	44	10.1
Dialysis duration				+		
0–24 months	2211	31.4	691	31.3	149	6.7
24–60 months	3315	47.1	1107	33.4	260	7.8
Over 60 months	1520	21.6	545	35.9	135	8.9
Hypertension	6023	85.5	1982	32.9	446	7.4[+]
Cardiovascular disease	1414	20.1	458	32.4	114	8.1
Diabetes	2387	33.9	824	34.5	177	7.4
Physical limitations	481	6.8	193	40.1[#]	33	6.9
Recipient smokes	255	3.6	82	32.2	19	7.5
Donor age				+		
0–19	869	12.3	304	35.0	63	7.3
19–55	4444	63.1	1429	32.2	339	7.6
Over 55	765	10.9	257	33.6	72	9.4
Living donor	975	13.8	315	32.3[+]	78	8.0
Cold ischemia time ≤24	4606	65.4	1522	33.0	350	7.6
25–36 h	1254	17.8	441	35.2	93	7.4
Over 36 h	211	3.0	65	30.8	23	10.9
Year of tx						[#]
1995–1997	1348	19.1	463	34.4	123	9.1
1998–2000	4361	61.9	1453	33.3	357	8.2
2001–2002	1337	19.0	427	31.9	64	4.8
Delayed graft function	1987	28.2	730	36.7[#]	167	8.4[#]
Calcineurin inhibitor				#		
Tacrolimus	2554	36.3	955	37.4	213	8.3
Cyclosporine	4492	63.8	1388	30.9	331	7.4
First-year complications						
Rejection	968	13.7	364	37.6[#]	83	8.6
Diabetes	824	11.7	274	33.3	69	8.4
GI condition	3536	50.2	1268	35.9[#]	292	8.3
Infection	1486	21.1	577	38.8[#]	142	9.6*
Malignancy	401	5.7	138	34.4	38	9.5

[†]The percentage of the population in the indicated cohort.
[‡]The percentage of the cohort poorly compliant or having >50% dose reduction.
Significance by chi-square for the covariate are indicated by [#]$p < 0.001$, *$p < 0.01$, [+]$p < 0.05$.

recipient age, African American ethnicity, smoking, pretransplant hypertension, cardiovascular disease and posttransplant rejection, GI condition and infection. When censoring death with a functioning graft, poor and low compliance cohorts had increased hazard of graft loss but not dose reduction.

Models constructed to test the robustness of these results are summarized in Table 4. As expected, when first year complications were eliminated as competing risks, the hazards associated with poor compliance, dose reductions and discontinuation all increased. Removing discontinuation as a covariate increased the hazards due to poor compliance, but not the hazard due to dose reduction. Extending the date for calculating MPR from 30 to 90 days after the last fill increased the hazard of poor compliance. Removing discontinuation as a covariate and calculating MPR without regard to the discontinuation date resulted in stepwise increases in the hazard of graft loss associated with poor compliance. These results indicate the risk of graft loss was greatest during periods of discontinuation. Nonetheless, when discontinuation was included in the model as a competing risk, MPR values less than the mean as well as dose reductions after the first year were associated with an increased hazard of graft loss (Table 2). We also considered the possibility that poor initial compliance rates may be due to patients being discharged after the initial hospitalization with medication or that extended gaps may be due to dual prescription coverage. These possibilities were not supported since delaying the start of the MPR calculation to 60 days after the transplant increased the poor compliance hazard as did removing patients with gaps longer than 45 days.

Discussion

MMF has been shown to be an effective adjunct to calcineurin inhibitor (CNI) regimens for preventing acute (27) and chronic rejection (28,29) of renal allografts, and has become the standard adjunct immunosuppressant at most transplant centers in the United States (30). Despite its efficacy, use of MMF is associated with a high incidence of GI, hematologic and metabolic complications (6,27,31). We previously reported an increased risk of graft failure for kidney transplant recipients with GI complications whose MMF dose was reduced or discontinued (16,17). In the current study, we provide evidence suggesting that two types of dose reductions, (i) halving the number of pills dispensed in a prescription and (ii) detectable increases in the time gap between prescription refills, were both associated with poor graft outcome.

We observed increased risk of graft loss with decreasing rates of compliance. Patients in the lower MPR quartiles defined as poor, low and medium compliance had a 43–46% increased risk of graft failure compared to those in the highest quartile. The general consensus from previous studies indicates compliance is a problem for approximately 30% of recipients (1,2). Previous studies have treated compliance as a dichotomous, yes/no covariate. This study indicates compliance should be considered as

Table 2: Adjusted clinical correlates of poor compliance and dose reductions

		Poor compliance at month 12		>50% Dose reduction at month 24	
	Reference group	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Recipient age 0–18	25–44	1.71 (1.11–2.63)	0.014		
19–24		1.57 (1.23–2.00)	<0.001		
African American	Caucasian			1.26 (1.02–1.56)	0.034
Other				1.49 (1.05–2.10)	0.024
Hypertension	No hypertension			0.78 (0.61–0.99)	0.044
Physical limitations	No limitation	1.30 (1.07–1.58)	0.007		
Post TX factors					
Delayed graft function	Immediate function	1.17 (1.05–1.32)	0.006		
Cyclosporine	Tacrolimus	0.77 (0.69–0.86)	<0.001		
Complications during the first year post-tx					
Rejection	No rejection	1.21 (1.05–1.39)	0.011		
GI condition	No GI condition	1.20 (1.08–1.33)	0.001		
Infection	No infection	1.30 (1.15–1.47)	<0.001	1.34 (1.09–1.64)	0.006
Malignancy	No malignancy			1.37 (0.96–1.95)	0.085

OR = odds ratio; CI = confidence interval.

a continuum and that up to 75% of patients may benefit from interventions aimed at improving immunosuppression compliance. The increased hazards after censoring at death with a functioning graft may indicate that poor compliance affects immune regulation rather than the general health of the recipient since a similar effect is seen with patients receiving HLA-matched transplants (32).

Our study design included two refinements to examine the impact of poor compliance on graft outcome. We used a time-varying covariate model, where a patient serves as his or her own control with times at risk for graft loss during periods of good compliance compared to those times when compliance is poor. Secondly, we separated the effect of sporadic prescription filling from discontinuation on our MPR measure by considering the date 30 days after the last prescription fill as the last date compliance was assessed. As illustrated in Figure 1, without this refinement, MPR rates would decrease with time after discontinuation. Sensitivity analyses indicate periods after discontinuation were associated with the greatest hazards of graft loss. Increasing the time after discontinuation for the final MPR calculation increased the hazard, but censoring at the discontinuation date did not change the hazard associated with poor compliance.

The retrospective nature of this study allows us to make descriptive but not explanatory conclusions. We cannot distinguish whether MMF discontinuation contributed to graft loss or whether patients discontinued medication

Table 3: Cox proportional hazards of graft loss and death-censored graft loss associated with level of compliance, dose reduction and discontinuation

		Graft failure		Death censored graft failure	
	Reference	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Poor compliance	High	1.43 (1.11–1.84)	0.005	1.70 (1.22–2.36)	0.002
Low		1.46 (1.13–1.88)	0.004	1.47 (1.04–2.08)	0.030
Medium		1.32 (1.00–1.75)	0.053	1.10 (0.74–1.64)	0.644
<50% Dose reduction	No reduction	0.65 (0.36–1.18)	0.155	0.57 (0.25–1.28)	0.171
>50% Reduction		1.69 (1.15–2.50)	0.008	1.47 (0.88–2.48)	0.142
Discontinuation		8.34 (6.85–10.2)	<0.001	7.39 (5.70–9.57)	<0.001
Recipient age 0–18	25–60	1.97 (1.03–3.77)	0.042	2.22 (1.10–4.46)	0.026
18–24		1.59 (1.09–2.32)	0.016	1.88 (1.25–2.82)	<0.001
Over 60				0.49 (0.33–0.73)	<0.001
African American	White	1.55 (1.27–1.88)	<0.001	2.07 (1.59–2.70)	<0.001
Diabetes	No diabetes			0.69 (0.50–0.96)	0.027
Smokes		1.70 (1.16–2.50)	0.007	2.09 (1.29–3.39)	0.003
Hypertension	No hypertension	1.30 (1.01–1.69)	0.046	1.57 (1.11–2.22)	0.011
Cardiovascular disease	No CVD	1.41 (1.08–1.85)	0.012		
Complications during the first year post-tx					
Rejection	No rejection	1.54 (1.29–1.85)	<0.001	1.70 (1.36–2.14)	<0.001
GI condition	No GI condition	2.53 (1.96–3.27)	<0.001	3.00 (2.08–4.32)	<0.001
Infection	No infection	1.64 (1.38–1.96)	<0.001	1.96 (1.56–2.47)	<0.001

HR = hazard ratio.

Table 4: Sensitivity analysis examining hazards of graft loss associated with poor compliance, dose reductions and discontinuation with alternate models and methods for calculating MPR

	Poor compliance		Greater than 50% dose reduction		MMF discontinuation	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Remove first year complications	1.75 (1.36–2.24)	<0.001	1.66 (1.19–2.31)	0.003	4.80 (3.93–5.85)	<0.001
Remove discontinuation as a covariate	2.14 (1.67–2.74)	<0.001	1.48 (1.14–1.92)	0.003		
Censor at discontinuation date	1.44 (1.00–2.08)	0.048	1.57 (1.06–2.33)	0.005		
Calculate MPR without regard to discontinuation	3.27 (2.48–4.31)	<0.001	1.46 (1.12–1.89)	0.003		
Calculate MPR 60 days after last fill	1.96 (1.48–2.61)	<0.001	1.66 (1.19–2.31)	0.003	4.48 (3.66–5.48)	<0.001
Calculate MPR 90 days after last fill	2.21 (1.65–2.95)	<0.001	1.64 (1.20–2.24)	0.002	3.45 (2.78–4.27)	<0.001
Start MPR calculation at day 60	1.64 (1.27–2.13)	<0.001	1.68 (1.20–2.34)	0.002	4.77 (3.91–5.82)	<0.001
Remove patients with a 45-day gap	1.72 (1.28–2.33)	<0.001	1.71 (1.11–2.65)	0.016	4.05 (3.17–5.17)	<0.001

after graft function deteriorated to the point that resumption of chronic dialysis was imminent. Similarly, we can describe the association between MMF compliance and the increased risk of graft loss but cannot prove causality. Patients who were poorly compliant to MMF may have also been poorly compliant to medications that we did not study. Rejection, GI conditions and infection were associated with increased risk of poor compliance and may be a contributory cause of graft loss. On the other hand, factors associated with poor compliance were consistent with other literature (5). Children and young adults were more likely poorly compliant. These findings indicate MPR may be a suitable method for measuring compliance to immunosuppressive medications. MPR has been used to assess compliance to anti-hyperglycemic, lipid-lowering and anti-hypertensive therapies (13). The advantage over electronic monitoring and self-reporting is that it is a less intrusive and time-consuming measure. This approach enabled us to examine compliance rates in over 7000 kidney transplant recipients using an existing dataset.

Economic studies have been hindered by a lack of suitable endpoints attained with previous methods for assessing compliance (2,11). An economic model estimated a cost of $35 021 per quality adjusted life-year gained in adherent relative to nonadherent patients (33). That estimate was based on a 35% 1-year graft loss rate in 13 patients noncompliant to azathioprine compared to 5% in 107 compliant patients (7). Most other studies have either used rejection as an endpoint or estimated the percentage of graft losses attributable to poor compliance (2,11). Although this study was not designed to examine causes of poor compliance, others have shown the inability to pay for medications reduces compliance rates (2,11,34–36).

Several terms have been used to describe medication-taking behavior. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) consider compliance and persistence to be synonymous and define them as the extent which a patient acts in accordance with the prescribed interval and/or dose of a dosing regime (13). Adherence, on the other hand, is defined as the time from initiation to discontinuation of therapy, therefore, discontinuation used in the context of this study can be compared to nonadherence in other literature.

Certain aspects of the study design limit the generalizability of results. The study cohort represented 8% of primary kidney transplants during the study period. Study subjects had medical coverage provided by Medicare. This may have introduced sampling bias as indicated by the smaller fraction of young and living donor recipients and the smaller fraction of patients in the early years of the study. Compliance rates may differ in patients whose medical coverage is provided by Medicaid or employer health plans. The copay amount for medications purchased through Medicare may be more expensive than copay amounts through employer health plans. If this is the case, the actual MPR may be higher in patients with sporadic eligibility in a different health plan. Our study design introduced sampling bias. We focused our examination on compliance to MMF regimens. We excluded patients with prescriptions for other anti-proliferatives. We did not examine the effect of switching among anti-proliferatives, nor did we examine compliance to CNI regimens. A smaller fraction of patients in the early years of the study received MMF. Our method to define dose reductions in terms of the mode first-year dose made it necessary to assess clinical correlates for compliance and dose reduction at different points in time. We assumed first-year tapering may be associated with adjustments aimed at finding optimal levels of immunosuppression whereas those after the first year were more likely due to intolerability. Censoring bias also limits the generalizability of results. Requiring 1 year of medications eliminated patients who lost their graft during the first year. Since Medicare coverage ends for many recipients 3 years after the transplant, we were only able to study the effect of compliance on graft outcome during the second and third years posttransplant. The impact of poor compliance on graft outcome may be even greater in later periods after transplantation (37). Prescription information was not available for 3 years for many patients transplanted in the later years of the study.

In addition to MPR, another novel outcome research methodology is introduced in this study. In 1987, Charlson

developed a prognostic taxonomy of comorbid conditions (23). This index consisted of 10 broad groups of conditions that were weighed and used to derive a score that accurately predicted the survival of patients with breast cancer. By broadly defining comorbidities, we simplified the multivariate propensity and outcomes models. For instance, if diabetes was the cause of end-stage renal disease (ESRD) or if it was indicated that the patient suffered from diabetes on the recipient registration survey, we considered that patient to be a diabetic. If angina, chronic heart failure, myocardial infarction or cardiovascular disease were indicated on the registration survey, we considered the patient to have a cardiovascular condition.

Many methods for classifying comorbid conditions have been proposed. A recent report compared the Charlson Comorbidity Index to three other indices and found that it was the best at predicting death among kidney transplant recipients reported to the Canadian Organ Replacement Registry (38). Another study devised a comorbidity index that they found correlated with residual renal function and death in patients with ESRD (26). One aspect of comorbidity indices that make them particularly useful for outcomes research is that they have been adapted for use with administrative claims data (24,25).

Administrative claims data probably provides an accurate measure of the use of CNI and adjunctive agents. We found a high concordance between prescriptions for these agents and data reported to the OPTN (39). Administrative claims data is proving to be a useful supplement to survey data collected by the OPTN. Here we demonstrate that compliance rates can be derived from these data. Other data available from administrative claims include costs associated with medical care (40) and posttransplant complications not collected on the OPTN survey forms (15,16,18,19). Recently, we performed a data-driven analysis to examine the incidence and conditions associated with hospitalizations after transplantation and found a large percentage were due to infections (41).

Study of Medicare claims indicates that kidney transplant recipients who were poorly compliant to their MMF regimen have increased risk of graft loss. Compliance appeared to be a continuum with increased risk of graft loss with succeeding quartiles of patients when compared to those most diligently filling prescriptions. These results indicate that compliance should be stressed not only for patients thought to be at risk for poor compliance, but also for those with less than optimal compliance.

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