ESAs in Transplant Anemia: One Size Does Not “Fit All”

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Anemia, a risk factor for cardiovascular events in patients with CKD, is a common problem following transplantation and has been reported in up to 40% of kidney transplant recipients (KTRs).1–3 It is well established that post-transplant anemia (PTA) is associated with poor clinical outcomes. PTA is associated with increased mortality (18% versus 10% over 4 years), an increased risk of acute rejection (24% versus 12% over 4 years), and an increased risk of graft loss (17% versus 6% over 4 years).4–6 Despite such a high prevalence and association with adverse sequelae, only a small minority of KTRs with anemia are treated with erythrocyte stimulating agents (ESAs).1–3,7 Under-treatment of PTA may be secondary to a lack of convincing evidence regarding the risks and benefits of treatment in this particular population, as few randomized controlled trials have examined the safety and efficacy of ESAs for treatment of PTA.

Small studies in KTRs show improvements in levels of hemoglobin and quality of life with ESA-based correction of PTA.8,9 In addition, a small single-center retrospective study by Becker et al.10 suggested that treatment of PTA with ESAs may delay progression of renal allograft dysfunction. In nontransplant patients with CKD, however, recent trials (Correction of Hemoglobin and Outcomes in Renal Insufficiency [CHOIR], Trial to Reduce Cardiovascular Events with Aranesp Therapy) demonstrate increased rates of adverse cardiovascular outcomes with ESAs targeting normal or higher hemoglobin levels.11,12 Whether these findings can be extrapolated to KTRs is unclear, as the pathogenesis of anemia and response to ESAs in this population is likely to be different from the general CKD population, given the presence of an allograft and the ongoing need for immunosuppressive therapy. In a retrospective study of 1794 KTRs, Heinze et al.13 reported higher mortality in patients receiving ESAs compared with patients who did not. When specifically examining the ESA group, however, the authors found that mortality was increased at levels of hemoglobin above and below 12.5 g/dl.13 As in the general population of patients with CKD, the therapeutic target hemoglobin in KTRs has not been established, and the safety of ESA-based correction of anemia is uncertain.

In this issue of JASN, a study by Choukroun et al.14 challenges current concepts of anemia management with respect to the kidney transplant population. The Correction of Anemia and PRogression of Renal Insufficiency in Transplant Patients (CAPRIT) study is a 2-year, randomized, controlled, open-label, French multicenter trial of epoetin-β (EPO) treatment in anemic kidney transplant recipients with moderate graft dysfunction. The primary endpoint was change in estimated GFR (eGFR; calculated by Cockcroft-Gault) from baseline to 24 months, and secondary outcomes included Nankivell and Modification of Diet in Renal Disease estimation of eGFR, doubling of serum creatinine (Cr), and proteinuria. In addition, graft survival and progression to ESRD, cardiovascular event rate, and patient survival were analyzed. One hundred twenty-five patients with an eGFR between 20 and 50 ml/min and hemoglobin < 11.5 g/dl were randomized to either achieve a hemoglobin target of 13.0–15.0 g/dl (complete correction of anemia) or 10.5–11.5 g/dl (partial correction of anemia) and were followed for progression of renal disease. The baseline characteristics and immunosuppressive regimens of both groups were similar. The higher target group achieved hemoglobins of 12.9±2.1 g/dl and the lower target group achieved hemoglobins of 11.3±1.1 g/dl by the end of the study at 24 months. As expected, more patients used EPO in the higher target group (89.1% versus 60.9%; P<0.05). The mean weekly EPO dose was higher in the higher target group throughout the study. The investigators found that patients randomized to the lower hemoglobin target suffered a greater reduction in renal function over the 2-year follow-up period compared with the group of patients randomized to the higher hemoglobin target (eGFR decline of 5.9±1.1 versus 2.4±1.1 ml/min; P=0.03). Furthermore, fewer patients in the higher hemoglobin group progressed to ESRD (4.8% versus 21.0%; P<0.01). Importantly, there was no difference in mortality or overall adverse events between groups, but the low hemoglobin target group experienced an increased number of cardiac disorders (specifically acute cardiac failure, arrhythmia, and myocardial infarction, 8% versus 0%; P=0.03), which is in stark contrast to studies of normalizing hemoglobin in nontransplant patients with CKD and similar to hemodialysis patients with naturally high hemoglobins.15 The authors conclude that targeting hemoglobin ≥13 g/dl is associated with a reduction in the rate of progression to chronic allograft nephropathy in kidney transplant recipients.

The findings of the CAPRIT study are perhaps unexpected, but undoubtedly provocative in the current climate of black box warnings for ESAs. Thus far, national and international guidelines for anemia management have grouped kidney transplant recipients with the general CKD population. The results of the CAPRIT study, however, pose a challenge to the one size fits all approach of anemia management in CKD. The kidney transplant population may represent a unique cohort of patients that may benefit from individualized therapy. While encouraging, the results of CAPRIT must be interpreted with caution given the underlying limitations of the study. The
sample size of the study was quite small compared with studies of ESAs in the general CKD population, and the overall rate of death and cardiovascular events in the study population was low. In comparison, the CHOIR study reported a nearly 30% overall mortality in the 16 months of median follow-up for all patients enrolled. Hence, CAPRIT may be underpowered to adequately assess cardiovascular events and mortality, or the patients in the study may simply represent a relatively healthier, “low-risk” group. These findings may not be generalizable to a population at higher risk for cardiovascular events, such as the CKD or kidney transplant population in the United States.

Furthermore, the underlying mechanism by which correction of anemia with ESAs preserves renal function is unclear, because no mechanistic or functional studies were performed. The CAPRIT investigators postulate that correction of anemia minimizes hypoxia and thus hypoxia-induced tissue injury to the graft. Other potential mechanisms by which correction of anemia may delay graft dysfunction include correction of left ventricular hypertrophy and improved cardiac function. While it has been assumed that any beneficial effect of ESAs is due to their known effects on stimulating red blood cell production, erythropoietin receptors are widely expressed,16–18 and recent evidence suggests that EPO has immunomodulatory functions. Several animal models and suggestive human data indicate that EPO is inhibitory toward immune responses,19–21 a phenomenon that would be highly relevant in the context of a transplanted organ. Further studies will be required to investigate these possibilities.

Nonetheless, the idea of potentially prolonging graft survival in kidney transplant recipients by correcting anemia is exciting. Despite advances in immunosuppression over the last 2 decades, long-term kidney transplant survival has not improved.22 Strategies to prolong allograft survival, including the use of ESAs to treat PTA, warrant aggressive investigation.

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DISCLOSURES

None.

REFERENCES

None.

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See related article, “Correction of Postkidney Transplant Anemia Reduces Progression of Allograft Nephropathy,” on pages 360–368.