Posttransplantation Anemia at 12 Months in Kidney Recipients Treated with Mycophenolate Mofetil: Risk Factors and Implications for Mortality

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Although posttransplantation anemia (PTA) is common in the mycophenolate mofetil era, its impact on patient survival is unknown. This retrospective cohort study characterized factors that are associated with PTA 12 mo after transplantation in mycophenolate mofetil–treated kidney recipients and explored whether 12-mo PTA affects outcomes. The records of 626 kidney recipients were examined for presence of anemia (hemoglobin <12 g/dl). Multivariate regression models, fit with covariates that had unadjusted relationships, investigated both risk factors for 12-mo PTA and whether 12-mo PTA contributes to mortality. Anemia prevalence was 72, 40, and 20.3% at 1, 3, and 12 mo, respectively. By multivariate logistic regression, anemia at 3 mo (odds ratio [OR] 10.0; 95% confidence interval [CI] 5.3 to 17.1; $P = 0.0001$), donor age (OR 1.0; 95% CI 1.1 to 1.3; $P = 0.005$), and 3-mo creatinine (OR 2.0; 95% CI 1.2 to 3.3; $P = 0.044$) were associated with 12-mo PTA. The PTA cohort had inferior patient survival ($P = 0.02$, log rank) and a higher proportion of cardiovascular deaths (6.3 *versus* 2.2%; $P = 0.017$) than nonanemic patients. By Cox regression, 12-mo PTA (hazard ratio [HR] 3.0; 95% CI 1.3 to 6.7; $P = 0.009$), 12-mo creatinine (HR 1.3; 95% CI 1.1 to 1.4; $P = 0.008$), age at transplantation (HR 1.1; 95% CI 1.1 to 1.2; $P = 0.004$), and hepatitis C seropositivity (HR 2.8; 95% CI 1.1 to 7.0; $P = 0.03$) were associated with mortality. There was no interaction between 12-mo PTA and serum creatinine. In conclusion, 12-mo PTA is associated with an increased risk for patient death. The presence of anemia 3 mo after kidney transplantation is a major determinant of 12-mo PTA. PTA in kidney recipients therefore should be defined by its persistence or occurrence beyond the third posttransplantation month.

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Chronic anemia is observed commonly in patients with kidney dysfunction. In nontransplant patients with chronic kidney disease (CKD), anemia has been associated with many cardiovascular complications, including left ventricular hypertrophy, congestive heart failure, and coronary ischemia (1–5). More recently, anemia has been implicated as an important risk factor for the excessive cardiovascular mortality that occurs in patients with CKD (6,7).

Posttransplantation anemia (PTA) occurs frequently, with prevalence rates between 20 and 60% depending on the criteria used for defining anemia (8–14). PTA has not been defined uniformly in terms of time frame or hemoglobin level after transplantation. Some authors have suggested distinguishing early from late PTA, with the cutoff between the two periods being the 6-mo posttransplantation time point (10,15–18). Several risk factors have been associated with PTA, including chronic allograft dysfunction, antiproliferative immunosuppression (*e.g.*, mycophenolate mofetil [MMF], sirolimus), chronic iron deficiency, and renin-angiotensin system blocking therapies (angiotensin-converting enzyme inhibitors [ACEI] and angiotensin II type 1 receptor blockers [ARB]) (10,13,18,19). PTA has been associated with an increased risk for congestive heart failure and left ventricular hypertrophy in kidney recipients (20–22). Given the high frequency of PTA and that cardiovascular disease is the leading cause of death with a functioning renal allograft, persistent anemia may be an important contributor to mortality in this population. However, the impact of PTA on kidney recipient outcomes is not well studied and is sparsely reported. The aims of this single-center, retrospective study were to characterize the factors that are associated with anemia at 12 mo after kidney transplantation in patients who were on a *de novo* MMF-containing regimen and to determine whether anemia at 12 mo after transplantation affects long-term patient outcome.

Materials and Methods

Patients

We conducted a retrospective cohort study of consecutive *de novo* MMF-treated kidney recipients who received a transplant at the Hospital of University of Pennsylvania between 1996 and 2002. Overall, 998 patients received a transplant during the study period. We excluded recipients of multiorgan transplants, patients with primary nonfunction or graft survival <1 yr, patients who did not receive MMF as *de novo* therapy, and patients whose charts were incomplete or unavailable. All

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626 remaining study patients received from the time of transplantation maintenance therapy that comprised MMF and prednisone, combined with a calcineurin inhibitor (cyclosporine A [CsA] or tacrolimus).

Anemia Definition and Treatment

Anemia was defined as hemoglobin <12 g/dl. This definition was selected because it fulfilled criteria for anemia in both men and women with CKD, as defined by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (23–25). The presence or absence of anemia at 1, 3, 6, and 12 mo after transplantation was documented. Chronic PTA was defined as the presence of anemia at the 12th posttransplantation month for the following reasons: (*1*) Anemia occurs more often than not during the early postoperative period; (*2*) drug- and other transplant-related complications are most common in the first few postoperative months, when rectification of the complications frequently results in resolution of the anemia; and (*3*) anemia typically is corrected by months 2 to 8 after kidney transplantation (26,27). During the study period, a workup for anemia was not performed routinely, and neither iron supplementation nor recombinant human erythropoietin typically was implemented as therapy. Patients with hemoglobin levels <11 g/dl were considered to have severe anemia.

Immunosuppression

Maintenance immunosuppression consisted of CsA (Novartis Pharmaceuticals, East Hanover, NJ) or tacrolimus (Astellas Pharmaceuticals, Deerfield, IL). Target tacrolimus levels were as follows: (*1*) Weeks 0 to 12, 7 to 12 ng/ml; (*2*) weeks 12 to 24, 7 to 10 ng/ml; and (*3*) beyond 24 wk, 5 to 10 ng/ml. Target CsA levels were as follows: (*1*) weeks 0 to 12, 200 to 300 ng/ml; (*2*) weeks 12 to 24, 150 to 250 ng/ml; and (*3*) beyond 24 wk, 80 to 150 ng/ml. MMF (Cellcept; Hoffman-La Roche, Nutley, NJ) was administered at 1 to 2 g/d in divided doses, as tolerated, and adjusted to maintain white blood cell count above 4×10^6/L; the dosage was titrated downward for adverse drug reactions. Steroids initially were given as bolus methylprednisone 500 to 1000 mg intraoperatively. Prednisone was started postoperative days 1 to 2 and tapered according to center protocol to 5 mg/d by 60 to 90 d after transplantation. Induction therapy consisted of one of the following: Rabbit antithymocyte gammaglobulin (Thymoglobulin; Genzyme, Cambridge, MA), dosed at 1 to 1.5 mg/kg intravenously over 4 h, commencing intraoperatively prereperfusion and infused daily for 3 to 7 d; equine antithymocyte gammaglobulin (ATGAM; Pharmacia-Upjohn Pharmaceuticals, Kalamazoo, MI), administered intravenously at a dosage of 15 mg/kg per d over 4 h for 7 to 10 d; or anti-CD3 mAb (OKT3; Ortho Pharmaceuticals, Raritan Bay, NJ) given as a 5-mg intravenous push as initial dose, followed by 2.5 mg/d intravenously for 5 to 7 d.

Rejection Monitoring and Treatment

Acute rejection was suspected by unexplained serum creatinine elevation, in the presence of clinical findings (including decreasing urine output, weight gain, increasing BP, and allograft tenderness). Whenever possible, suspected acute rejection was confirmed by percutaneous renal transplant biopsy before initiation of antirejection treatment. Pulse methylprednisone (10 mg/kg) was used for mild acute rejection episodes; OKT3 and Thymoglobulin were reserved for more severe grades of or steroid-resistant rejection.

Antibiotic Prophylaxis

Single-strength trimethoprim-sulfamethoxazole, 1 tablet daily for the first 6 mo after transplantation, was given for *Pneumocystis carinii* prophylaxis. Cytomegalovirus prophylaxis for 1996 and 1997 consisted of 12 wk of acyclovir, 800 mg twice daily if serum creatinine was >3.5 mg/dl and 800 mg four times a day if serum creatinine was <3.5 mg/dl. Between January 1, 1998, and December 31, 2001, oral ganciclovir (Cytovene; Hoffman-La Roche) was administered for the first 12 wk after transplantation for D+/R−, D+/R+ and D−/R+ patients. D−/R− patients received acyclovir, titrated to serum creatinine as described above. After January 1, 2002, oral ganciclovir was given for 24 wk for D+/R− recipients. Ganciclovir dosing was consistently 1000 mg thrice daily for patients with serum creatinine <3.5 mg/dl and 500 mg twice daily for serum creatinine >3.5 mg/dl.

Data that were collected included recipient age, gender, race, and cause and duration of ESRD; the dialysis, hepatitis C, and diabetes status of patients before transplantation; and previous transplant history. Donor age and source (deceased *versus* living) were recorded. Posttransplantation data collected included type of antibody induction, immunosuppressive regimen during the first 12 mo, use of ACEI and ARB, and serial serum creatinine and hemoglobin levels. The outcomes graft loss and patient death also were ascertained. Cause of death was obtained, whenever possible, from either inpatient or outpatient records or from local physicians for patients who died.

Statistical Analyses

Descriptive patient variables were analyzed according to the presence or absence of PTA. Numeric variables are shown as means ± SEM unless otherwise specified. Normally distributed variables were analyzed by *t* test and ANOVA. Categorical values were analyzed by χ^2 tests and by Fischer exact test when an individual cell size was less than five. $P < 0.05$ was considered statistically significant. A multivariate binary logistic regression model was fit in a forward manner with the variables that had a significant unadjusted association ($P < 0.10$) with the development of PTA within the first posttransplantation year. Variables were retained in the model at $P \leq 0.05$ by the Wald test. A Kaplan-Meier analysis was performed to compare patient and graft survival in patients with and without PTA, and significance was assessed by the log-rank method. Finally, a Cox regression model was fit to investigate whether PTA was a risk factor for mortality in this cohort. In addition to PTA, this model incorporated baseline demographic variables (age, gender, and ethnicity) as well as other covariates that previously have been associated with mortality in this population (pretransplantation diabetes, ESRD duration, serum creatinine, previous transplant, and hepatitis C). Given that anemia could be a consequence of allograft dysfunction, we included in the model an interaction term 12-mo PTA*12-mo serum creatinine. In a separate Cox regression model, we explored whether PTA was a risk factor specifically for death as a result of cardiovascular disease, incorporating all of the covariates that were used in the previous model; eight patients for whom we could not determine the cause of death were excluded from this second analysis. Statistical analysis was done using SPSS 10 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics of Population

A total of 626 patients with functioning kidney allografts at 12 mo were included in this study. Median posttransplantation follow-up was 64.8 mo (range 12 to 90 mo). All patients received MMF from time of transplantation. The most frequently used calcineurin inhibitor was tacrolimus (83%). All patients remained on prednisone for the study period.

Anemia Prevalence

The prevalence of anemia declined throughout the first year after transplantation. The proportion of patients with hemoglobin levels <12 g/dl was 72% by the end of the first posttransplantation month, 40% at 3 mo, and 20.3% at 12 mo (Figure 1). Severe anemia was observed in 51, 19, and 8% of recipients at 1, 3, and 12 mo after transplantation, respectively. The 127 recipients with PTA at 12 mo after transplantation served as case patients, and the remaining 499 nonanemic patients served as the control cohort. Baseline characteristics of these two groups are compared in Table 1.

Patient Characteristics

Compared with nonanemic patients, the 12-mo PTA cohort were more frequently female (65 *versus* 46%; $P = 0.004$) and more likely to have received pretransplantation dialysis (87 *versus* 77%; $P = 0.02$) (Table 1). Kidney allografts in the PTA cohort more often were derived from deceased donors (69 *versus* 60%; $P = 0.042$) and of older age (47 ± 2 *versus* 41 ± 1; $P = 0.006$). There were no significant differences between groups with regard to recipient age, autosomal dominant polycystic kidney disease (ADPKD) as cause of CKD, acute rejection, previous kidney transplantation, or hepatitis C seropositivity. PTA at 12 mo after transplantation was observed less frequently in black than nonblack patients. Hypertension occurred almost invariably in both groups.

From a therapy standpoint, use of antibody induction, tacrolimus, ACEI, or ARB was not significantly different between the two cohorts. MMF was discontinued in 32% of patients with PTA *versus* 19% of the group who were not anemic after the first posttransplantation year ($P = 0.002$).

Pertinent laboratory characteristics of patients with PTA are reflected in Table 2. Compared with the nonanemic cohort, patients with 12-mo PTA were almost three times more likely to have had anemia at 3 mo (83 *versus* 28%; $P = 0.0001$). Hemoglobin levels were significantly lower and serum creatinine levels were significantly higher in the PTA cohort.

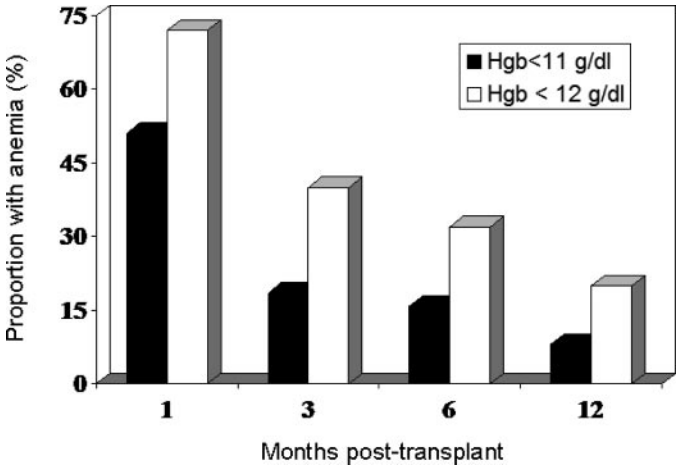

Figure 1. Frequency of posttransplantation anemia (PTA) in kidney transplant patients at 1, 3, 6, and 12 mo after kidney transplantation, defined according to a hemoglobin <11 g/dl (■) or <12 g/dl (□).

Multivariate Logistic Regression Model

We next fit a multivariate logistic regression model in a forward fashion with the following recipient covariates, all of which had unadjusted associations ($P < 0.10$) with the development of 12-mo PTA; male gender, black ethnicity, pretransplant dialysis requirement, ESRD duration, donor age, deceased donor source, acute rejection, anemia at 3 mo posttransplant, serum creatinine at 3 mo (Table 3). In this model, 3-mo serum creatinine (OR 2.0, CI 1.2 to 3.3, $P = 0.044$), donor age (OR 1.0, CI 1.1 to 1.3, $P = 0.005$) and the presence of anemia at 3-mo (OR 10.0, CI 5.3 to 17.1, $P = 0.0001$) were associated with 12-mo PTA. Interestingly, male gender was inversely associated with 12-mo PTA (OR 0.4, CI 0.2 to 0.6, $P = 0.001$).

Survival Analysis and Patient Outcomes

The impact of PTA at 12 mo after transplantation on overall patient and graft survival is shown in Figure 2. Compared with the nonanemic cohort, patients with 12-mo PTA had worse long-term patient and graft survival ($P < 0.02$ and $P < 0.0001$, respectively). Moreover, the graft and patient survival curves of the two cohorts started diverging soon after the first posttransplantation year. During the follow-up period, there were 37 deaths, 19 of which were due to cardiovascular disease. The proportion of cardiovascular deaths was greater in the 12-mo PTA group than in the nonanemic cohort (6.3 *versus* 2.2%; $P = 0.017$). Besides cardiovascular disease, other causes of mortality included infection ($n = 7$), cancer ($n = 1$), and suicide ($n = 2$). Cause of death could not be determined in eight patients.

Cox Regression Model

Finally, a Cox regression model was fit to examine risk factors for mortality among the patients with 12-mo PTA (Table 4). Besides PTA, we incorporated into this model all baseline demographic variables (age, gender, and ethnicity) as well as other covariates that previously have been associated with mortality in this population (pretransplantation diabetes, duration of ESRD, serum creatinine, previous transplant, and hepatitis C). Of these several factors, four variables remained significantly associated with death: 12-mo PTA (HR 3.0; 95% CI 1.3 to 6.7; $P = 0.009$), 12-mo serum creatinine (HR 1.3; 95% CI 1.1 to 1.4; $P = 0.008$), recipient age at transplantation (HR 1.1; 95% CI 1.1 to 1.2; $P = 0.004$), and seropositivity for hepatitis C virus (HR 2.8; 95% CI 1.1 to 7.0; $P = 0.03$). We further assessed for an interaction between 12-mo PTA and 12-mo serum creatinine, which was NS. In a separate analysis, another Cox regression model was fit to explore for risk factors for death specifically as a result of cardiovascular disease, incorporating the same covariates described in the above model. The eight patients for whom the cause of death could not be ascertained were excluded from this model. Twelve-month PTA (HR 3.0; 95% CI 1.1 to 8.0; $P = 0.04$) and recipient age (HR 1.1; 95% CI 1.0 to 1.1; $P = 0.007$) remained associated with cardiovascular mortality.

Table 1. Baseline patient characteristics according to presence or absence of PTA at 12 mo after transplantation[a]

Characteristic	PTA (n = 127)	No PTA (n = 499)	P
Female (%)	65	46	0.004
Age (yr)	45 ± 2	46 ± 1	0.555
Black ethnicity (%)	31	41	0.024
Pretransplantation dialysis (%)	87	77	0.020
ESRD duration (mo)	51 ± 9	36 ± 2	0.050
Previous transplant (%)	13	15	0.335
ADPKD (%)	8	17	0.054
Hypertension (%)	95	94	0.481
Donor age (year)	47 ± 2	41 ± 1	0.006
Deceased donor (%)	69	60	0.042
HCV+ (%)	11	8	0.281
Acute rejection (%)	19	13	0.068
Antibody induction (%)	75	74	0.846
Tacrolimus at transplantation (%)	84	87	0.867
MMF at transplantation (%)	100	100	1.000
Maintenance prednisone (%)	100	100	1.000
Use of ACEI/ARB (%)	46	40	0.236
Months after transplantation	59 ± 4	59 ± 1	0.972

[a]ACE, angiotensin-converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin II type 1 receptor blocker; HCV, hepatitis C virus; MMF, mycophenolate mofetil; PTA, posttransplantation anemia.

Table 2. Laboratory values of patients according to presence of PTA

Parameter	PTA (n = 127)	No PTA (n = 499)	P
PTA at 3 mo (%)	83	28	0.0001
Hemoglobin (g/dl)			
3 mo	10.5 ± 0.2	12.5 ± 0.7	0.001
12 mo	10.2 ± 0.2	13.7 ± 0.1	0.001
Serum creatinine (mg/dl)			
3 mo	1.8 ± 0.1	1.5 ± 0.1	0.001
12 mo	2.1 ± 0.2	1.5 ± 0.1	0.001

Discussion

In an MMF immunosuppression era, anemia remains a common kidney transplant complication. The presence of a hemoglobin <12 g/dl at 3 mo after kidney transplantation is a major risk factor for persistent anemia at the end of the first posttransplant year. Anemia at 12 mo after transplantation is independently associated with reduced patient survival.

In our study, almost 75% of kidney transplant recipients had hemoglobin <12 g/dl at the end of the first posttransplantation month. The prevalence of anemia declined to 43% by the third posttransplantation month and was 22% at the end of the first 12 mo. These declining frequencies of PTA over time during the first posttransplantation year are consistent with previously reported prevalence rates (8,12,14). Anemia is very common in the first posttransplantation month for several reasons, including low erythropoietin production that is common to patients with ESRD, erythropoietin resistance postoperatively in the setting of surgery and infectious complications, blood losses, and frequent phlebotomies early after transplant. Deficiencies of iron, B_{12}, folate, or other substrates for red blood cell production among transplant recipients and bone marrow suppression or other immunosuppressive complications further contribute to development of PTA (17). Whereas endogenous production of erythropoietin commonly begins within the first day after kidney transplantation, complete restoration of erythropoietin synthesis depends mostly on recovery of graft function (17). An exception to this occurs in patients with ADPKD, for whom higher endogenous erythropoietin levels and lower PTA rates have been reported (13). In accordance with this report, we have found that the prevalence of ADPKD was lower in the PTA cohort (8 *versus* 17% among nonanemic patients; P = 0.054).

We observed several risk factors for 12-mo PTA. The strongest predictor of this complication was anemia at 3 mo after

Table 3. Multivariate logistic regression of risk factors for PTA at 12 mo after transplantation[a]

Parameter	OR	95% CI	*P*
Black ethnicity (*versus* nonblack)	1.4	0.8 to 2.3	0.219
Pretransplantation dialysis (*versus* none)	1.7	0.8 to 3.4	0.149
Acute rejection (*versus* none)	1.3	0.6 to 2.7	0.431
ESRD duration (per month)	1.0	0.9 to 1.1	0.664
Deceased-donor kidney (*versus* living donor)	1.2	0.7 to 2.4	0.519
3-mo serum creatinine (per mg/dl)	2.0	1.2 to 3.3	0.044
Donor age (per year)	1.1	1.1 to 1.3	0.005
Male gender (*versus* female)	0.4	0.2 to 0.6	0.001
Anemia at 3 mo after transplantation (*versus* none)	10.0	5.3 to 17.1	0.0001

[a]CI, confidence interval; OR, odds ratio.

transplantation, present in 83% of individuals who ultimately developed PTA. We identified direct associations between 12-mo PTA and both older donor age and decreased levels of kidney function, as well as an inverse relationship with male gender, as previously reported (12,13,16). The significant association that was observed between 12-mo PTA and requirement for and duration of pretransplantation dialysis was not maintained after adjustment for potential confounders in the logistic regression model.

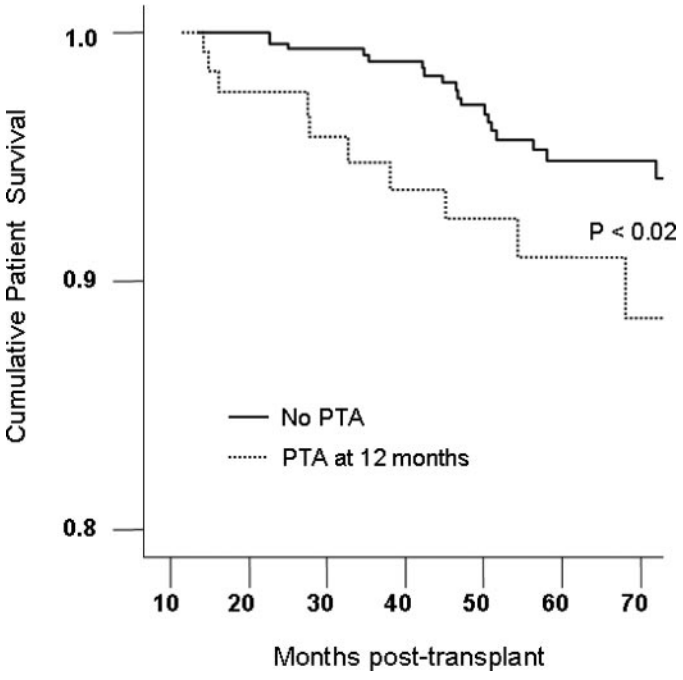

Figure 2. (A) Patient survival by Kaplan-Meier analysis, according to presence or absence of PTA at 12 mo after transplantation. Outcomes were conditioned on patient graft survival for at least 12 mo after kidney transplantation. Patients with (n = 127) and without (n = 499) PTA at 12 mo are depicted by the dotted and solid lines, respectively. (B) Graft survival by Kaplan-Meier analysis, according to presence or absence of PTA at 12 mo after transplantation. Outcomes were conditioned on patient graft survival for at least 12 mo after kidney transplantation. Patients with (n = 127) and without (n = 499) PTA at 12 mo are depicted by the dotted and solid lines, respectively.

MMF is the most widely used maintenance immunosuppressive agent in kidney transplantation (28). MMF may induce anemia by a direct myelosuppressive effect (29,30). The prevalence of PTA that we observed in MMF-treated patients is similar to what has been reported (8,13). Contrary to other studies, we did not find use of ACEI and ARB to be significantly associated with PTA (13). We believe that there are a few possible explanations for this discrepancy in our study. First, MMF, itself an established independent risk factor for PTA, was used in our entire cohort (*versus* 50% in the Transplant European Survey on Anemia Management [TRESAM]). Moreover, MMF was administered together with tacrolimus and prednisone in 85% of our cohort (*versus* 17% in the TRESAM) (13). We believe that uniform use of MMF in our patient population may have masked the potentially permissive effect of renin-angiotensin blockade on PTA. Second, the use of ACEI/ARB in our patient population (41% overall) was more widespread than in these other studies. Because patients in our center are only commenced on renin-angiotensin system blockers between 3 and 6 mo after transplantation, anemia already would have been present before initiation of this therapy in the vast majority of patients who ultimately developed PTA. It also is plausible that longer follow-up beyond 12 mo after transplantation (as was done in the TRESAM) may have revealed significant differences in use of renin-angiotensin system blockade between groups. Finally, whether the concomitant use with MMF of tacrolimus, which is associated with increased mycophenolic acid exposure relative to CsA, thereby could further augment the risk of anemia is not known.

Anemia has been linked to negative long-term outcomes in CKD. Most studies have focused on anemia in patients who are on dialysis. In the National Kidney Foundation K/DOQI clinical guidelines for anemia in CKD, anemia is recognized as being associated with increased cardiovascular morbidity, impaired cognitive abilities, and reduced quality of life in ESRD (23). In predialysis patients, anemia has been identified as an independent risk factor for progression to kidney failure (31). Treatment of anemia with erythropoietin has been found to slow the decline in kidney function (32). In our study, we found

Table 4. Cox regression analysis of risk factors for long-term mortality in patients with PTA[a]

Parameter	HR	95% CI	*P*
Acute rejection (*versus* none)	1.3	0.5 to 3.4	0.59
Duration ESRD (per year)	1.0	1.0 to 1.1	0.52
Weight at transplantation (per kg)	1.0	0.9 to 1.1	0.51
Black ethnicity (*versus* nonblack)	1.9	0.8 to 4.5	0.14
Previous transplant (*versus* none)	2.9	0.8 to 11.0	0.11
Diabetes pretransplantation (*versus* none)	2.4	0.9 to 6.9	0.09
HCV+ (*versus* HCV−)	2.8	1.1 to 7.0	0.03
PTA at 12 mo (*versus* none)	3.0	1.3 to 6.7	0.009
Creatinine at 12 mo (per mg/dl)	1.3	1.1 to 1.4	0.008
Age at transplantation (per year)	1.1	1.1 to 1.3	0.004

[a]HR, hazard ratio.

that graft and patient survival are markedly diminished in patients with PTA at 12 mo compared with nonanemic patients. Because our analysis focused primarily on the relationship between PTA and mortality, we did not investigate specifically the association between PTA and allograft failure in this article; however, we speculate that the inferior allograft outcomes that were observed in the PTA cohort in part reflect that allograft dysfunction itself is an important risk factor for anemia. Conversely, although anemia may be a surrogate for chronic disease severity and comorbidity, the persistent, independent effect of 12-mo PTA on mortality after adjustment in the Cox regression model is compelling evidence of its importance as a risk factor for patient outcome. The absence of a significant interaction between PTA and serum creatinine further strengthens this observation. Despite that the overall mortality in the study was low, death related to cardiovascular disease was observed more commonly in the 12-mo PTA patient cohort. The finding that cardiovascular disease was the leading cause of death in our patient population is entirely in keeping with all published studies in this regard. Because recombinant human erythropoietin was not used routinely in our patient cohort during this period of observation, it is unknown what impact this therapy might have had on patient outcomes. Certainly, recent studies have shown the efficacy and the safety of recombinant human erythropoietin in the correction of anemia in kidney recipients (32–36).

There are several limitations to our study. First, our data were collected retrospectively, as has typically been the case with studies on this subject. Unlike most previous studies, however, we examined PTA-related outcomes in a transplant population that was treated with a relatively homogeneous immunosuppressive regimen, which also is the most widely used regimen in the United States. Second, although our transplant program did not use recombinant human erythropoietin routinely during this study period, we cannot exclude the possibility that some patients may have received this therapy through prescription by their community nephrologists. However, the fact that kidney recipients typically are followed in our transplant program exclusively for the first 6 to 12 mo after transplantation largely mitigates against this possibility. Moreover, even in the event that a small proportion of patients were receiving recombinant human erythropoietin, the risk factors and implications of anemia that were identified in this study still are very relevant regardless of whether this hormonal treatment was administered. Third, we were unable to ascertain the cause of death in eight of the patients who died. However, we established that cardiovascular disease by far was the most common cause of mortality and that patients with 12-mo PTA had an increased risk for death in this manner. Although most of the traditional risk factors for cardiovascular disease were examined in this study, we lacked information regarding tobacco use or body mass index (although weight at the time of transplantation was captured). Fourth, in our center, we do not measure or estimate GFR or creatinine clearance for quantifying renal function in kidney recipients (37). However, we believe that these measurements are imprecise and not validated in this population, as supported by several recent publications (38–41). Last, we cannot exclude the contribution of residual confounding to our findings from unmeasured factors.

Conclusion

We have shown that PTA at 12 mo after transplantation is a common complication in kidney recipients who are on an MMF-containing regimen. Moreover, PTA is associated with an increased risk for subsequent graft loss and patient mortality. Our study shows a particularly strong association of anemia at 3 mo after transplantation with 12-mo PTA, with consequent adverse effects on patient and graft outcomes. We therefore conclude that PTA in kidney recipients should be defined by its persistence or occurrence beyond the third posttransplantation month. We further recommend that physicians who care for kidney recipients in the posttransplantation setting strongly consider investigating persistent anemia and commencing appropriate repletion of substrate deficiencies and recombinant human erythropoietin at this earlier time point. Prospective studies are urgently required to establish a uniform, consensus definition of PTA and to examine the timing and the effectiveness of interventional therapies on improving patient outcomes.

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References

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32[Suppl 3]: S112–S119, 1998
2. Alpert MA: Cardiac performance and morphology in end-stage renal disease. *Am J Med Sci* 325: 168–178, 2003
3. Muntner P, He J, Astor BC, Folsom AR, Coresh J: Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: Results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 16: 529–538, 2005
4. Philipp S, Ollmann H, Schink T, Dietz R, Luft FC, Willenbrock R: The impact of anaemia and kidney function in congestive heart failure and preserved systolic function. *Nephrol Dial Transplant* 20: 915–919, 2005
5. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, Sarnak MJ: Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J Am Soc Nephrol* 16: 1803–1810, 2005
6. Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, Levey AS, Sarnak MJ: Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: The impact of chronic kidney disease. *J Am Soc Nephrol* 16: 3403–3410, 2005
7. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 38: 955–962, 2001
8. Augustine JJ, Knauss TC, Schulak JA, Bodziak KA, Siegel C, Hricik DE: Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. *Am J Transplant* 4: 2001–2006, 2004
9. Mahmud SN, Aziz R, Ahmed E, Akhtar F, Zafar MN, Naqvi A, Rizvi A: Anemia characteristics after renal transplantation. *Transplant Proc* 34: 2428, 2002
10. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA: Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? *Am J Transplant* 2: 429–435, 2002
11. Winkelmayer WC, Kewalramani R, Rutstein M, Gabardi S, Vonvisger T, Chandraker A: Pharmacoepidemiology of anemia in kidney transplant recipients. *J Am Soc Nephrol* 15: 1347–1352, 2004
12. Mix TC, Kazmi W, Khan S, Ruthazer R, Rohrer R, Pereira BJ, Kausz AT: Anemia: A continuing problem following kidney transplantation. *Am J Transplant* 3: 1426–1433, 2003
13. Vanrenterghem Y, Ponticelli C, Morales JM, Abramowicz D, Baboolal K, Eklund B, Kliem V, Legendre C, Morais Sarmento AL, Vincenti F: Prevalence and management of anemia in renal transplant recipients: A European survey. *Am J Transplant* 3: 835–845, 2003
14. Mitsnefes MM, Subat-Dezulovic M, Khoury PR, Goebel J, Strife CF: Increasing incidence of post-kidney transplant anemia in children. *Am J Transplant* 5: 1713–1718, 2005
15. Hricik DE: Anemia after kidney transplantation: Is the incidence increasing? *Am J Transplant* 3: 771–772, 2003
16. Yorgin PD, Belson A, Sanchez J, Al Uzri AY, Sarwal M, Bloch DA, Oehlert J, Salvatierra O, Alexander SR: Unexpectedly high prevalence of posttransplant anemia in pediatric and young adult renal transplant recipients. *Am J Kidney Dis* 40: 1306–1318, 2002
17. Al-Uzri A, Yorgin PD, Kling PJ: Anemia in children after transplantation: Etiology and the effect of immunosuppressive therapy on erythropoiesis. *Pediatr Transplant* 7: 253–264, 2003
18. Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, Roth D, Scandling JD, Singer GG: Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. *J Am Soc Nephrol* 11[Suppl 15]: S1–S86, 2000
19. Gossmann J, Thurmann P, Bachmann T, Weller S, Kachel HG, Schoeppe W, Scheuermann EH: Mechanism of angiotensin converting enzyme inhibitor-related anemia in renal transplant recipients. *Kidney Int* 50: 973–978, 1996
20. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J: Congestive heart failure in renal transplant recipients: Risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol* 13: 1084–1090, 2002
21. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P: Electrocardiographic left ventricular hypertrophy in renal transplant recipients: Prognostic value and impact of blood pressure and anemia. *J Am Soc Nephrol* 14: 462–468, 2003
22. Ponticelli C, Villa M: Role of anaemia in cardiovascular mortality and morbidity in transplant patients. *Nephrol Dial Transplant* 17[Suppl 1]: 41–46, 2002
23. National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1–S266, 2002
24. Djamali A, Becker YT, Simmons WD, Johnson CA, Premasathian N, Becker BN: Increasing hematocrit reduces early posttransplant cardiovascular risk in diabetic transplant recipients. *Transplantation* 76: 816–820, 2003
25. National Kidney Foundation K/DOQI clinical practice guidelines for anemia of chronic kidney disease. *Am J Kidney Dis* 37: S182–S238, 2001
26. Kim HC, Park SB, Han SY, Whang EA: Anemia following renal transplantation. *Transplant Proc* 35: 302–303, 2003
27. Kahng K, Kang C, Kwak J: Changes in hemoglobin levels after renal transplantation. *Transplant Proc* 30: 3023–3024, 1998
28. Shapiro R, Young JB, Milford EL, Trotter JF, Bustami RT, Leichtman AB: Immunosuppression: Evolution in practice and trends, 1993–2003. *Am J Transplant* 5: 874–886, 2005
29. European Mycophenolate Mofetil Cooperative Study Group: Mycophenolate mofetil in renal transplantation: 3-year results from the placebo-controlled trial. *Transplantation* 68: 391–396, 1999
30. Arbeiter K, Greenbaum L, Balzar E, Muller T, Hofmeister F, Bidmon B, Aufricht C: Reproducible erythroid aplasia caused by mycophenolate mofetil. *Pediatr Nephrol* 14: 195–197, 2000
31. Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD: Anemia and end-stage renal disease in pa-

tients with type 2 diabetes and nephropathy. *Kidney Int* 66: 1131–1138, 2004
32. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC: Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial. *Kidney Int* 66: 753–760, 2004
33. Becker BN, Becker YT, Leverson GE, Heisey DM: Erythropoietin therapy may retard progression in chronic renal transplant dysfunction. *Nephrol Dial Transplant* 17: 1667–1673, 2002
34. El Haggan W, Vallet L, Hurault de Ligny B, Pujo M, Corne B, Lobbedez T, Levaltier B, Ryckelynck JP: Darbepoetin alfa in the treatment of anemia in renal transplant patients: A single-center report. *Transplantation* 77: 1914–1915, 2004
35. McDevitt LM, Smith LD, Somerville KT, Corbett JL, Shihab FS: A retrospective assessment of pre-treatment variables on the response to darbepoetin alfa after renal transplantation. *Am J Transplant* 5: 1948–1956, 2005
36. Ayus JC, Go AS, Valderrabano F, Verde E, de Vinuesa SG, Achinger SG, Lorenzo V, Arieff AI, Luno J: Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin <10 g/dL. *Kidney Int* 68: 788–795, 2005
37. Gill JS, Tonelli M, Mix CH, Pereira BJ: The change in allograft function among long-term kidney transplant recipients. *J Am Soc Nephrol* 14: 1636–1642, 2003
38. Poge U, Gerhardt T, Palmedo H, Klehr HU, Sauerbruch T, Woitas RP: MDRD equations for estimation of GFR in renal transplant recipients. *Am J Transplant* 5: 1306–1311, 2005
39. Raju DL, Grover VK, Shoker A: Limitations of glomerular filtration rate equations in the renal transplant patient. *Clin Transplant* 19: 259–268, 2005
40. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16: 459–466, 2005
41. Mariat C, Alamartine E, Afiani A, Thibaudin L, Laurent B, Berthoux P, De Filippis JP, Thibaudin D, Mayor B, Elessawy AB, Berthoux F: Predicting glomerular filtration rate in kidney transplantation: Are the K/DOQI guidelines applicable? *Am J Transplant* 5: 2698–2703, 2005

See the related editorial, "Anemia after Kidney Transplantation: Time for Action," on pages 2962–2963.