Posttransplantation Anemia: Mechanisms and Management

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Treatment of anemia in patients with chronic kidney disease (CKD), may be relevant to kidney transplant recipients because the majority of these recipients have an estimated GFR (eGFR) of <60 ml/min per 1.73 m² (1–3). In addition, anemia may lead to other adverse outcomes, such as impaired cognition, reduced quality of life, and decreased exercise capacity in patients with CKD and ESRD (4,5). Cardiovascular disease (CVD) remains the leading cause of death in kidney transplant patients, exceeding the cardiovascular mortality of age-matched control subjects in the general population (6,7). Furthermore, a few studies have shown that anemia is associated with higher mortality in kidney transplant recipients (8,9).

In the past 20 years, kidney transplantation has achieved excellent 1-year graft and patient survivals, mostly secondary to advances in immunosuppression. However, long-term graft survival has not improved in a similar way, thereby leading to a shift in emphasis toward minimizing the adverse effects of overimmunosuppression, including infection, malignancy, and cardiovascular risk factors. Consequently, posttransplantation anemia (PTA), which may be a marker or risk factor for CVD and chronic allograft nephropathy, has received increased attention in transplantation care and investigation. The purpose of this article is to review our most current understanding of the prevalence, pathogenesis, and management of PTA.

Prevalence

PTA is estimated to occur in 30% to 40% of patients. Prevalence estimates vary, however, because the definitions of anemia used are inconsistent, and average time since transplantation varied across study populations (10–12). Both the World Health Organization (WHO) and the American Society of Transplantation (AST) define anemia as hemoglobin <13 mg/dl for men and <12 mg/dl for women (13).

At the time of kidney transplantation, almost all patients have anemia secondary to reduced endogenous erythropoietin (EPO) synthesis and response and iron deficiency in patients with advanced CKD and as a consequence of customary treatment targets for these patients. Target hemoglobin and hematocrit levels are set forth in Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines updated in 2007 that reflect regulation by the Food and Drug Administration, fiscal policies driven by Centers for Medicare and Medicaid Service reimbursement, and clinical trial results (14). Immediately after transplantation, surgical blood loss, induction immunosuppression, frequent phlebotomy, and allograft dysfunction causing a persistent uremic state contribute to continued anemia (15). In patients with well-functioning allografts, anemia usually resolves by 3 to 6 months after transplantation (16). However, some patients have persistent anemia, and late PTA, defined as anemia occurring ≥6 to 12 months after transplantation, is common and understudied (11).

The TRanplant European Survey on Anemia Management (TRESAM) was a cross-sectional questionnaire-based analysis involving 72 centers and 4263 patients (12). Patients were categorized according to time since transplantation: 6 months, 1 year, 3 years, and 5 years. The authors reported the prevalence of anemia (defined by the WHO/AST criteria) at 38.6%, with 8.5% having severe anemia defined as hemoglobin ≤11 mg/dl in men and ≤10 mg/dl in women. As in most studies, impaired graft function was the risk factor most strongly associated with PTA. TRESAM
reported reduced transplant function, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), donor age, and recent infections as correlates of PTA. A recent European follow-up survey of 5834 patients from 10 outpatient transplant clinics using the WHO/AST definition of anemia found that 42% of kidney transplant recipients had anemia, with 11% receiving treatment with erythropoiesis-stimulating agents (ESAs) (17). In addition, that study showed substantial practice variations across centers in anemia management. Similar to previous studies, transplant function (eGFR) was the strongest correlate of anemia. Karthikeyan et al. (1) investigated the prevalence of CKD and its complications in 459 kidney transplant recipients who were at a large academic center in Ottawa and were at least 6 months after transplantation. Ninety percent of kidney transplant patients had stages 3 through 5 CKD according to K/DOQI guidelines (14) or evidence of kidney damage defined by hematuria, proteinuria, interstitial fibrosis, or recurrent or de novo kidney disease. The prevalence of anemia (defined as hemoglobin <11 g/dl) and EPO use significantly increased with CKD stage. Overall, only 27% of patients with anemia received EPO.

Late PTA is also common, especially in patients with impaired graft function. Mix et al. (16) studied 240 kidney transplant recipients who were followed at an academic medical center in Boston and reported that 76% of patients had hematocrit <36% at the time of transplantation and 21% and 36% at 1 and 4 years after transplantation, respectively. Another study with 128 patients, using the WHO/AST definition of anemia, reported the incidence of anemia as 26% at 5 years after transplantation (11). Again, transplant function was the most important correlate of anemia, and the number of patients with anemia doubled when patients who had received azathioprine were converted to mycophenolate mofetil (MMF) with otherwise unchanged immunosuppressive regimen. Patients who return to dialysis after transplant failure are a unique group to consider, given the effects of continuing immunosuppression and ongoing inflammation from chronic rejection. Gill et al. (18) reported a high prevalence of anemia in transplant patients who returned to dialysis, who had a mean hematocrit of 27.5%, similar to a general incident dialysis population. Therefore, all studies indicated that anemia is common in kidney transplant recipients, especially late after transplantation and in the setting of impaired graft function. Moreover, all studies seemed to indicate that the use of ESAs in kidney transplant recipients is low.

Pathogenesis

Mechanisms that lead to anemia after kidney transplantation are not completely understood. PTA is likely a multifactorial process, and the identification of the underlying cause is important in selecting the appropriate therapy. We review some of the more common causes (Table 1).

**EPO and Iron Deficiency**

With normalization of kidney function after transplantation, the excretory and endocrine functions should normalize, including EPO production by the transplanted kidney. Sun et al. (15) studied 31 consecutive recipients of a kidney transplant (29 from a deceased and two from a living donor) and reported that EPO production occurs quickly and exhibits a short-lived peak within a few days of transplantation. Naturally, this peak is insufficient to generate a meaningful increase in hemoglobin concentrations. A second and smaller but more sustained peak occurs after 28 days, which then translates into more significant erythropoiesis (15). However, delayed graft function or chronic allograft dysfunction may cause damage or dysregulation of EPO-producing peritubular interstitial

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cells, resulting in diminished endocrine capacity of the kidney transplant and decreased EPO production. In addition, iron deficiency, hyperparathyroidism, inflammation, immunosuppression, and infections all may contribute to EPO resistance (16).

In the setting of rapid erythropoiesis early after transplantation (15), functional or absolute iron deficiency inevitably occurs, especially when there is also surgical blood loss and residual uremic milieu. Observational studies indicated that iron status is often not included in the assessment of PTA (12,16). In addition, an accurate assessment of iron deficiency is limited by the currently used assays, which are often unreliable in the posttransplantation setting. Ferritin, an acute-phase reactant, is frequently elevated after transplantation as a result of inflammation, infection, increased iron absorption, or rejection (10,19). Furthermore, we do not have a good definition of what constitutes adequate iron status in the transplant population. Lorenz et al. (10) found that ferritin and transferrin saturations were poor markers of functional iron deficiency: Only 10.1% of patients with severe anemia had ferritin <12 μg/ml, and only 29% had transferrin saturation <15%. However, the majority of patients with anemia had a high proportion of hypochromic red blood cells (RBCs), which may be a better marker of functional iron deficiency.

Conversely, some studies have reported a high incidence of iron deficiency in kidney transplant patients using fer- ritin and transferrin saturation. Karthikeyan et al. (1) found ferritin levels <100 ng/ml in 50% of kidney transplant patients whose transplant function corresponded with stages 3 through 5 CKD and transferrin saturation <20% in 75% of patients with stage 5 CKD. Zheng et al. (20) followed 39 consecutive kidney transplant recipients during the first 12 weeks after transplantation, quantified the amount of blood loss, and estimated iron losses. In that single-center study, the prevalence of anemia was 67% (defined by WHO/AST criteria), with 44% having iron deficiency. With baseline hemoglobin of 11.8 g/dl, the authors estimated that iron-deficient patients would need an additional 330 mg of iron to normalize hemoglobin to 13 g/dl and 605 mg to achieve hemoglobin of 14 g/dl. Collectively, these studies show that iron deficiency is an important and underdiagnosed contributor to PTA, although further studies need to identify the optimal diagnostic tests to define iron deficiency.

**Medications**

Immunosuppressive medications contribute to early and late PTA. The anti-metabolite medications, including azathioprine, MMF, and mycophenolic acid, cause anemia via bone marrow suppression (8,12,21,22). A recent study investigated whether genetic factors could predict the development of mycophenolate-associated anemia (23). In this multicenter study of 978 kidney transplant recipients, 87 (9.5%) developed anemia. Three single-nucleotide polymorphism genes, IL-12A (IL12A), checkpoint homolog protein (HUIS), and cytochrome P4502C8 (CYP2C8), were associated with time to anemia. The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus also cause anemia via myelosuppression in addition to other unique mechanisms in a dosage-dependent manner, which is often more severe than that observed with MMF (24,25). Unique to mTOR inhibitors, the anemia of mTOR inhibitors is characterized by microcytosis (26). The mechanism is hypothesized to involve decreased proliferation of erythroid precursors or interference in iron homeostasis (27,28). Furthermore, the combination of sirolimus and MMF is associated with more severe anemia, likely secondary to synergistic mechanisms (29). Although calcineurin inhibitors (CNIs) do not typically cause marrow suppression, Winkelmayr et al. (22) reported an association between tacrolimus use and anemia. The mechanism may involve the vasoconstrictive properties of CNIs that impair renal function and, subsequently, EPO production. The CNIs cyclosporine and tacrolimus and, less frequently, the mTOR inhibitors can also cause thrombotic microangiopathy (30,31). The lymphocyte-depleting agents antithymocyte globulin and muromonab-CD3 (OKT3) suppress the bone marrow and lead to anemia early after transplantation. Conversely, corticosteroids can enhance proliferation of erythroid cells (32) and sustain the formation of murine erythroid colonies in vitro (33).

Other medications that cause anemia are inhibitors of the renin-angiotensin-aldosterone system that are increasingly used in transplant recipients for their antihypertensive and renoprotective properties. Both ACEIs and ARBs cause anemia, which is exploited in the treatment for posttransplantation erythrocytosis (12,22). The mechanism is thought to involve inhibition of erythropoiesis in a dosagerelated manner. Prophylactic antimicrobial agents, including ganciclovir, valganciclovir, dapsone, and trimethoprim-sulfamethoxazole, can cause myelosuppression and anemia. Glucose 6-phosphate dehydrogenase is an essential enzyme for normal RBC life span and oxidizing processes, and in its absence, dapsone and, less commonly, trimethoprim-sulfamethoxazole, can lead to sudden destruction of RBCs and hemolytic anemia (16,34). Ganciclovir and valganciclovir induce bone marrow suppression in 8% to 25% of solid-organ transplant patients (35).

**Infections**

Viruses, including parvovirus B19, hepatitis B, hepatitis C, herpetoviruses, cytomegalovirus, Epstein-Barr virus (EBV), HIV, and, rarely, BK virus, cause aplastic anemia (36). The molecular mechanism whereby parvovirus B19 causes anemia is known: the virus replicates in proliferating and differentiating erythroid precursors and causes RBC aplasia by inducing RBC precursor apoptosis (37,38). The virus binds to the erythrocyte P-antigen, its cellular membrane ligand, and causes apoptosis of erythrocye progenitors via the NS1–caspase pathway with a subsequent arrest in erythropoiesis (37,39). Because parvovirus B19 antibodies are prevalent in the normal population, diagnosis is made using parvovirus-PCR DNA detection. Treatments include reducing immunosuppression and intravenous Ig. Similarly, EBV is thought to infect bone marrow progenitor cells and may lead to aplastic anemia (40). The EBV genome and antigens were reported in patients with aplastic anemia (40). Cytomegalovirus, conversely, is thought to infect bone marrow stromal cells (41). Other indolent infections, including bacterial, fungal, viral,
tuberculosis, and parasitic causes, can lead to anemia of chronic disease secondary to impaired erythropoiesis (42).

**Allograft Function and Rejection Episodes**

Most studies showed that allograft function strongly correlates with anemia. TRESAM showed that creatinine clearance <50 ml/min and serum creatinine >2 mg/dl correlated with anemia (12). In addition, transplant recipients who experienced rejection episodes or received more than one transplant have been reported to have a higher incidence of anemia (12). The underlying factors causing anemia in the setting of rejection may include suboptimal kidney function, more intensified immunosuppression, acute inflammation, or perhaps a chronic inflammatory state leading to EPO resistance. Acute rejection can lead to a rapid decrease in EPO levels that is reversible on treatment of rejection (43). Molecular studies have shown that inflammatory genes are upregulated in deceased-donor kidney biopsies in patients with PTA (44). In pediatric patients with anemia and concurrent rejection, genes involved in both hemoglobin transcription and synthesis as well as iron and folate binding and transport were downregulated in the peripheral blood (45). Furthermore, compared with patients without anemia, kidney transplant patients with anemia have higher levels of hepcidin, a peptide hormone produced in the liver in response to anemia, hypoxia, or inflammation (46,47). Investigators have found that hepcidin levels correlated with kidney transplant function, ferritin, and inflammatory markers (47). However, elevated hepcidin levels in kidney transplant patients likely represent inflammation and impaired kidney function rather than a pathogenic role (46,47).

**Donor and Recipient Factors**

Recipients of kidneys from older donors (especially older than 60 years), older recipients, and women, possibly secondary to iron deficiency from menses and androgen deficiency, were more likely to have anemia (12,16). Despite the trend toward both older donors and recipients in the past decade, a recent European study showed that the prevalence of anemia has remained unchanged (17).

**Immune-Related Causes**

Immune-mediated hemolysis caused by the production of donor-derived antibodies against the recipient’s RBCs, known as the passenger lymphocyte syndrome, is a rare cause of anemia in kidney transplant recipients (48). Rarely, antithymocyte globulin, CNIs, or intravenous Ig preparations can lead to immune-mediated hemolysis (49). Posttransplantation lymphoproliferative disorder and other hematologic malignancies are associated with bone marrow infiltration and immune hemolytic anemia (50).

**Approach to Diagnosis**

Transplant providers should screen all kidney transplant patients regularly for anemia as per the routine laboratory schedule for allograft function (51). The diagnostic evaluation of kidney transplant recipients with anemia should include both causes of anemia in the general population and more specific causes unique to the transplant population. The initial evaluation includes iron studies (ferritin, iron, and transferrin saturation), RBC indices, reticulocyte count, and occult blood for stool. Low reticulocyte count indicates possible infection with parvovirus B19 or aplastic anemia secondary to anti-EPO antibodies. If hemolytic anemia is suspected, then bilirubin, haptoglobin, and lactic dehydrogenase should be measured and direct and indirect Coombs tests should be performed. A peripheral blood smear with schistocytes indicates microangiopathic hemolytic anemia. Other tests, such as vitamin B12, folate levels, or hemoglobin electrophoresis, can be ordered on a case-by-case basis depending on the clinical history and physical examination.

**Consequences of PTA**

It remains controversial whether we can extrapolate the adverse effects of anemia in patients with CKD and ESRD to the kidney transplant population. Some studies have shown that PTA is a risk factor for cardiovascular events including congestive heart failure and left ventricular hypertrophy, as well as mortality and graft failure (8,9,52,53). In a single-center, prospective study of 938 kidney transplant patients, Molnar et al. (9) reported that anemia (defined by WHO/AST criteria) was significantly associated with mortality (hazard ratio 1.69; 95% confidence interval 1.15 to 2.50) and graft failure (hazard ratio 2.56; 95% confidence interval 1.48 to 4.10). In a retrospective study of 404 kidney transplant recipients with type 1 diabetes, Djamali et al. (54) reported that increasing hematocrit levels >30% was associated with a significant cardiovascular event risk reduction compared with a reference hematocrit of 30%. Another single-center, retrospective study of 626 kidney transplant recipients reported an association between 12-month PTA defined as hemoglobin <12 g/dl and an increased risk for patient death and CVD (8).

The relationship between anemia and adverse outcomes has not been supported in other analyses (55,56). In a prospective, single-center study, Winkelmayer et al. (56) followed 438 kidney transplant recipients for 7.8 years and examined all-cause mortality and allograft loss. A high percentage of hypochromic RBCs (possibly indicating functional iron deficiency) was associated with increased mortality, although anemia, defined as hemoglobin <10 g/dl, was associated with neither mortality nor graft loss. In a larger study with two cohorts and 825 transplant patients, Winkelmayer et al. (55) showed in multivariate analysis that anemia was not related to all-cause mortality but was associated with a 25% risk for allograft loss. Therefore, there is not a clear consensus that anemia is associated with increased mortality and adverse cardiovascular events. From these data, we cannot conclude that anemia directly causes adverse outcomes but may rather be a marker for an underlying pathologic process.

**Treatment**

Although anemia is common in kidney transplant recipients, only a minority of those who have anemia are treated with ESAs, even among those with severe anemia. The potential reasons for this may include concerns about the lack of convincing evidence on the benefits and risks of therapy, as well as cost and inadequate insurance coverage. In TRESAM, ESA therapy was used in 5.2% over-
all and in 17.8% of patients with severe anemia (12). In addition, patients with PTA are often not evaluated fully. Even among patients with a hematocrit of <30%, one study showed that only 36% had iron studies completed, 46% received iron supplementation, and 40% received ESAs (16).

Few randomized, prospective studies have specifically addressed the efficacy, effectiveness, and safety of ESA in kidney transplant patients. In an open-label, randomized, single-center study in Belgium, patients with hematocrit <30% were randomly assigned to receive EPO (n = 14) or not (n = 15) immediately after transplantation (57). In the EPO-treated group, hematocrit increased from a nadir of 22 ± 4% at 2 weeks after transplantation to 30 ± 4% at 4 weeks and 36 ± 4% at 6 weeks (P < 0.001 and P < 0.0001, respectively, versus week 2) compared with the non–EPO-treated group (25 ± 6% [not significant], 28 ± 6% [not significant], and 32 ± 6% [P < 0.05 versus week 2, respectively). The EPO-treated group required fewer posttransplant blood transfusions despite greater postsurgical blood loss and more surgical and infectious complications. The authors did not comment on adverse effects related to EPO therapy.

The Correction of Anemia and Progression of Renal Insufficiency in Transplanted patients study (CAPRIT) is the first multicenter, randomized trial of kidney transplant recipients to assess the normalization of anemia on the progression of graft dysfunction (58). This European study randomly assigned 125 patients who were >12 months after transplantation and had hemoglobin <11.5 g/dl and eGFR 20 to 50 ml/min per 1.73 m² to either high-normal hemoglobin 13 to 15 g/dl or low hemoglobin 10.5 to 11.5 g/dl targets. After 2 years of follow-up, the higher hemoglobin group had a significantly higher eGFR (32.6 versus 27.9 ml/min per 1.73 m²; P < 0.05) (59,60). The Kaplan-Meier death-censored graft survival was 20% higher in the higher hemoglobin group with three patients reaching ESRD before 2 years in the high hemoglobin group and 13 in the low hemoglobin group. As expected, more patients used ESAs in the high hemoglobin group (89% versus 61%). The numbers of adverse events, cardiovascular events, strokes, and thrombosis were not significantly different in the two groups. Although the preliminary analyses indicated that a higher hemoglobin target may improve graft survival and kidney function, the overall number of cardiovascular events was low. These findings may not be applicable to other demographic populations—such as the United States—that exhibit a higher cardiovascular event incidence. The Neorecormon and Prevention of Delayed Graft Function (Neo-PDGF) study was a French, open-label, multicenter, randomized study of 104 patients that evaluated the efficacy of high-dosage EPO before transplantation and during the first 2 weeks after transplantation on delayed graft function and kidney function measured at 1 month after transplantation (61). The hypothesis was that EPO might ameliorate ischemia-reperfusion injury. Although there was no change in graft function, high-dosage EPO was efficacious in increasing hemoglobin levels during the early posttransplantation period without any serious adverse events.

In a retrospective cohort study of 1794 kidney transplant recipients, Heinz et al. (62) reported significantly higher mortality in patients who received ESAs and had hemoglobin levels >12.5 to 14.0 g/dl. In patients who did not receive ESAs, the relationship between hemoglobin concentrations and mortality was linear. However, in patients who did receive ESAs, the relationship between hemoglobin levels and mortality was a U-shaped curve with patients with a hemoglobin concentration lower or higher than 12.5 mg/dl experiencing increased mortality. These findings are more in line with findings in patients with CKD (63–65). There may be a narrow window of therapeutic target hemoglobin levels in kidney transplant recipients that can be evaluated only with prospective studies. Other known beneficial effects of treating anemia with iron and ESAs include decreasing the need for transfusions that may lead to allo sensitization and improving symptoms of anemia and quality of life. Small studies showed that the use of ESAs to correct anemia in patients with chronic allograft dysfunction improved hemoglobin levels and quality of life (66,67). Another retrospective study suggested that correction of anemia may delay progression in chronic allograft dysfunction (68).

Because the evidence on anemia treatment among kidney transplant recipients is limited, it is important to take into account relevant findings from patients who had CKD and did not receive a transplant. Three large clinical trials have investigated the use of ESAs in patients with CKD (Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR], Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin β [CREATE], and Trial to Reduce Cardiovascular Events with Aranesp Therapy [TREAT]) and suggested that targeting normal or higher hemoglobin levels in patients with CKD and ESRD did not confer survival or cardiovascular benefits but rather led to increased rates of adverse cardiovascular outcomes (63–65). It is unclear whether these findings should be extrapolated to kidney transplant patients who may have different mechanisms causing anemia and EPO resistance. Although most kidney transplant recipients can be classified as having CKD by K/DOQI guidelines (69), the presence of a transplant and the need for lifelong immunosuppression changes the pathophysiology of anemia. The foreign allograft can cause ongoing immune activation and a chronic inflammatory state from infection and rejection. Therefore, any guidelines on the treatment of anemia need to be drawn from studies performed in kidney transplant patients.

Given the high prevalence of iron deficiency (10,20), especially early after transplantation, and the unclear interpretation of iron studies after transplantation, on the basis of K/DOQI guidelines for anemia in CKD, transplant physicians often recommend treating all patients who have anemia with oral iron supplementation and consider intravenous or subcutaneous iron supplementation in the setting of poor tolerance or absorption (14,51). We need further studies of kidney transplant patients to determine the optimal diagnostic tests and treatment regimen, including the dosage and the mode of administration of iron. After a thorough diagnostic workup to rule out less common causes of anemia, providers can consider adjusting medi-
cations that contribute to anemia, including ACEIs, ARBs, antimicrobial agents, and immunosuppression. Medication adjustments should be done only in selected cases with close follow-up after carefully weighing the risks and benefits of withdrawing or reducing medications.

Finally, on the basis of studies showing that impaired allograft function is the main risk factor for PTA, one universal approach to treating anemia is to focus on strategies to optimize allograft function by minimizing nephrotoxicity from medications, preventing and treating infections, decreasing ischemia-reperfusion injury, and optimizing donor quality.

Conclusions

From our review, PTA is highly prevalent and undertreated and has multifactorial causes, including compromised graft function, immunosuppressive and other medications, EPO resistance, and iron deficiency. It is unclear whether PTA is causally linked to CVD and mortality in kidney transplant patients. Studies have shown that ESAs are effective in increasing hemoglobin levels even during the early posttransplantation period, but randomized studies informing therapy remain elusive. Many questions remain unanswered. We do not know whether aggressive treatment of anemia will improve outcomes or lead to unwarranted adverse effects. In addition, we do not know which kidney transplant patients would benefit from treatment and at which period after transplantation. In light of recent clinical trials of patients who had CKD and did not receive a transplant indicating adverse effects and lack of improved outcomes with higher hemoglobin targets, it is prudent to err on the side of conservative therapy and individualize treatment until larger well-designed, randomized trials are performed.

Disclosures

None.

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