Assessing Medication Adherence in Solid-Organ Transplant Recipients

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Abstract

Objectives: **We sought to determine and compare the prevalence of nonadherence in lung, kidney, and liver transplant recipients, and identify potential risk factors for nonadherence.**

Materials and Methods: **This cross-sectional, single-center, retrospective cohort study, evaluated 225 outpatient lung, kidney, and liver transplant recipients' adherence to immunosuppressant medication. Based on immunosuppressant dosages and dispensing records, medication possession ratio (days of medication supplied/actual days) and gaps in prescription refills (> 30-day lapse between expected depletion of supply and next refill) were used as surrogate markers in assessing adherence for 2 years. Patients were adherent to their immunosuppressant medication regimens if their medication possession ratio was ≥ 80%.**

Results: **The mean age of the subjects was slightly greater than 50 years of age, and they were a median of 2.0, 1.3, and 1.1 years posttransplant at the start of data collection for lung, kidney, and liver recipients. Overall medication possession ratios were 95.4% ± 7.5%, 95.9% ± 7.6%, and 92.7% ± 12.3% in our lung, kidney, and liver recipients. Only 7.1% of patients had a medication possession ratio lower than 80%, which was the cutoff for nonadherence. No statistical analyses were performed to identify potential factors for nonadherence because of the small number of nonadherent patients.**

Conclusions: **Immunosuppressant medication adherence at our center was high for all 3 organ cohorts, as measured by a medication possession ratio of 80% or better. Further study is needed to evaluate immunosuppressant adherence over time after transplant, and confirm the clinical factors that optimize adherence in high-risk patients.**

Key words: *Compliance, Immunosuppressants, Kidney transplant, Liver transplant, Lung transplant*

Introduction

In solid-organ transplant recipients, nonadherence (NA) to immunosuppressant medications is associated with poor allograft and patient outcomes.[1] The 3 major types of NA are accidental, invulnerable, and decisive.[2,3] One meta-analysis investigating NA in solid-organ transplant recipients found that the rate of NA was 22.6 cases per 100 persons per year, while other studies have reported NA in 2% to 70% of transplant recipients, depending on definitions used and organs studied.[4-8] NA rates differ greatly among organ groups. In kidney recipients, there are 35.6 cases per 100 persons per year, with an overall incidence of NA of 4.7% to 25.9%, depending on the unit of measure.[5,9] In liver recipients, there are 6.7 cases per 100 persons per year, and 9.7% to 73% of them are nonadherent.[5,7,10] Dew and associates reported that 19.7% of lung transplant recipients are nonadherent 2 years after the transplant.[11]

A recent study based on the self-reports of NA suggests liver recipients are the most nonadherent population, with only 18% of kidney recipients exhibiting NA, compared with 38.5% of lung

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recipients and 46.6% of liver recipients.[8] In addition to the organ transplanted, other risk factors in solid-organ transplant recipients for NA include female sex, socioeconomic status, psychiatric comorbidity, substance abuse, prior noncompliance, patient's beliefs on immunosuppressant pharmacokinetics, pretransplant and posttransplant education, the patient's relationship with the transplant team, the immunosuppressant medication regimen, the number of medications, and the expense of the medications.[2]

Regardless of the type of NA, in the United States, the cost of NA that results in acute rejection episodes and graft failures ranges from $15 to $100 million each year.[1,4] The risk of late acute rejection, graft dysfunction, and graft failure is also greater in nonadherent organ recipients compared with adherent recipients.[1,2,9,12]

Our outpatient transplant program can track all immunosuppressant drugs dispensed to ambulatory transplant recipients. In a prior pilot study, we analyzed data on adherence rates in our lung transplant population using the medication possession ratio ([MPR] which is defined as *the number of days of medication supplied to the patient over a specified time)*. The MPR was used as a surrogate marker for adherence based on methods described previously in a large renal transplant population.[13] Our goal in this quality assurance audit is to expand information collected from our lung transplant recipients and determine the prevalence of NA in our kidney and liver transplant populations. Here, we present the results of the 3 organ cohorts.

Materials and Methods

Our primary aim is to describe adherence to the immunosuppressant medication by kidney and liver transplant recipients within 5 years of transplant and our entire lung population using the MPR. Our secondary aims described adherence to the immunosuppressant drugs based on gaps in prescription filling and characterizing the demographic and clinical factors that may be associated with suboptimal adherence. Because this is a quality assurance audit for our outpatient transplant clinic, ethics approval from our institution was not required; however, all protocols did conform with the ethical guidelines of the 1975 Helsinki Declaration.

Study population

This was a cross-sectional, retrospective cohort study using prescription dispensing information and patient health care records. Patients were included as follows: all lung transplant recipients followed by our transplant clinic on August 31, 2010; kidney and liver recipients transplanted between January 1, 2006, and December 31, 2010, who were being followed by our transplant clinic on June 30, 2011. To standardize the cohort size, data were collected from a random sample of 75 patients from the kidney and liver cohorts to match the total number of lung transplant patients included in our previous data collection. After all of the patients meeting our inclusion criteria were identified, we performed random selection using a random number generator. We excluded those patients who were institutionalized longer than 6 months during data collection, had less than 6 months of medication fill information, were transferred to another transplant center, or died. Patients enrolled in a pharmaceutical clinical trial were also excluded because their adherence would likely not reflect a nonclinical trial patient population.

Data collection and statistical analyses

Data collection included all ambulatory immunosuppressant prescriptions filled, and prescribed immunosuppressant dosing during the following 2 years: all lung transplant recipients with data collection between September 1, 2008, and August 31, 2010; and a random sample of kidney and liver recipients with data collection between July 1, 2009, and June 30, 2011. There were no changes in prescribing or dispensing protocols between these times. Patient demographics including baseline factors known to contribute to NA, comorbidities, clinical parameters and immunosuppressant dosing data obtained via outpatient health care records and electronic database, and medication dispensing information were obtained via medication reimbursement information (ie, a public payer with centralized dispensing of all immunosuppressants). Prescription fill date and number of units dispensed were used to calculate duration of supply, using dosage information obtained through health care record reviews. All data collected were analyzed using descriptive statistics. To identify potential risk factors for NA, logistic regression was planned to test the influence of continuous or categorical variables on the presence or absence of an overall MPR of less

than 80% (suboptimal adherence). Multivariate logistic regression analyses were planned to identify variables associated with the suboptimal adherence independently. Predictors with a *P* value < .2 in univariate analyses were included in the multivariate analyses. Odds ratio (OR) and 95% confidence intervals were calculated by exponentiation of logistic regression coefficients. All tests were 2 tailed, and *P* values < .05 were considered statistically significant.

Definitions

Medication possession ratio was calculated using the days' supply of medication dispensed, divided by follow-up in days.[13-14] Medication possession ratio for each recipient was calculated individually for each immunosuppressant medication and then averaged, to obtain the overall MPR. Suboptimal adherence was defined as a *MPR < 80%*.[14] Gaps in refills were defined as *having > 30 days between estimated end date of the current supply and the next refill date.*[15]

Results

Seventy-five patients were included in each of the 3 cohorts (kidney, liver, and lung). Baseline demographic data are summarized in Table 1. For the lung cohort, where all patients followed by our clinic were screened, 10 patients were excluded because they were multiorgan transplant recipients, or because they had < 6 months' follow-up. For the liver and kidney cohort, where a random sample was collected, 25 liver and 33 kidney patients were excluded because they were deceased, transferred to another center, were multiorgan recipients, part of another study, or had graft failure before the study's commencement. Mean age and sex distribution across the cohorts were similar. Median time posttransplant was similar across the cohorts. Lung recipients had slightly higher median time posttransplant (2 years), with 1 patient being 18.5 years posttransplant, compared with the kidney and liver cohorts (median 1.3 and 1.1 years).

Across the cohorts, there were more white patients than there were other ethnicities, with white patients comprising 94.6% of the lung cohort. Most patients from each cohort were on multiple immunosuppressants for their anti-rejection regimen, with tacrolimus being the most-common calcineurin inhibitor, mycophenolic acid the most common antimetabolite, and only a few patients on cyclosporine, azathioprine, or sirolimus (Table 1). Prednisone was prescribed in 22 kidney, 27 liver, and 69 lung recipients. History of acute rejection was present in 13.3% of kidney, 45.3% of liver, and 54.7% of lung recipients. These numbers are similar to the percentages of acute rejection rates from each organ population in the first year posttransplant.

Of the 225 patients studied, NA, as defined by an MRP of < 80%, was present in only a minority of patients (Figure 1). Three kidney, seven liver, and six lung recipients were nonadherent, making only 7.1% of the total study population. Medication possession ratios > 95% were most common, occurring in

Table 1. Baseline Demographics

Variable	Kidney (n=75)	Liver (n=75)	Lung (n=75)
Age; mean ± SD (y)	51.1 ± 13.3	52.5 ± 10.1	53.2 ± 12.5
Time after the transplant; median (min, max) (y)	1.3 (0, 3.4)	1.1 (0, 3.4)	2 (0, 18.5)
Female sex; n (%)	31 (41.3)	33 (44.0)	28 (37.3)
Ethnicity; n (%)			
White	37 (49.3)	56 (74.6)	71 (94.6)
Pacific Asian	15 (20.0)	10 (13.3)	1 (1.3)
South Asian	14 (18.7)	4 (5.3)	0 (0)
First nations	0 (0)	2 (2.7)	3 (4.0)
Other	9 (12.0)	3 (4.0)	0 (0)
Indication for transplant; n (%)	GN: 30 (40.0) Diabetes: 19 (25.3) Hypertension: 2 (2.7) Other: 24 (32.0)	HCV/HBV: 35 (46.7) PSC/PBC: 11 (14.6) Alcohol: 10 (13.3) Other: 19 (25.3)	COPD: 15 (20.0) CF: 20 (26.7) PF: 19 (25.3) Other: 21 (28.0)
Immunosuppressant regimen; n (%)			
Tac/MPA/Pred	20 (26.7)	24 (32.0)	62 (82.7)
Tac/MPA	54 (72.0)	25 (33.3)	0 (0)
History of acute rejection; n (%)	10 (13.3)	34 (45.3)	41 (54.7)

Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; MPA, mycophenolic acid derivatives (mycophenolate mofetil or sodium); PBC, primary biliary cholangitis; PF, pulmonary fibrosis; Pred, prednisone; PSC, primary sclerosing cholangitis; Tac, tacrolimus

55 kidney (73.3%), 49 liver (65.3%), and 54 lung recipients (72.0%). When assessed by gaps in prescription refills of greater than 30 days, NA occurred in 19 kidney recipients, 28 liver recipients, and 21 lung recipients (Figure 1). All patients with an MPR < 80% had gaps in prescription refills. There was a small number of kidney, liver, and lung patients with MPRs > 95% who had at least 1 documented gap in prescription refills. Interestingly, in our liver population, 3 patients with history of intravenous drug use and 1 patient currently on methadone maintenance had an MPR of > 90%. Mean overall MPRs (± SD) were 95.9% ± 7.6%, 92.7% ± 12.3%, and 95.4% ± 7.5% in our kidney, liver, and lung populations (Figure 2). Interestingly, in our nonadherent kidney and liver patients, most were women despite having more men in the study populations.

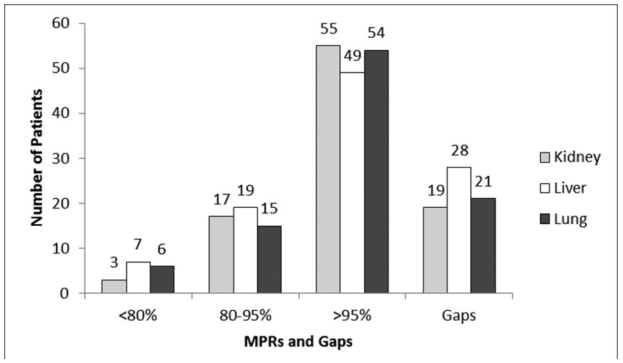
Characteristics of the NA patients (MPR < 80%) are summarized in Table 2. Given the small number of patients who met our criteria for NA, statistical analyses of characteristics or clinical factors possibly associated with NA was not done. Most kidney and liver recipients with suboptimal adherence were > 2 years posttransplant. However, in our lung recipients, two-thirds of nonadherent patients were < 2 years posttransplant. Most nonadherent patients were white, were on triple immunosuppressive therapy, and had a history of acute rejection. A minority of patients had comorbidity of depression, which has been associated with NA. All nonadherent patients had gaps in their immunosuppressant refills. The age distribution of nonadherent patients was evenly spread between younger and older patients, with 7 patients in the nonadherent population < 40 years old. The geographic proximity of the nonadherent patients with our transplant center was similarly distributed among the entire population.

Table 2. Suboptimal Adherence (MPR < 80%) Patient Characteristics

Characteristic	Kidney (n=3)	Liver (n=7)	Lung (n=6)
Overall MPR; mean ± SD	65.8 ± 11.2	59.6 ± 12.2	72.6 ± 5.7
Time posttransplant; mean ± SD (y)	30.9 ± 9.5	42.0 ± 11.4	42.0 ± 12.3
Women; n (%)	2 (66.7)	5 (71.4)	2 (33.3)
White; n (%)	2 (66.7)	6 (85.7)	6 (100.0)
Immunosuppressant regimen at time of data collection; n (%)			
Tac/MPA/Pred	2 (66.7)	1 (14.3)	6 (100)
Tac/MPA	1 (33.3)	4 (57.1)	0 (0)
Tac/Aza	0 (0)	2 (28.6)	0 (0)
Comorbidity of depression; n (%)	1 (33.3)	2 (28.6)	2 (33.3)
History of acute rejection; n (%)	1 (33.3)	5 (71.4)	5 (83.3)

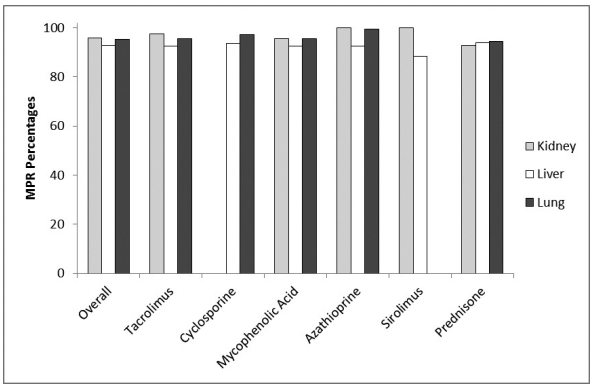
Abbreviations: Aza, azathioprine; MPA, mycophenolic acid derivatives (mycophenolate mofetil or sodium); MPR, medication possession ratio; Pred, prednisone; Tac, tacrolimus

Figure 1. Medication Possession Ratios and Gaps in Prescription Refills



Abbreviations: MPR, medication possession ratio

Figure 2. Medication Possession Ratios for Overall and Individual Immunosuppressants



Discussion

While "adherence" and "compliance" are often used interchangeably, there is a subtle difference. *Adherence* suggests therapeutic relation between the patient and physician, and *compliance* suggests the extent to which the patient follows the physician's orders.[3,4] The term adherence is favored because of the implication of therapeutic collaboration.[3,4] At the 2008 Nonadherence Consensus Conference in Florida, USA, the definition of NA in solid-organ transplant was defined as a *deviation from the prescribed medication regimen sufficient to influence adversely the regimen's intended effect*.[4] However, differing definitions in clinical studies of NA have led to a lack of standardized measuring of NA in solid-organ transplant patients.

Generally, adherence rates to chronic medications are approximately 50% depending on the underlying disease state.[3] In chronic diseases such as human immunodeficiency virus and diabetes, adherence rates are approximately 70%, and adherence rates to inhalers (for chronic respiratory conditions) and medication for psychiatric conditions (such as depression and schizophrenia) are 40%.[3] In organ transplant populations, adherence rates vary significantly; however, a rate of approximately 80% has been reported in a meta-analysis.[5] Laederach-Hofmann and associates have reported that 91% of organ recipients who are nonadherent to their immunosuppressants and follow-up appointments in the clinic experienced graft rejection or died, compared with only 18% of their adherent counterparts.[1]

Organ recipients at our center demonstrated excellent adherence to immunosuppressants as measured by MPR and gaps in prescription refills. The percentage of nonadherent recipients from our transplant center is significantly lower than that which has been reported in the literature. Of our recipients, 7.1% from our sample size of 225 (16 transplant recipients: 3 kidney, 7 liver, and 6 lung recipients) were nonadherent as defined by an MPR < 80%, and they had at least 1 gap in prescription refills. Given the small number of patients sampled, it was difficult to determine any significant baseline characteristics that might contribute to NA.

Although patients across all 3 of our organ cohorts had gaps in their prescription refills, most still adhered to our definitions and some had high MPRs (> 95%). This could be the result of stockpiling medication early after the transplant, where patients refill their immunosuppressants before they run out of them, winding up with extra stock at home. Some patient with gaps in prescription refills were on multiple immunosuppressants and were only nonadherent to one. This resulted in gaps in prescriptions refills and a lower overall MPR, but it was still greater than 80%.

Long-term strategies are required to maintain adherence for transplanted recipients, and these can be targeted as risk factors for NA. Higher education levels increase the likelihood of NA to immunosuppressants.[2,6] Time after transplant also may be a factor, where generally, adherence to immunosuppressants seems to decrease, as time after the transplant increases.[1,2,6,11,14,16] This is supported by a study of kidney recipients in which all study participants received their immunosuppressants for free for 12 months; adherence to immunosuppressants declined after 9 months, despite removing cost as a factor.[14]

Age is a factor in assessing NA in organ recipients. In kidney patients, as the patients' age increases, their risk for NA increases as well.[17] However, the opposite was found in liver patients who received prednisolone and were younger than 40 years at the time of transplant. This also was a risk factor for NA and for taking drug holidays lasting 48 hours or more.[18] Interestingly, in our cohort, the age of nonadherent kidney transplant recipients was younger than other organ cohorts. Increased dosing frequency not only was a risk factor for NA, but it also was a cause for decreased quality of life in kidney and liver recipients.[2,3,16,19,20] In one study of liver recipients that examined adherence rates to tacrolimus, decreasing the dosing frequency from twice a day to once a day, with extended-release tacrolimus, improved adherence by 11.8%.[19]

Counseling targeted toward NA improved immunosuppressant adherence over the short term, but patients reverted back to NA after 9 months.[21] One study attempted to identify factors that promoted immunosuppressant adherence in kidney patients who had maintained their grafts for 25 years or longer. The authors found 4 factors that were particularly important. These included reminder methods (eg, visual cues), obtaining medications, maintaining routines (eg, habit forming activities), and using problem-solving strategies (eg, backup medication at the work place, anticipating problems taking their medication, and devising strategies deal with these).[22]

Several factors may have played a role in our transplant center achieving lower rates of NA than previously reported, some of which have been identified in other cohorts. First, extensive patient education is offered by the nursing and pharmacy staffs who teach transplant recipients about their immunosuppressants and help patients develop a sense of responsibility for their health. A self-medication program begins in hospital soon after the transplant that helps patients identify different immunosuppressants and medications they must take after the transplant. This training continues with frequent multidisciplinary outpatient clinic follow-up posttransplant, where patients meet with nurses,

physicians, pharmacists, dieticians, and social workers.

Pharmacists focus on ensuring optimal immunosuppressant use in transplant recipients by managing adverse events, screening for drug interactions, and monitoring their other drug therapies. Multiple contacts between the health care team and the patients ensure that patient education is ongoing and provides the opportunity to identify nonadherent behaviors. Another strategy is the teaching of problem-solving skills to manage the medications during follow-up. These behaviors are taught to kidney recipients early after the transplant, and have been associated with patients maintaining long-term optimal adherence to their immunosuppressant regimens.[22]

Further, all immunosuppressants are provided free of cost to transplant recipients in our program, removing this as a potential barrier to adherence.[2,14] Dispensing of the medications is done through a centralized dispensing system where only select pharmacies may dispense the immunosuppressants. According to Ruppar and Russell,[22] a major factor promoting adherence in kidney recipients is obtaining the actual immunosuppressants. With the centralized pharmacy in the outpatient clinic, patients may fill their immunosuppressants while attending clinic follow-ups. However, for patients who live elsewhere, this method actually may impede the patients' ability to obtain medications between visits. The on-call transplant physician system at our hospital also allows for patients to contact a transplant physician after hours, and the on-call physician can authorize the hospital's pharmacy and/or transplant ward to dispense an emergency supply of immunosuppressants with follow-up planned during regular business hours. This system has enhanced immunosuppressant adherence and reinforced the need for adherence.

Our study has several limitations. First, filling prescriptions does not guarantee that the patient is using the medications as directed at home, and our study did not address this. This limitation is mitigated by the fact that serum trough levels of tacrolimus/cyclosporine and sirolimus are routinely monitored by the solid-organ transplant clinic—a practice that most likely would increase appropriate medication-taking behavior. Unfortunately we did not capture serum levels in this study. Also, while the MPR is a good indicator of adherence, it does not indicate the timeliness of medication refills by the patient; therefore, gaps in prescription refills are a better indicator of patients' prescription-taking and prescription-filling habits.[13,15]

The surrogate nature of MPR and gaps in prescription refills make them imperfect indicators of adherence. It has been shown that patient interviews, combined with physicians' and nurses' assessments of patient adherence and serum concentrations provide the highest sensitivity and specificity when assessing patients adherence to immunosuppressants.[4]

A further limitation is this study's retrospective design, relying on health care record reviews to obtain patients' immunosuppressant dosage information to calculate the days' supply of immunosuppressants given to the patient, which may result in inaccurate information.

In addition, the sample size of our study was small, with only 225 patients across the 3 cohorts. Because of this, and because of the low number of nonadherent patients, we could not address our secondary endpoint of performing logistic regression to identify potential risk factors associated with NA.

Because there was a discrepancy in the time after transplant between our lung cohort, and the kidney and liver cohorts—the lung cohort (including all patients followed in our clinic) represents a good cross-sectional picture of posttransplant patients, both early and late, to get a balanced look at adherence over time. Despite this, our lung recipients maintained high MPRs, regardless of time since the transplant. Our kidney and liver cohorts were transplanted more recently, meaning our MPRs for these 2 cohorts might have been falsely high, as NA tends to increase as the time after transplant increases.[1,2,6,11,14,16] Finally, no link to long-term graft outcomes could be made because of the short duration of follow-up in these patients.

Despite the limitations of our study, we conclude that immunosuppressant adherence at our solid-organ transplant outpatient clinic is high, with most of our patients having an adequate supply of medication for their prescribed dosages during the 2 year follow-up period. Future transplant studies are needed to assess adherence trends over time, and with sample sizes large enough to identify risk factors for NA. These risk factors can then be used to target strategies for improving adherence to these high-risk groups.

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