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Depression and Immunosuppressive Therapy Adherence Following Renal Transplantation in Military Healthcare System Beneficiaries

To the Editor: Kidney transplantation improves survival and quality of life for patients with end-stage renal disease. Lifelong immunosuppressive therapy (IST) is required for kidney transplant (graft) survival, at an average cost of >$20,000 per year.[1] More than 10% of graft failure cases are attributed to IST nonadherence.[1] Under current US policy, Medicare IST coverage is limited to 3 years after transplantation for nondisabled recipients <65 years of age. Transplant survival rates in the United States are lower than those in developed nations that provide lifelong government-funded IST.[2] Patients with lifelong Medicare coverage have substantially better >3-year outcomes than those whose Medicare is limited to 3 years after transplantation,[2] and 51% of surveyed adult US transplant centers reported deaths or graft failures due to cost-related IST nonadherence.[3] Advocates for legislation to increase the duration of Medicare IST coverage contend that this would likely improve IST adherence.[1,2] However, IST adherence has not been reported in a cohort of US transplant recipients who receive lifelong IST at no out-of-pocket cost. We studied IST adherence rates in adult US Military Healthcare System beneficiaries, who receive free lifelong IST after transplantation.

This study was approved by Walter Reed National Military Medical Center's institutional review board. Informed consent was obtained from adult (≥18 years of age) kidney transplant recipients seen in the Walter Reed National Military Medical Center nephrology or organ transplant clinics. Demographic and clinical characteristics were ascertained by an electronic medical record review. Patients were recruited consecutively and were administered the Immunosuppressive Therapy Adherence Scale (ITAS) and Beck Depression Inventory-II (BDI-II). The ITAS is a questionnaire that consists of 4 questions measuring IST nonadherence, each scored by percentage of nonadherence (0 points for >50% of the time, 1 point for 21%–50% of the time, 2 points for 1%–20% of the time, 3 points for 0% of the time).[4] ITAS scores range from 0 (score of 0 for each question) to 12 (score of 3 for each of the 4 questions). Subjects with ITAS scores of 12/12 were considered to have perfect adherence,[5] and were compared with subjects with ITAS scores of ≤11/12. The BDI-II is a self-report instrument that contains 21 items. BDI-II scores range from 0 to 63, with higher scores indicating the presence and severity of depressed mood.[6]

Univariate analyses were performed with χ^2 testing for categorical variables (Fisher exact test used for violations of Cochran's assumptions) and Student's *t*-test for continuous variables. To assess whether the BDI-II score is independently associated with the likelihood of perfect versus not perfect adherence, we performed exact logistic regression, adjusting for date of transplant, sex, race, and age (STATA 13 SE; StataCorp, College Station, TX).

Of 40 enrolled subjects, 39 (98%) completed the ITAS. A total of 37 (95%) subjects reported ITAS scores of ≥10, with 27 subjects (69%) reporting perfect adherence. Demographic, socioeconomic, and clinical data for subjects with perfect and not perfect adherence are listed in Table 1. There were no statistically significant demographic or socioeconomic differences between the 2 groups. Donor-specific antibody was positive in 3 of 24 (13%) tested subjects with perfect adherence, compared with 6 of 9 (67%) with not perfect adherence, a significant difference ($P = 0.005$) (Figure 1). There were otherwise no significant differences in clinical indicators between the 2 groups. Perfectly adherent subjects had significantly lower mean BDI-II scores (6.7 ± 7.2 vs. 13.6 ± 8.8; $P = 0.01$), and on exact multivariable logistic regression, a 5-point BDI-II score increase was associated with a significantly lower likelihood of perfect adherence (adjusted odds ratio, 0.61; 95% confidence interval, 0.32–0.98).

To our knowledge, this is the first report of IST adherence in US transplant recipients who receive lifelong IST at no cost, regardless of time since transplant, age, or disability status. Subjects in our study reported high levels of adherence, irrespective of demographic or socioeconomic factors, in contrast to prior studies where non-white race[7,8] and low income[8] were associated with nonadherence. Less adherent subjects had higher BDI scores, and modest increases in BDI score associated significantly with a lower likelihood of perfect adherence. Subjects with less than perfect adherence on the ITAS were

Table 1. Demographic and clinical characteristics of study subjects, and ITAS and BDI-II results

Variables	Perfect adherence (ITAS 12/12) (n = 27)	Not perfect adherence (ITAS ≤ 11/12) (n = 12)	*P*-value
Age at the time of study (yr)	51 ± 16	56 ± 12	0.3
Gender, n (%)			
Male	18 (67)	4 (33)	0.08
Female	9 (33)	8 (67)	
Race, n (%)			0.8
White	13 (48)	4 (33)	
Black	9 (33)	5 (42)	
Asian	3 (11)	3 (25)	
Hispanic	2 (7)	0	
Age (yr) at transplant	49.81 ± 14.16	51.58 ± 11.20	0.7
Time since transplant, n (%)			
<3 yr	18 (67)	5 (42)	0.2
>3 yr	9 (3)	7 (58)	
History of prior transplant, n (%)			
Yes	4 (15)	0 (0)	0.3
No	23 (85)	12 (100)	
Type of transplant, n (%)			
Deceased donor	18 (67)	11 (92)	0.1
Living donor	9 (33)	1 (8)	
Prior history of rejection, n (%)			
Yes	2 (7)	4 (33)	0.06
No	25 (93)	8 (67)	
Donor-specific antibody at the time of survey			
Positive	3 (11)	6 (50)	0.005
Negative	21 (78)	3 (25)	
Unknown	3 (11)	3 (25)	
Serum Cr at the time of survey (mg/dl)	1.90 ± 1.51	1.43 ± 0.42	0.1
Spot urine protein/Cr ratio at the time of survey	0.65 ± 1.60	0.53 ± 0.76	0.8
Education level, n (%)			
≥College degree	13 (48)	5 (42)	0.7
<College degree	12 (45)	6 (50)	
Unknown	2 (7)	1 (8)	
Marital status, n (%)			
Married	20 (74)	8 (67)	0.7
Unmarried	7 (26)	4 (33)	
Annual household income, n (%)			
>$75,000	14 (52)	7 (58)	0.9
≤$75,000	9 (33)	4 (33)	
Unreported	4 (15)	1 (8)	
ITAS score	12 ± 0.00	10.42 ± 1.00	<0.001
BDI-II score	6.7 ± 7.17	13.58 ± 8.76	0.01

Data are n (%) or mean ± SD.
BDI-II, Beck Depression Inventory-II; ITAS, Immunosuppressive Therapy Adherence Scale.

significantly more likely to have positive donor-specific antibody, emphasizing the clinical relevance of modest degrees of nonadherence. Limitations to our study include the small sample size and cross-sectional design. An alternative explanation for the association between depression and nonadherence is that the use of self-reporting to quantify adherence

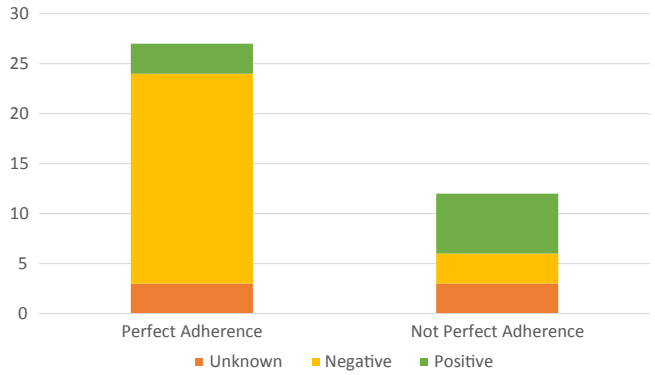

Figure 1. Results of donor-specific antibody testing in subjects with and without perfect adherence.

may have led to a positive response bias whereby subjects overestimated their IST adherence, which may have been present to a lesser degree in patients with depressed mood. Therefore, the inverse association between the BDI score and self-reported adherence should be interpreted with caution. Strengths include detailed characterization of the cohort's broad demographic, socioeconomic, and clinical characteristics. Our results support the provision of a large, prospective, controlled study to investigate the effect of providing long-term IST at no cost to US renal transplant recipients, and highlight the importance of identifying and treating depression after kidney transplantation.

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DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Tanriover B, Stone PW, Mohan S, et al. Future of Medicare immunosuppressive drug coverage for kidney transplant recipients in the United States. *Clin J Am Soc Nephrol*. 2013;8:1258–1266.
2. Gill JS, Tonelli M. Penny wise, pound foolish? Coverage limits on immunosuppression after kidney transplantation. *N Engl J Med*. 2012;366:586–589.
3. Evans RW, Applegate WH, Briscoe DM, et al. Cost-related immunosuppression nonadherence in among kidney transplant recipients. *Clin J Am Soc Nephrol*. 2010;5:2323–2328.
4. Chisholm MA, Lance CE, Williamson GM, Mulloy LL. Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Educ Couns*. 2005;59:13–20.
5. Cukor D, Rosenthal DS, Jindal RM, et al. Depression is an important contributor to low medication adherence in hemodialyzed patients and transplant recipients. *Kidney Int*. 2009;75:1223–1229.
6. Beck AT, Steer RA, Brown GK. *BDI-II: Beck Depression Inventory Manual*. 2nd ed. San Antonia, TX: Psychological Corporation; 1996.
7. Pinsky BW, Takemoto SK, Lentine KL, et al. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009;9:2597–2606.
8. Dew MD, DiMartini AF, De Vito Dabbs A, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation*. 2007;83:858–873.

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