OPEN

Long-term Immunosuppression Adherence After Kidney Transplant and Relationship to Allograft Histology

Elizabeth C. Lorenz, MD,[1] Byron H. Smith, PhD,[1] Fernando G. Cosio, MD,[1] Carrie A. Schinstock, MD,[1] Nilay D. Shah, PhD,[2] Paul N. Groehler, PharmD, RPh,[3] Jayson S. Verdick, PharmD, RPh,[3] Walter D. Park,[1] and Mark D. Stegall, MD[1]

Background. Nonadherence to immunosuppression after kidney transplant is an important contributor to graft failure. Little is known about how nonadherence changes 3 years posttransplant when Medicare coverage of immunosuppression ends and how that nonadherence impacts allograft histology. The goal of this study was to compare rates of nonadherence during posttransplant years 1 to 3 to years 3 to 5 and examine the relationship between nonadherence during years 3 to 5 and 5-year allograft histology. **Methods.** We retrospectively analyzed 552 conventional kidney allografts in patients transplanted at our center between January 1, 1999, and June 1, 2010, who used the Mayo Clinic Specialty Pharmacy for the first 5 years posttransplant. Nonadherence was defined as less than 80% proportion of days covered. Overall adherence to immunosuppression appeared to be higher during years 3 and 5 compared to between years 1 and 3 (89.4% vs 82.9%, respectively; $P < 0.0001$ [paired t test]). **Results.** Overall nonadherence during posttransplant years 3 to 5 appeared to be associated with fibrosis and inflammation on 5-year allograft biopsy but not with transplant glomerulopathy (16.9% vs 5.9%, $P = 0.004$; 10.4% vs 8.5%, $P = 0.61$, respectively). After adjusting for nonadherence to calcineurin inhibitor and prednisone therapy, only nonadherence to antimetabolite therapy remained significantly associated with 5-year fibrosis and inflammation (odds ratio, 10.6; 95% confidence interval, 1.5-76.1; $P = 0.02$). **Conclusions.** Efforts to improve long-term adherence, possibly through the use of specialty pharmacies and increased adherence to antimetabolite therapy, may improve long-term allograft histology and survival, although further studies are needed to confirm these findings.

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Unfortunately, long-term allograft survival after kidney transplant remains suboptimal. Nearly one third of all kidney transplant recipients will require a second kidney transplant within 10 years of their first transplant.[1,2] Nonadherence may be a modifiable risk factor for poor long-term outcomes. Nonadherence after kidney transplant is associated with acute cellular and antibody-mediated rejection[3-5] and allograft failure.[4,6-9] In fact, nonadherent patients have a sevenfold greater odds of experiencing graft failure compared to adherent patients.[10]

Little is known about nonadherence to immunosuppression late posttransplant. Currently, Medicare covers the cost of maintenance immunosuppression for all kidney transplant recipients for only the first 3 years after transplant.[11] Multiple studies have examined nonadherence during the first 3 years posttransplant using Medicare pharmacy claims data.[6,7] However, it is possible that nonadherence increases significantly after Medicare coverage of immunosuppression ends given that medication cost is an important contributor to nonadherence.[11-13] If nonadherence does increase after year 3, interventions aimed at improving financial coverage of immunosuppression after that time point may improve graft outcomes. In addition, little is known about the relationship between nonadherence more than 3 years after transplant

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[1] *William J von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN.*

[2] *Health Sciences Research, Mayo Clinic, Rochester, MN.*

[3] *Mayo Clinic Specialty Pharmacy, Rochester, MN.*

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Correspondence: Elizabeth C. Lorenz, MD, Mayo Clinic, 200 1st St. SW, Rochester, MN 55905. (lorenz.elizabeth@mayo.edu).

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and late allograft histology. A better understanding of how nonadherence impacts chronic allograft injury could inform future adherence interventions.

The first aim of our study was to compare rates of nonadherence during posttransplant years 1-3 to years 3-5 using refill records from the Mayo Clinic Specialty Pharmacy. The second aim of our study was to determine whether nonadherence during years 3 to 5 is associated with 5-year renal allograft histology obtained via surveillance biopsies. We hypothesized that nonadherence would increase after the third year posttransplant and that nonadherent patients would be more likely to develop allograft fibrosis associated with inflammation and transplant glomerulopathy on 5-year allograft biopsies.

MATERIALS AND METHODS

Patient Population

This was a retrospective cohort study consisting of all adult patients who received conventional kidney alone transplants at Mayo Clinic Rochester between 1/1/1999 and 6/1/2010 (n = 1797) and used the Mayo Clinic Specialty Pharmacy for posttransplant immunosuppression (n = 1290, 71.8%). Patients who received a multiorgan transplant or experienced allograft failure or death within the first year posttransplant were excluded from the study. Patient monitoring included the following: (1) annual clinic visits at our center, (2) serum creatinine monitoring every 3 months, (3) protocol renal allograft biopsies 5 years posttransplant. At each annual clinic visit (or more frequently if needed), patients were provided with prescriptions with refills for their immunosuppressive medications for the following year. Donor-specific antibody (DSA) testing was performed using HLA-coated microspheres (One Lambda, Canoga Park, CA) and was routinely performed beginning in 2006. However, for those patients who did not have pretransplant measurements of DSA performed, frozen serum was used for testing.[14] Allograft function was estimated using the Modification of Diet in Renal Disease equation.[15] Clinical information was abstracted from electronic databases. Our study was approved by the Mayo Clinic Institutional Review Board.

Defining Adherence

Refill records for immunosuppression from the Mayo Clinic Specialty Pharmacy were examined. During the study period, the patients did not receive routine phone calls, reminders or automatic refills from the Specialty Pharmacy. Adherence for azathioprine (AZA), mycophenolate (MMF), prednisone, tacrolimus (tac), cyclosporine (CSA) and sirolimus was measured by proportion of days covered (PDC). To calculate the PDC, we developed a medication possession timeline for each of the following classes of immunosuppression: AZA/MMF, prednisone, tac/CSA and sirolimus. Overall adherence was calculated as the PDC for the patient's entire immunosuppressive regimen. The PDC was calculated as the number of days that the patient had immunosuppression over a 360-day period divided by 360 days.[7] The PDC calculation was censored when a patient had no drug information for 90 days. Once a patient was censored, their last compliance value was assumed as representative of their compliance level for the remainder of that year. Average adherence between posttransplant years 1 to 3 and years 3 to 5 was calculated. Nonadherence was defined as less than 80% PDC.

Allograft Histology

Five-year protocol biopsies were examined by experienced renal pathologists using Banff criteria.[16-18] Histological changes on biopsy were classified according to the following phenotypes that relate to death-censored graft survival[19]: normal histology defined by the absence of any pathologic diagnosis and normal Banff scores; mild graft interstitial fibrosis defined as a "ci" score = 1 without inflammation (ie, "i" score = 0); moderate or severe graft interstitial fibrosis defined by the presence of "ci" score > 1 and "i" score = 0; fibrosis associated with inflammation in nonfibrotic areas (ie, "ci" score > 0 and "i" score > 0); transplant glomerulopathy defined by a "cg" score > 0 regardless of any other score. The relationship between 5-year renal allograft histology and adherence during posttransplant years 3 to 5 was examined.

Statistical Analysis

Data were expressed as means and standard deviation or median and range as appropriate. Continuous data were compared by student's *t* test and nonparametric tests (Kruskall-Wallis) for normally distributed and skewed data, respectively. Proportions were compared with the χ^2 test. Paired comparisons were done by paired *t* test. The origin time for time-to-event analyses was 365 days after transplant. The relationship between adherence years 3 to 5 posttransplant and 5-year allograft histology was examined using logistic regression.

RESULTS

Study Cohort

Of the 1290 patients who used the Mayo Clinic Specialty Pharmacy for posttransplant immunosuppression, refill data for the first 5 years posttransplant was available in 570 (44.2%) allografts. Of these patients, 18 did not provide Minnesota Research Authorization and were excluded. Among the remaining cohort, recipient age was 52.4 ± 13.9 years, 331 (60.0%) were male, 520 (94.2%) were Caucasian, 444 (80.4%) received living donor transplants and 155 (28.1%) were diabetic. Baseline demographics of this cohort are displayed in Table 1. Pretransplant testing for class I DSA was performed on 441 (79.9%) recipients and for class II DSA on 456 (82.6%) recipients. Mean follow-up time among the cohort was 112.6 ± 32.1 months.

Posttransplant Adherence

Median overall adherence 3 to 5 years posttransplant as measured by the PDC was 92.6% (interquartile range, 83.7-98.2%) with 21.6% (n = 119) of patients nonadherent to their overall regimen (PDC < 80%). Patients who were nonadherent were significantly younger, had younger donors and were less likely to have class II DSA (see Table 1). The prevalence of 3- to 5-year nonadherence for individual class of immunosuppressive medications is described in Figure 1 and was highest for sirolimus and prednisone. On multivariate analysis, risk factors for 3- to 5-year overall nonadherence included younger recipient age and sirolimus-based immunosuppressive therapy (see Table 2).

In general, adherence increased between years 3 and 5 compared to between years 1 and 3 (paired *t* test). For

TABLE 1.

Patient characteristics

Pretransplant parameters	All patients (n = 552)	3- to 5-year overall adherent (n = 433)	3-5 year overall nonadherent (n = 119)	P[a]
Recipient age at transplant, y	52.4 ± 13.9	54.1 ± 13.2	46.5 ± 14.9	<0.0001[b]
Male (%)	331 (60.0)	265 (61.2)	66 (55.5)	0.26[c]
White (%)	520 (94.2)	412 (95.2)	108 (90.8)	0.09[c]
Diabetes (%)	155 (28.1)	120 (27.7)	35 (29.4)	0.72[c]
Living donor (%)	444 (80.4)	342 (79.0)	102 (85.7)	0.09[c]
Donor age, y	42.6 ± 13.1	43.3 ± 12.8	39.9 ± 14.0	0.02[b]
Prior dialysis (%)	278 (50.4)	212 (49.0)	66 (55.5)	0.21[c]
Months dialysis	19.4 ± 18.8	20.1 ± 19.7	17.2 ± 15.7	0.58[b]
Cause of ESRD				0.41[c]
Glomerular disease	150 (27.2)	117 (27.0)	33 (27.7)	
Diabetes	103 (18.7)	79 (18.2)	24 (20.2)	
Polycystic kidney disease	75 (13.6)	66 (15.2)	9 (7.6)	
Hypertension/vascular	55 (10.0)	44 (10.2)	11 (9.2)	
Retransplant	54 (9.8)	41 (9.5)	13 (10.9)	
Other	76 (13.8)	56 (12.9)	20 (16.8)	
Unknown	39 (7.1)	30 (6.9)	9 (7.6)	
History of prior kidney transplant	65 (11.8)	47 (10.9)	18 (15.1)	0.21[c]
HLA mismatches				0.76[c]
0	76 (13.8)	60 (13.9)	16 (13.5)	
1	27 (4.9)	20 (4.6)	7 (5.9)	
2	94 (17.0)	72 (16.6)	22 (18.5)	
3	116 (21.0)	91 (21.0)	25 (21.0)	
4	76 (13.8)	56 (12.9)	20 (16.8)	
5	109 (19.7)	88 (20.3)	21 (17.7)	
6	54 (9.8)	46 (10.6)	8 (6.7)	
Pretransplant DSA				
Class I	64 (14.5)	48 (13.9)	16 (16.8)	0.47[c]
Class II	92 (20.2)	80 (22.1)	12 (12.8)	0.04[c]
Delayed graft function	44 (8.0)	37 (8.6)	7 (5.9)	0.33[c]
Thymoglobulin induction	403 (73.0)	320 (73.9)	83 (69.8)	0.37[c]
Maintenance immunosuppression				0.08[c]
MMF/pred/tac	481 (87.1)	380 (87.8)	101 (84.9)	
MMF/tac	41 (7.4)	34 (7.9)	7 (5.9)	
MMF/pred/CSA	12 (2.2)	10 (2.3)	2 (1.7)	
MMF/pred/SRL	15 (2.7)	8 (1.9)	7 (5.9)	
MMF/pred/tac/SRL	3 (0.5)	1 (0.2)	2 (1.7)	

[a] Adherent vs nonadherent.
[b] χ^2.
[c] Kruskall-Wallis.

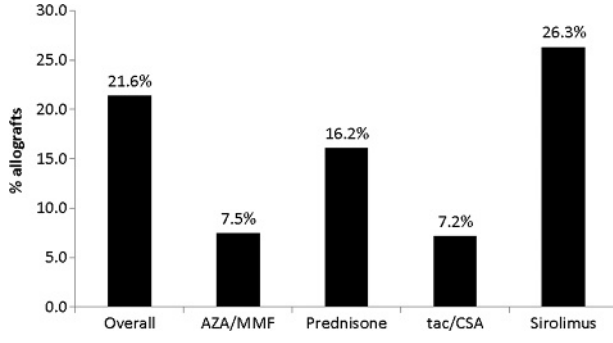

FIGURE 1. Prevalence of nonadherence to immunosuppression 3 to 5 years after kidney transplant.

example, overall adherence increased from 82.9% to 89.4% ($P < 0.0001$) (n = 428), adherence to prednisone increased from 87.6% to 92.6%, $P < 0.0001$ (n = 394) and adherence to tac/CSA increased from 93.1% to 95.3%, ($P < 0.0001$) (n = 424). Adherence to MMF/AZA and sirolimus remained stable between years 1 to 3 and 3 to 5 (93.2% to 92.6% ($P = 0.24$) (n = 427); 94.0% to 94.2% ($P = 0.86$) (n = 4), respectively). The distribution of adherence continuously over time is depicted in Figure 2.

Relationship Between Nonadherence and Allograft Histology

Three hundred eighty-two (69.2%) patients had a renal allograft biopsy 5 years posttransplant. Prevalence of fibrosis and inflammation was 8.1% (n = 31) and prevalence of transplant glomerulopathy was 8.9% (n = 34). Both of these

TABLE 2.

Variables related to 3-5 year overall nonadherence

Variable	Univariate model		Multivariate model	
	OR (CI)	*P*	OR (CI)	*P*
Recipient age (per 10-y increase)	0.67 (0.58-0.79)	<0.0001	0.68 (0.58-0.78)	<0.0001
Male	0.79 (0.52-1.19)	0.22		
White	0.50 (0.24-1.11)	0.09		
Diabetes	1.09 (0.69-1.69)	0.72		
Living donor	1.60 (0.93-2.89)	0.09		
Prior dialysis	1.30 (0.86-1.96)	0.21		
Cause of ESRD		0.41		
Glomerular disease	Reference			
Diabetes	1.08 (0.59-1.95)			
Polycystic kidney disease	0.48 (0.21-1.03)			
Hypertension/vascular	0.89 (0.40-1.86)			
Retransplant	1.12 (0.53-2.30)			
Other	1.27 (0.66-2.39)			
Unknown	1.06 (0.44-2.39)			
History of prior kidney transplant	1.46 (0.80-2.59)	0.21		
Married	0.70 (0.46-1.09)	0.11		
Sirolimus-based maintenance immunosuppression	3.85 (1.47-10.10)	0.007	4.00 (1.48-10.78)	0.004
CSA-based maintenance immunosuppression	0.72 (0.11-2.79)	0.67		
Months since transplant	0.99 (0.99-1.01)	0.89		

OR, odds ratio; CI, confidence interval.

histologic changes have been previously associated with shortened allograft survival.[19] Fibrosis and inflammation on 5-year biopsy was associated with 3- to 5-year overall nonadherence, whereas transplant glomerulopathy was not (see Table 3 and Figure 3). The relationship between fibrosis and inflammation and 3- to 5-year overall nonadherence was independent of other variables, including induction immunosuppression, maintenance immunosuppression and history of acute rejection (see Table 4). After adjusting for nonadherence to tac/CSA and prednisone therapy, only 3- to 5-year nonadherence to AZA/MMF remained significantly associated with fibrosis and inflammation (odds ratio, 10.6; 95% confidence interval, 1.5-76.1; $P = 0.02$). In patients with fibrosis and inflammation on 5-year biopsy (n = 31), mean eGFR at 5 years posttransplant was 13.3 mL/min per 1.73 m^2 less than mean eGFR at 1 year posttransplant (39.3 mL/min per 1.73 m^2 vs 52.7 mL/min per 1.73 m^2, respectively; $P < 0.0001$ [paired t test]).

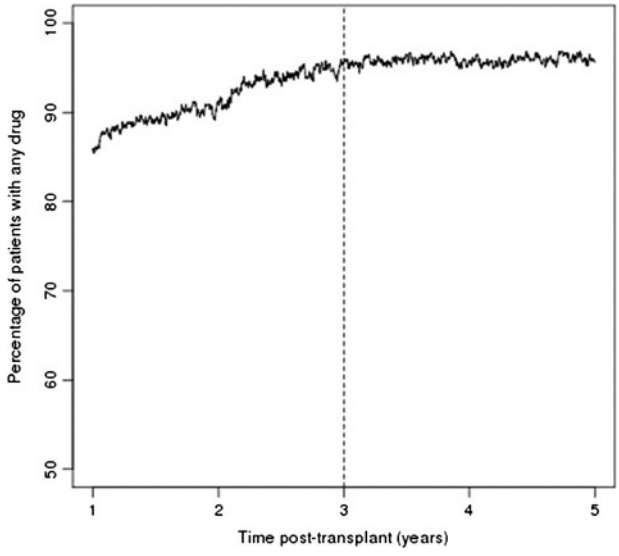

FIGURE 2. Distribution of overall nonadherence over time after kidney transplant.

DISCUSSION

Our study is the first to examine: 1) whether nonadherence changes 3 years after kidney transplant when Medicare coverage of immunosuppression ends and 2) the relationship between nonadherence during years 3 to 5 and allograft histology. Among patients who used the Mayo Clinic Specialty Pharmacy for the first 5 years posttransplant, we found that overall adherence increased during years 3 to 5 compared with years 1 to 3 after kidney transplant. In addition, we found that overall nonadherence during posttransplant years 3 to 5 was associated with fibrosis and inflammation on 5-year allograft biopsy, but not with transplant glomerulopathy. After adjusting for nonadherence to other immunosuppressive therapy, only

TABLE 3.

Five-year allograft histology according to overall adherence during posttransplant years 3 to 5

5-y Histology	3- to 5-y Overall adherent (n = 305)	3- to 5-y Overall nonadherent (n = 77)	*P*[a]
Normal	0 (0%)	0 (0%)	n/a
Mild interstitial fibrosis	112 (36.7%)	29 (37.7%)	0.88
Moderate/severe interstitial fibrosis	28 (9.2%)	8 (10.4%)	0.75
Fibrosis and inflammation	18 (5.9%)	13 (16.9%)	0.004
Transplant glomerulopathy	26 (8.5%)	8 (10.4%)	0.61

[a]χ^2 comparing the proportion of histologic findings in patients with 3- to 5-year overall adherence vs nonadherence.

n/a, not applicable.

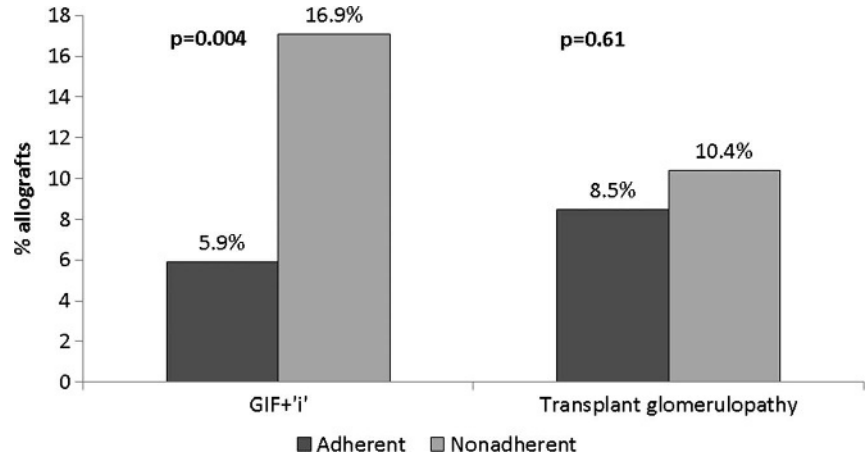

FIGURE 3. Relationship between overall adherence to immunosuppression 3 to 5 years after kidney transplant and 5-year allograft histology.

3- to 5-year nonadherence to AZA/MMF remained significantly associated with fibrosis and inflammation.

Our study had several surprising findings. The first is that adherence increased between posttransplant years 1 to 3 and 3 to 5, despite loss of Medicare coverage at year 3 in patients younger than 65 years. The few studies that have examined long-term adherence after kidney transplant suggest that adherence declines over time.[20,21] The increasing adherence over time seen in our cohort may reflect the benefits of using a specialty pharmacy for immunosuppression. Transplant specialty pharmacies have been associated with higher rates of adherence after kidney transplant.[22] In addition, patients at our center receive education about the loss of Medicare coverage 3 years after transplant and may proactively take steps to find alternative sources of coverage before the transition. A second intriguing finding in our study was that nonadherence to particular immunosuppressive medications during posttransplant years 3-5 appeared to be associated with graft fibrosis and inflammation on 5-year surveillance biopsies. After adjusting for nonadherence to calcineurin inhibitor and prednisone therapy, only 3-5 year nonadherence to antimetabolite therapy remained significantly associated with fibrosis and inflammation. Mycophenolate has proven to be a powerful deterrent to rejection after kidney transplant and dose reduction has been associated with allograft failure.[23-25] Our findings suggest that patients with fibrosis and inflammation on allograft biopsy should be questioned regarding nonadherence, especially nonadherence with antimetabolite therapy.

A third surprising finding of our study is that nonadherence to immunosuppressive medications during posttransplant years 3 to 5 was not associated with transplant glomerulopathy on 5-year surveillance biopsies. Nonadherence is a well-documented risk factor for the development of de novo DSA which in turn contributes to chronic antibody mediated injury.[26] However, it is possible we did not see a relationship between nonadherence and transplant glomerulopathy because the prevalence of transplant glomerulopathy may peak later than 5 years posttransplant and longer follow-up time is needed.[27]

Strengths of our study include the relatively large cohort of patients with refill records available during the first 5 years posttransplant, in addition to 5-year surveillance biopsies. Limitations include the single-center design, the retrospective nature of the study, the lack of insurance information and the fact that only a subset of our patients used the Mayo Clinic

TABLE 4.

Variables associated with fibrosis and inflammation on 5-year allograft biopsy (n = 382)

	Univariate model		Multivariate model	
	OR (CI)	*P*	OR (CI)	*P*
Recipient age (per 10-y increase)	0.80 (0.61-1.04)	0.10		
Donor age (per 10-y increase)	1.07 (0.81-1.42)	0.65		
HLA mismatch[a]	1.05 (0.86-1.29)	0.64		
Pretransplant class I DSA[b]	1.06 (0.30-2.96)	0.91		
Pretransplant class II DSA[b]	0.92 (0.30-2.37)	0.87		
Delayed graft function	0.98 (0.15-3.56)	0.98		
Thymoglobulin induction	1.61 (0.68-4.45)	0.29		
Sirolimus-based maintenance immunosuppression	<0.1 (<0.1-1.96)	0.15		
CSA-based maintenance immunosuppression	12.9 (2.90-57.14)	0.002	12.97 (2.51-68.01)	0.003
Prednisone-free maintenance immunosuppression	<0.1 (<0.1-0.66)	0.02	<0.1 (<0.1-0.72)	0.02
Time since transplant (per month)	0.98 (0.97-0.99)	0.009	0.98 (0.97-0.99)	0.01
History of acute rejection	4.33 (1.97-9.36)	0.0004	2.78 (1.16-6.44)	0.02
History of BK nephropathy	2.74 (0.75-7.99)	0.12		
3- to 5-y Overall nonadherence	3.24 (1.48-6.91)	0.004	2.60 (1.10-6.00)	0.03

Specialty Pharmacy for the first 5 years posttransplant. For example, our finding that patients taking sirolimus-based immunosuppression were more likely to be nonadherent may be confounded by the fact that only 18 patients were on sirolimus-based therapy. Another limitation of our analyses is the use of medication refill records to estimate adherence. Refill records are an imperfect estimate of adherence and may be erroneously affected by medication dose adjustment, the use of multiple pharmacies, and patient hospitalizations which contribute to fewer refills. Unfortunately, we lacked information about all of these variables in this study. However, measuring long-term adherence is a challenging issue and using refill records in a closed pharmacy system is a promising solution which is often more feasible and less expensive than direct monitoring of medication use or patient self-report. When using medication refills to estimate adherence, calculating the PDC is often the preferred method because it does not overestimate adherence, unlike another commonly used calculation called the medication possession ratio.[28-31] Lastly, we would ideally have had data on the incidence of de novo DSA, but before 2006, we did not routinely monitor for de novo DSA. In light of these limitations, results of our study should be interpreted with caution. The findings of our study may not generalize to other patient populations and need to be confirmed in future, multicenter studies. However, they pave the way for future studies of the important and understudied topic of long-term adherence to immunosuppressive therapy.

In conclusion, we found that adherence to immunosuppression does not decline after loss of Medicare coverage 3 years posttransplant, but rather increases in patients who use a specialty pharmacy. Nonadherence to immunosuppression during posttransplant years 3 to 5 appears to be associated with fibrosis and inflammation but not with transplant glomerulopathy on 5-year surveillance biopsies. Efforts to improve late medication nonadherence, especially with antimetabolite therapy, may improve long-term allograft histology and survival, but additional studies are need to replicate our findings.

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