Predictive Patterns of Early Medication Adherence in Renal Transplantation

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Background. Patients' adherence with posttransplant immunosuppression is known to affect renal transplant outcomes.
Methods. Prospectively, individual medication adherence patterns in 195 kidney transplant recipients were quantified with electronic medication monitors. Monitored drugs were mycophenolate mofetil, sirolimus, or azathioprine. Monitoring began at hospital discharge and continued an average of 15±8 months. Patient follow-up for clinical outcomes averaged 8±3 years. Each month's adherence percentage was calculated as the sum of daily adherence percents, divided by the number of evaluable days.
Results. During the first 3 months after transplantation, patients (n=44) with declining medication adherence, defined as dropping by 7% or higher (equal to missing 2 days) between months 1 and 2, later experienced lower mean medication adherence for months 6 to 12, 73% versus 92% respectively ($P<0.0001$). Compared to patients with stable adherence, they also had more frequent ($P=0.034$) and earlier ($P=0.065$) acute rejection episodes. This was additionally associated with more frequent ($P=0.017$) and earlier ($P=0.046$) death-censored graft loss.

In addition, daily medication adherence, expressed as the percentage of doses taken, decreased as the number of prescribed daily doses increased. During the first 3 months after transplantation, adherence with four doses per day averaged 84%, compared to 91% for patients on twice-daily dosing ($P=0.024$) and 93.5% for patients on once-daily dosing ($P=0.008$).
Conclusions. Early declining medication nonadherence is associated with adverse clinical outcomes. This pattern is detectable during the first 2 months after transplantation. Early detection of nonadherence provides opportunities to target interventions toward patients at the highest risk for adverse behaviors and events.

Keywords: Drug monitoring, Immunosuppression, Transplantation, Medication adherence.

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Renal transplantation is the optimal therapy for many patients with end-stage renal disease. Currently, except for identical twins, long-term successful transplantation requires lifelong daily immunosuppression. Surprisingly, a significant number of transplant recipients fail to consistently follow their prescribed immunosuppressive regimen. This medication nonadherence (med-NA) ranges from accidental and rare to complete cessation of a drug. Although definitions of med-NA vary somewhat, individual studies (*1–4*), database reviews (*5*), and meta-analyses (*6, 7*) have all demonstrated substantial med-NA rates after renal transplantation. Indeed, med-NA rates in renal transplant recipients are higher than those for any other solid organ transplant (*6*). Posttransplant med-NA has clearly been shown to be a critical factor associated with increased rates of graft dysfunction and loss (*1–3, 7*).

Despite the obvious importance of med-NA (*8, 9*), there are only a few studies of posttransplant med-NA with the more potent, contemporary immunosuppressive drugs (*5*). We showed in a previous study of once-daily azathioprine (Aza) adherence that there was a significant association of early, declining compliance with increased rates of acute rejection and death-censored graft loss (*1*). These early-declining compliance ("drop2") patients were those with at least two more days of missed doses in month 2 compared to month 1 after transplantation, that is, adherence dropped by at least 2 days from month 1 to month 2. In the present study, we report prospective electronic monitoring of contemporary immunosuppression confirming our earlier observations and demonstrating that the drop2 patients remain at increased

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risk for adverse outcomes, even when prescribed more potent medications.

RESULTS

From August 1998 through August 2006, 1802 patients received kidney or kidney-pancreas transplants at the University of Minnesota Medical Center-Fairview. Of these, 868 (48.2%) were eligible, contacted, and invited to participate in this drug-monitoring study; 452 patients (52.1%) consented to participate. Study patients were given an electronic medication event-monitoring system cap (MEMS cap; AARDEX Group Ltd., 1950 Sion, Switzerland) to record adherence with one of their immunosuppressive medications beginning at discharge from their hospitalization for renal transplant.

By study design, prospective medication adherence monitoring was planned to extend to at least 1 year. One hundred ninety-five patients (43%) provided data for all or part of the first study year, 192 patients had evaluable data for the first three consecutive months after hospital discharge. Of these, 125 patients were prescribed twice-daily mycophenolate mofetil (MMF), 17 Aza and 28 sirolimus (Rapa) patients were prescribed their medication once daily. Of the 195 patients, 153 (78.5%) completed electronic monitoring through the end of their first year after transplantation. The mean length recorded by the MEMS cap was 15.8±7.8 months. Follow-up for clinical outcomes averaged 7.9±3 years. Outcome data are available for 166 patients (85%) at 5 years after transplantation and for 96 patients at 8 years after transplantation.

Of 195 participants, 44 patients (22.6%) demonstrated adherence declines of 7% or more (equivalent to missing two or more additional days in month 2 versus month 1; "drop2"). The remaining 151 patients had either stable or improving rates of adherence during their second month after transplantation. Although the assignment of each patient's immunosuppressive drug protocol was not randomized, there were no significant demographic differences between patient groups stratified by their drug regimens other than donor source and transplant number. Also while nonadherence was higher in patients taking more than one dose daily, the proportion of drop2 patients did not significantly differ by initial dosing regimen (Table 1). The drop2 group had experienced significantly more cases of early (≤90 days) acute rejection. The only demographic factor associated with the drop2 group was being nonwhite, with no other significant differences noted (Table 2).

These early adherence patterns persisted. Longer-term follow-up demonstrated that during months 6 to 12 after transplantation, drop2 patients had mean medication adherence rates of 73%±30%, while adherence in the stable group is 93%±14% ($P<0.0001$). Drop2 patients experienced twice the rate of acute rejection ($P=0.034$) and death-censored graft loss ($P=0.017$) seen in the stable adherence group (Table 2). Drop2 patients' first rejection event tended to appear sooner (Fig. 1A, $P=0.065$) than patients with stable adherence. Similarly, allograft losses also appeared earlier (Fig. 1B, $P=0.046$). There were no significant differences in death rates or time to death between drop2 patients and the stably adherent participants. Setting aside the 15 patients who experienced early rejections (7 in drop2 and 8 in the stable adherence group), both rejection ($P=0.099$) and graft loss ($P=0.050$) remained twice as frequent in the drop2 group.

TABLE 1. Demographic characteristics of patients divided by initial drug and dose prescription at hospital discharge

	All (N=195)	AZA (N=17)	RAPA (N=28)	MMF-2[a] (N=128)	MMF-4[a] (N=22)	*P*
Female	43%	59%	32%	40%	59%	0.115
Age	48±14	44±11	45±14	49±14	45±13	0.141
Donor						
DD	44%	24%	36%	48%	46%	0.024
LRD	36%	71%	39%	29%	45%	
LURD	20%	6%	25%	23%	9%	
TX number						
1	83%	65%	93%	80%	100%	0.036
2	14%	24%	7%	17%	0	
3	2%	12%	0	1.5%	0	
4	1%	0	0	1.5%	0	
Kidney and pancreas	31%	35%	32%	27%	55%	0.072
DM at TX	47%	47%	54%	41%	68%	0.109
Nonwhite	7%	0	14%	5%	14%	0.096
Teenaged	3%	0	4%	4%	0	0.669
Early acute rejection[b]	8%	6%	4%	9%	5%	0.667
Drop2[c]	23%	24%	25%	19%	41%	0.144

[a] MMF-2 indicates dosing twice daily, and MMF-4 indicates four times-daily dosing.
[b] Acute rejection during the first 90 days after hospital discharge after transplantation.
[c] Drop2 indicates subjects whose calculated percentage of adherence declined by a total of two or more days during the second monitored month compared to the first month.
Values are percent or mean±standard deviation.
P value for comparison between four drug-dose groups by χ^2 test or analysis of variance *F* test.
DD, deceased donor; LRD, living related donor; LURD, living unrelated donor; TX, transplant; DM, diabetes mellitus.

TABLE 2. Demographic characteristics and transplant outcomes – drop2 patients versus the remaining steady adherence patient group

	Drop2[a] (n=44)	Steady adherence (n=151)	P
Female	43%	42%	0.925
Age	46±14	48±14	0.356
Donor type			
DD	50%	42%	0.397
LRD	36%	36%	
LURD	14%	22%	
TX number			
1	80%	83%	0.482
2	16%	14%	
3	5%	1%	
4	0	1%	
Kidney and pancreas	20%	34%	0.078
Diabetes at TX	34%	50%	0.057
Nonwhite	18%	3%	0.002
Teenaged	2%	3%	0.726
Drug-dose[b]			
AZA	9%	9%	0.144
RAPA	16%	14%	
MMF – 2 times daily	55%	69%	
MMF – 4 times daily	20%	9%	
Corticosteroids after discharge	34%	37%	0.716
Initial immunosuppression			
CSA	66%	62%	0.849
Tacrolimus	32%	35%	
Only MMF	2%	3%	
Early acute rejection (<90 d)	16%	5%	0.020
Transplant outcomes			
Acute rejection[c,d]	6.4±1.6	2.5±0.5	0.034
Loss before death[c]	3.7±1.2	1.6±0.4	0.017
Death[c]	3.7±1.1	2.7±0.5	0.327

[a] Drop2 indicates subjects whose calculated percentage of adherent days declined by a total of two or more days during the second monitored mo. compared to the first mo.

[b] Drug-dose is initial drug and dose regimen at the time of hospital discharge.

[c] Rates per 100 patient-years±standard error.

[d] For acute rejection, rates include repeated occurrences of acute rejection, whereas log-rank test compares product-limit curves to first rejection (see Fig. 1A). Acute rejections during the first 90 days after transplant were omitted.

Values are percent, or mean±standard deviation, or rate per 100 patient-years±standard error.

P value for comparison by χ^2 test or *t* test.

DD, deceased donor; LRD, living related donor; LURD, living unrelated donor; TX, transplant; CSA, cyclosporine A; AZA, azathioprine; RAPA, sirolimus.

Of the 195 recipients, 45 had their monitored drug (Aza or Rapa) prescribed as a single daily dose. The remaining 150 patients were initially prescribed MMF at a frequency of twice daily (n=128) or, in an empiric effort to minimize side effects, four times daily (n=22). Independent of the specific drug monitored, the 3-month medication adherence rates varied inversely with the number of daily drug doses prescribed. During the first month after discharge, 43% of patients taking single daily doses of a monitored medication missed at least one dose. This percentage increased to 49% during month 3. During the same intervals, 73% of patients prescribed four doses per day missed at least one dose of medication during month 1 and 76% missed doses in month 3 (Fig. 2). During the first 3 months, patients prescribed single daily doses of medication took a mean of 93.5% of their medication; and twice-daily doses, a mean of 91%. Patients prescribed medication four times per day took 84% of their prescribed doses. Medication adherence rates for once-daily (*P*=0.008) and twice-daily dosing (*P*=0.024) were significantly better than four-times-per-day dosing. Comparing adherence rates, there was no statistically significant difference between once-daily and twice-daily dosing.

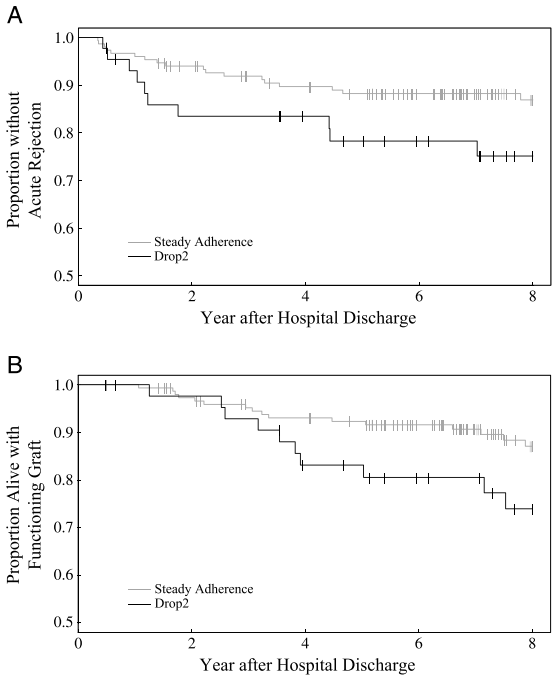

FIGURE 1. A, Time to first acute rejection beginning 90 days after hospital discharge. Kaplan-Meier curves defining the rejection-free survival of patients with steady or declining (drop2) medication adherence; *vertical dashes* mark censoring events. The table indicates the number of patients at risk in 2-year intervals. There is a trend toward earlier and more frequent rejections in the drop2 group compared to the steadily adhering group (log-rank, *P*=0.065). B, Time to death–censored graft loss. The Kaplan-Meier curves defining the death-censored allograft survival for patients with steady or declining (drop2) medication adherence; *vertical dashes* mark censoring events. The table indicates the number of patients at risk in 2-year intervals. There were more frequent and earlier graft losses in the drop2 group compared with the steadily adhering group (log-rank, *P*=0.046).

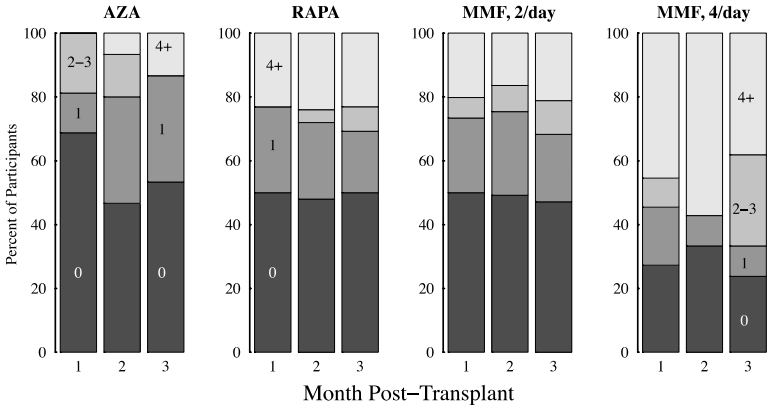

FIGURE 2. Sorted by drug and dose schedule, the *stacked bar graph* displays the percentage of patients missing no, one, two to three, and four or more doses per month during the first 3 months after transplant. There were 16 patients on once-daily azathioprine (Aza), 26 on once-daily sirolimus (Rapa), 124 on twice-daily mycophenolate mofetil (MMF), and 22 on four times-daily MMF. Seven patients were excluded because they either changed drug or dose schedule during the first month or had less than five evaluable days in any month.

Rank ordering each patient's mean proportional adherence during the first 3 months, according to prescription of once or more than once daily, produces similar patterns (Fig. 3), indicating that at least two thirds of patients in both groups took more than 90% of their medication. Focusing exclusively on patients prescribed MMF twice a day (n=128), the mean interdose interval in months 1 to 3 after transplant, expected to be about 12 hours, was 19±13 hours for the 24 drop2 patients and 13±6 hours for the 104 stably adherent patients (P=0.0014). Longer-term differences in adherence persisted: mean adherence during months 6 to 12 was 63%±33% in the drop2 group and 92%±15% in the stable group (P<0.0001). On overall follow-up, drop2 patients experienced four times the rate of acute rejection (P=0.021) and almost three times the rate of death-censored graft loss (P=0.012) observed in stably adherent patients (data not shown). Even omitting patients with early rejections (five patients from the drop2 group and seven from the stably adherent patients), the rates in the drop2 group remained more than twice as high as in the rates in the stably adherent patients for both rejection (P=0.256) and death-censored graft loss (P=0.030).

DISCUSSION

Data in this study highlight two important early patterns in med-NA. First, this prospective patient cohort confirms that med-NA appears early after transplant and that the pattern of early declining adherence is associated with significantly poorer late allograft outcomes. Second, the complexity (i.e., doses per day) of the immunosuppressant medication regimen directly affects adherence rates.

Quantitative medication adherence has been reported in a variety of chronic clinical conditions, including seizures (*10, 11*), glaucoma (*12, 13*), human immunodeficiency (*14–17*), hypertension (*18, 19*), chronic anticoagulation (*20, 21*), and congestive heart failure (*22*). Although most studies were of short duration and used differing adherence definitions, they all observed that med-NA 1) was detectable in each study and 2) was regularly associated with adverse outcomes. Med-NA occurs commonly in asymptomatic medical conditions requiring chronic medication. In a wide variety of chronic diseases, 15% to 25% of patients have been reported to rapidly reduce or discontinue their prescribed drug shortly after the initial prescription (*11, 12, 17, 18, 20*). Individually, adherence rates vary, perhaps reflecting each patient's perception of the clinical importance of the condition being treated (*23*) and the anticipated risks associated with

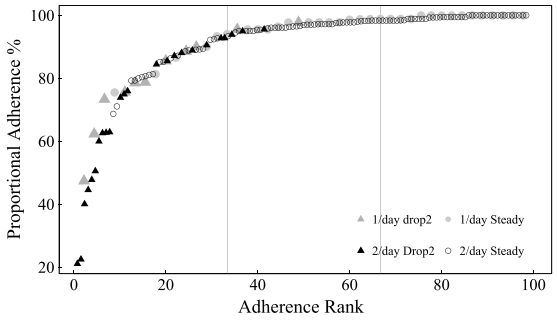

FIGURE 3. Two distributions of mean proportional adherence per patient during the first 3 months for patients taking one versus multiple daily medication doses. Patients taking MMF two or more times a day (n=150) are represented by *black symbols*, whereas the 45 patients taking medication once daily (Aza, n=17; Rapa, n=28) are represented by *gray symbols*. In each subgroup, drop2 patients are represented by *triangles* and steadily adhering patients are represented by *circular symbols*. *Vertical lines* divide subjects into tertiles. Note that drop2 patients are not limited to the lowest tertile. Note the highly similar distribution curves indicating that the proportional definition of adherence identifies a similar adherence distribution in either single- or multiple-dose patients.

missing medication. In this regard, solid organ transplant recipients consistently demonstrate better overall rates of adherence with their medications compared to patients with asymptomatic conditions such as hypercholesterolemia (*23*) or hypertension (*18*).

Remarkably although solid organ transplant recipients are regularly reminded that immunosuppressive NA may result in graft loss or even death, med-NA seems ubiquitous (*6*). With improving transplant protocols, decreasing rates of early rejection, and patient care advances, med-NA has emerged as a critical barrier to achieving optimal long-term transplant outcomes (*1–3, 24, 25*).

We previously reported that significant posttransplant med-NA could be detected during the first few weeks after hospital discharge (*1, 2*). In that analysis of a natural history cohort, a 7% decline (e.g., two missed doses over 30 days) in Aza adherence during the second month after transplantation identified patients who experienced significantly earlier and more frequent episodes of acute rejection as well as increased rates of allograft loss. Now analyzing twice-daily MMF using a proportional adherence model, the distribution of adherence is virtually identical to that seen with once-daily Aza or Rapa (Fig. 3) (*1*). Despite historically lower rejection rates (*26*), the present *prospective* study confirms our earlier finding that early declining adherence was associated with significantly more frequent and earlier episodes of rejection (Fig. 1A). Using contemporary immunosuppression, acute rejection rates are 250% higher in patients with early declining adherence compared to stably adherent patients, demonstrating that even today's potent immunosuppressive drugs are ineffective at preventing rejection if taken inconsistently. Clearly, med-NA will remain a concern during the development and study of future immunosuppressant drugs.

Declining medication adherence is further associated with both earlier and higher rates of death-censored graft loss (Fig. 1B; P=0.046). The drop2 group exhibits a 200% increase in graft loss when compared to stably adherent allograft recipients at 5 years after transplantation.

Recognition of early (first 2–3 months) declining adherence consistently identifies patient groups at risk for early discontinuation or significant med-NA to their therapeutic regimen (*9*). These dynamic patterns are only demonstrable with quantitative data such as those provided by MEMS technology (*11, 22*). Clinically, this drop2 measure of dynamic declining adherence is available immediately for each patient because it is derived from the patient's own records without reference to any outside group or norm. The pivotal importance of this observation is that early recognition of med-NA permits targeting adherence-promoting interventions to a defined subset of patients at high risk for adverse behaviors and outcomes. Newer generations of electronic medication monitors provide adherence data in "real time." Ideally, effective and sustained interventions will provide enduring improvements in adherence and subsequent clinical benefits for both renal transplant recipients and other patient populations (*11, 13, 18, 22*).

It has long been recognized that the complexity of a medication regimen affects adherence. Our data demonstrate that after transplantation, the more times per day a patient is expected to take a medication, the more likely he or she is to miss doses. A previous review of quantitative medication adherence by Claxton et al. (*27*) linked the prescribed number of daily doses to the electronically documented adherence rates in 76 separate studies across diverse medical conditions. They demonstrated that, on average, a single daily dose yields the highest adherence rate at 79%. More frequent doses resulted in less adherence; twice-daily dosing yielded 69%, three doses per day produced 65%, and four doses per day resulted in adherence declining to 51%. Our patients' adherence patterns are strikingly similar. However, perhaps because of the importance of a renal transplant, the mean adherence rates are all proportionately higher. Similar to Claxton et al., our data do not show statistical differences in adherence between once-daily and twice-daily dose schedules. Clinically, any expected benefit from more frequent medication dosing must be balanced against the likelihood that patients will not take all of the prescribed doses.

Certainly, medication costs present yet another barrier to adherence. In this cohort of renal transplants, medication costs were covered by Medicare and supplemented by additional third party insurance. This was critically true during those first 2 to 3 months after transplantation when the drop2 pattern was detected. Unfortunately, Medicare prescription coverage abruptly ends 3 years after transplantation and thus becomes an added barrier to individual medication adherence (*28*) and successful transplantation.

This study has some limitations related to both sampling bias and technology. We could only measure adherence in those patients who consented to be observed. This may limit the generalizability of our findings. But since we may have sampled a group of patients likely biased to be more adherent, med-NA in the entire transplant population is perhaps even more prevalent than we observed. Even after consenting, patients sometimes dropped out or failed to return their monitor cap, further limiting our assessment. Although the MEMS technology is an excellent tool to measure adherence (*9*), there is no certain proof that a patient removing the monitor cap actually takes the prescribed dose of medication at that time. Also, because all patients were informed that their medication taking was being monitored, this may have masked some early med-NA. Finally, the extent to which our renal transplant data accurately characterize adherence for other solid organ transplants including liver or heart is not known (*6*).

In conclusion, med-NA is a major clinical problem in renal transplantation. We demonstrated that it is possible to prospectively identify patients at increased risk for adverse events including acute rejection and graft loss based on their adherence patterns observed during the first 2 to 3 months after transplantation. The sign of early declining adherence deserves more careful attention because it predicts an increased risk of chronic med-NA as well as later adverse outcomes (*2, 24*). Also it should now be possible to focus behavioral intervention efforts on these vulnerable patients early when their med-NA pattern is first recognized. Similarly, the observation that medication regimens consisting of more frequent daily doses are less likely to be precisely followed has management implications because simpler drug regimens (i.e., fewer doses per day) should promote better adherence. The consistency of our findings in two prospective renal transplant patient cohorts as well as the findings of other

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