TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Anemia and Erythrocytosis in patients after kidney transplantation

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Keywords
anemia, complications, erythrocytosis, immunosuppression, kidney clinical, transplantation.

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Conflicts of Interest
Dr Malyszko and Dr Watschinger have participated as an Advisory Board member for Amgen, Dr Oberbauer reports receiving lecture fees from Amgen.

Received: 16 December 2011
Revision requested: 10 January 2012
Accepted: 21 May 2012
Published online: 21 June 2012

doi:10.1111/j.1432-2277.2012.01513.x

Summary

Anemia is a highly prevalent disorder in recipients of renal allografts. Despite its frequent occurrence, there is still uncertainty with regard to treatment targets and treatment options. This includes questions on appropriate iron management, the choice and dosage of erythropoietin stimulating agents, criteria for the timing of treatment initiation and the targeted hemoglobin values. The review summarizes available data on recent therapeutic strategies for post-trasnplant anemia, as well as for post transplant erythrocytosis, another hematological disorder, that has decreased in recent years.

Introduction

Despite the common belief that kidney transplantation is the best treatment option for patients with end stage renal disease, one has to appreciate that kidney function is usually not totally restored as only one kidney is transplanted and renal mass is reduced, compared to healthy individuals. Most patients exhibit a decreased glomerular filtration rate (GFR) and are prone to side effects associated with chronic kidney disease (CKD). Anemia is more prevalent in transplant recipients than in GFR-matched CKD-patients, as a series of additional reasons come into play in the transplant situation [1]. A subpopulation of transplant patients acquires post-transplant erythrocytosis (PTE) which itself has complex and multifactorial causes [2]. The aim of this review is to summarize the current knowledge of two hemoglobin (Hb) abnormalities in kidney transplant recipients, post-transplant anemia (PTA) and post-transplant erythrocytosis (PTE).

Post-transplant anemia (PTA)

Definition of anemia

The initial WHO definition of anemia, Hb-levels <13 g/dl in men and <12 g/dl in women, are derived from observations in international nutrition studies [3]. Subsequently it has become clear, that these ''normal'' values may not apply to special populations. More definitions of anemia in renal patients are given in Table 1 [3–7].

Table 1. Definitions of anemia.

Institution	Country	Year	Hb level		References
			Men	Women	
WHO (World Health Organization)	Switzerland	1968	<13 g/dl	<12 g/dl	3
AST (American Society of Transplantation)	USA	2001	<13 g/dl In patients living below 1500 m	<12 g/dl	4
EBPG (European Best Practice Guidelines)	Europe	2004	<13.5 g/dl (<12 g/dl in age >70 years)	<11.5 g/dl	5
NKF/KDOQI (National Kidney Foundation/Kidney Outcome Quality Initiative)	USA	2006/2007	<13.5 g/dL	<12.0 g/dL	6
Anemia Working Group of the EBPG	Europe	2009	<13.5 g/dl	<12 g/dl	7

Epidemiology of PTA

Depending on the definition used, the prevalence of PTA is variable. The European TRESAM Survey published in 2003 reported a prevalence of 38.6%, with 8.5% of these patients demonstrating severe forms of anemia [8]. Studies from the US, Austria and Australia reported prevalences of 20%, 41.1% and 30.8% respectively [1,9,10] A practically indentical prevalence of 42% (severe grades in 9%) was reported in 10 European centers in 2010 [11].

Anemia after kidney transplantation shows a biphasic pattern. Early after the surgical procedure many transplant patients are anemic. With the restoration of kidney function during the first 3 months, Hb-levels increase and can achieve normal-range values within the first year [10]. In contrast after a primarily successful transplant a decline of graft function is associated with a rise in anemia occurrence. But even despite good and stable graft function anemia can be present in 10–42% of patients after the first post- transplant year [12–15].

Risk factors for PTA

In addition to general risk factors for anemia, a series of additional risk factors for the development of PTA have been identified.

Early post-transplant period
A low pre-trasnplant Hb-level in a dialysis patient impacts on Hb-levels in the early post-transplant period. Anemia can be aggravated by blood losses during surgery, and frequent blood sampling early after the operation. Delayed graft function, associated with a deferred restoration of erythropoietin levels can contribute to a time-delayed normalization of Hb-levels [16]. Aggressive hydration in the early postoperative period may lead to dilutional anemia, concurrent infections or side effects of immunosuppressive therapy may further induce a reduction of Hb-values. With the resolution of post-trasnplant complications and the restoration of kidney function, Hb-levels usually increase and reach normal values in the majority of patients.

Late post-transplant period
Anemia late after transplantation is predominantly associated with a decline of kidney function, but other reasons may play an additional role.

Allograft function

After transplantation kidney function is usually not completely restored. The majority of patients achieves a GFR <60 ml/min (equaling CKD stage 3 or less) [17–19]. Several studies demonstrated an association of anemia with reduced allograft function, reaching up to 44% in patients with CKD Stage 5 [18,20,21]. Serum creatinine at 6 months is an independent predictor for anemia at 1 year [22]. Patients with eGFR <41 ml/min/1.73 m^2 at 12 months post transplant were more likely to have persistent anemia [23].

Delayed graft function and acute rejections

Kamar and Rostaing reported that delayed graft function and renal function are independent risk factors for anemia at 1 year [22]. Likewise acute rejections were associated with anemia in the TRESAM study [8]. Acute rejections were shown to account for an average decrease in the Hb-concentration of 0.5 g/dl and decreased erythropoietin levels were discussed as a putative reason [24].

Donor age and donor type

The type of donor (living versus deceased) does not seem to play a role with regard to anemia occurrence [9,10]. However a higher donor age, in particular when above 60 years, was associated with anemia in the recipient [8] and predictive of anemia at 1 year after transplantation [22].

Iron status

Iron status and iron deficiency is not well studied in kidney allograft recipients. Inadequate iron stores at the time of transplantation, blood losses due to surgery or due to frequent post-transplant phlebotomy may contribute to iron deficiency in kidney allograft recipients. Effective erythropoiesis due to recovery of renal function may further deplete iron stores. Up to 60% of kidney allograft recipients without initial iron deficiency become iron deficient by 6 months [25]. Iron deficiency can even be present in long-term kidney transplant recipients with normal Hb-values. Jimeno *et al.* [26] reported a prevalence of 62.4%. Lorenz *et al.*, [12] using a definition of ≥2.5% hypochromic red blood cells, detected 20% iron deficient patients at a mean time of 4.9 years after transplantation. Even though PTA is highly prevalent, iron status is often not assessed [27,28], rendering iron deficiency widely underdiagnosed. Repletion of iron stores in a patient with restored graft function may require approximately 1 g of iron within the first 3 months after surgery [29].

Folate and vitamin B12

Folate and vitamin B12 levels are not investigated with regard to anemia in kidney allograft recipients, but referred to in small studies on folate on homocysteine levels [30,31]. Al-Khoury *et al.* [32] showed that compared to non-anemic patients, anemic transplant recipients had similar folate, but slightly higher vitamin B12 levels [32]. Thirty percent of anemic patiens in a Pakistani transplant center had low red blood cell folate or vitamin B12 levels [33]. Pneumocystis jiroveci prophylaxis with trimethoprim/sulfamethoxazole may lead to acute folate deficiency in patients with marginal stores [34].

Infections

All kind of infections can cause or aggravate anemia in the post-trasnplant period. Viral infections (e.g. cytomegalovirus, BK-virus, varicella zoster virus, parvovirus B19, herpes viruses) play an important role [35,36].

Drugs

Immunossuppressants

Antiproliferative agents: Azathioprine and mycophenolic acid (MMF) have a direct antiproliferative effect on bone marrow cells and may result in a Hb-reduction of approximately 0.2–0.3 g/dl [9,10,37]. Azathioprine can cause macrocytic anemia [38]. mTOR inhibitors can lead to microcytic anemia [38–40], by as yet unidentified mechanisms. Maiorano *et al.* [41] suggested that sirolimus interferes directly with iron metabolism and that its anemia is not inflammation-related. In contrast, Thaunat *et al.* [42] reported that sirolimus induces a chronic inflammatory state possibly due to defective IL10-dependent inflammatory autoregulation. Further it was postulated, that functional iron deficiency and impaired gastrointestinal iron absorption may contribute to microcytic anemia in sirolimus treated patients [43]. Furthermore, cases of hemolytic anemia have been reported under sirolimus treatment [44–46].

Calcineurin inhibitors (CNI): In general, calcineurin inhibitors do not contribute to the development of anemia, although one study suggested an association with tacrolimus [47].

Biological agents: Mono- or polyclonal antibodies such as OKT3 and anti thymocyte globulin (ATG) can exert toxic effects on bone marrow leading to decreased Hb-concentrations [47]. Low-dose ATG with basiliximab, led to significantly less frequent cases of anemia than standard-dose ATG therapy [48]. Alemtuzumab-based maintenance therapy resulted in a high incidence of severe acquired red cell aplasia, autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura in pancreas transplant recipients [49]. Belatacept, a recently introduced fusion protein, is not associated with increases in the incidence or prevalence of anemia [50–52].

Other drugs

Inhibitors of the renin-angiotensin-system: Angiotensin-converting-enzyme-Inhibitors (ACEi) and/or Angiotensin-Receptor-Blockers (ARB) treated transplant patients are more likely to develop anemia [32,53]. ACEi/ARB can lower Hb-concentration by 0.2–0.3 g/dl. ACEi decrease the vascular resistance in efferent arterioles, enhance the oxygenation in the peritubular region and thus decrease the signal for erythropoietin synthesis. The tetrapeptide Ac-SDKP (goralatide), a normal inhibitor of the entry of pluripotent stem cells into the S-phase, is metabolized by ACE. In the presence of an ACEi, Ac-SDKP can accumulate and thereby diminish erythropoiesis [54]. ARBs may reduce erythropoietin production in the graft or decrease the sensitivity of red cell precursors to erythropoietin.

Gancyclovir, trimethoprim/sulfamethoxazol, theophyllin, retinoic acid or lamivudine, interferon and ribavirin are other examples of drugs that can induce anemia in transplant patients [9,55].

Prognostic relevance of PTA: The impact of anemia on graft and patients survival is shown in Table 2.

Early PTA and outcome: Patients with early PTA carry an increased risk for cardiovascular events that persists beyond 30 days after transplantation and remains elevated at 6 months post transplant [56].

Late PTA and outcome: mortality and graft loss

Conflicting results have been reported with regard to the role of late PTA for graft and patient related end points [10,22,57–65]. PTA is associated with increased overall mortality [37,58–60,65] and kidney graft loss [10,22,23,58–61,65] in several studies, but had no effect on graft loss [62,63] or patient survival [10,23,61,63–65] in other studies.

PTA as a predictor of graft outcome

Winkelmayer *et al.* [10] observed no association between anemia and mortality, but an association of anemia with a 25% greater risk of allograft loss. In a subsequent analysis of over 19.000 Hb-values in 1014 patients between 3 and 12 months after transplantation we were able to confirm a degree dependent influence of anemia on graft outcome [65]. Other reports confirmed an association between allograft loss and PTA diagnosed at 3 months [59], 12 months [22] or thereafter [10,58,60]. In a Polish study, persistent and late-onset PTA was associated with the increased risk of graft loss [23]. Anemia was associated with poorer graft survival also in recipients of living donor organs [62].

PTA as a predictor of patient outcome

Studies on the impact of anemia on patient survival demonstrate conflicting results. PTA was associated with reduced 1-year patient survival in one study [22]. PTA at 1 year was associated with reduced patient survival in subsequent years [37]. In a large Hungarian cohort anemia was associated with an increased risk of mortality and allograft failure at 4 years [58]. In contrast, an analysis of 825 Austrian kidney transplant recipients found no influence of anemia on mortality [10]. Other studies, demonstrating an association between PTA and increased mortality were limited by the small number of fatal endpoints [22,60,66]. No effect of anemia on overall mortality was found in a large study in cyclosporine-treated patients [37]. Similarly in the study by Gheith *et al.* anemia did not affect patient survival [62].

Treatment of PTA

Frequency of anemia treatment in renal transplant recipients: The number of patients treated for anemia varies widely between centers and is often lower than in non transplanted renal patients [32,47,57]. Erythropoiesis-stimulating agents (ESA) were given in only 41% of anemic kidney allograft recipients (compared to 79% in non-transplanted anemic CKD-patients) in Canada [64]. In the TRESAM population, 5% of all patients received ESA, with 17.8% of severely anaemic patients being treated [8]. Molnar *et al.* reported that 24% of patients with Hb-values <11 g/dl were treated with ESA [11]. Ott *et al.* [60] reported that ESA was given in 55.5% of patients with severe anemia, 53% with moderate anemia, and in 11.6% with mild anemia. Depending on the CKD stage the percentage of patients on ESA-therapy increased from 1.3% to 68% [21].

Studies on the treatment of PTA and effects of ESA in the transplant setting are scarce, typically small, with short follow-up periods and performed in highly selected patient populations [67–72].

A recent randomized controlled trial of iron supplementation found no difference between per oral and intravenous route with regard to restoration of Hb-levels to >11 g/dl postoperatively, but long term iron supplementation has not been investigated in controlled trials [73]. Except for a recent trial on Hb-correction by ESA therapy [85], there is no randomized controlled study of sufficient size that allows definitive answers to questions as: when to treat, how to treat and to which levels, Hb-values should be raised.

Correction of PTA by ESAs

Studies on the correction of anemia in the immediate post-transplant period are underpowered and therefore not suited to give definitive answers. A Belgian study in 40 patients demonstrated that large amounts of erythropoietin (EPO) – beta are necessary for a marginal advantage in raising Hb-levels faster and to a higher level [67]. Other small studies showed that ESA treatment (Darbepoetin alfa) can facilitate Hb-values >12 g/dl within 1 month [68], improves quality of life (erythropoietin-alfa) [69] and can correct Hb-values despite a relative EPO resistance [70]. An EPO response seems to occur faster in patients that have received their transplant more recently [71]. Furthermore it was suggested that later initiation of EPO may be beneficial for long term graft survival [72]. Darbepoetin alfa given twice monthly for 3 months lead to an increase but not to a normalization of Hb-values, with on third of patients still requiring ESA therapy a year later [74], and was effectively used in extended intervals to raise Hb-levels

Table 2. Impact of anemia on graft and patients survival.

References	Number of pts Tx type Time of Hb assessment after Tx Follow up	Patient survival HR 95% CI *P*-value	Graft survival HR 95% CI *P*-value	CV event HR 95% CI *P*-value
Djamali *et al.* [56]	404 KTx, KTx/PTX during first year –			Hct > versus <30% 0.65 0.33–0.91 0.022
Imoagene-Oyedeji *et al.* [37]	626 KTx 12 months 64.8 months	Hb < versus > 12 g/dl 3.0 1.3–6.7 *P* = 0.009		Hb < versus > 12 g/dl 3.0 1.1–8.0 *P* = 0.04
Molnar *et al.* [58]	938 KTx – 4 years median	Anemia versus normal 1.69 1.11–2.56 0.013	Anemia versus normal 2.46 1.48–4.09 <0.001	
Chhabra *et al.* [59]	1023 KTx @ 90 days 4 years median	Hb < versus > 11 g/dl 3.18 1.74–5.82 *P* = 0.0002	Hb < versus > 11 g/dl 2.67 1.85–3.85 *P* = 0.0001	
Gheith *et al.* [62]	832 live donor KTx @ 180 days up to 10 years	Anemia versus normal @ 10 years 96% versus 98.4% *P* = 0.09	Anemia versus normal @ 10 years 84.8% versus 93.9% *P* = 0.0001	
Kamar *et al.* [22]	339 KTx, graft > 1 year @ 1 year 5 years	Anemia versus normal 6.9% versus 1.7% *P* = 0.04	Anemia versus normal 88.9% versus 97% *P* = 0.004	
Winkelmayer *et al.* [10]	825 KTx – 8.2 years	Anemia versus normal 1.08 0.80–1.45 0.63	Anemia versus normal 1.25 1.02–1.59 0.04	
Kolonko *et al.* [23]	385 KTx, graft > 1 year – 5 years	Anemia versus normal 0.75 0.29–3.67 *P* = 0.56	Anemia versus normal 4.11 2.02–8.37 *P* < 0.001	
Moore *et al.* [61]	3859 Ktx pts, graft > 6 months – –	No association of anemia with decreased patient survival	1 g/dl rise in Hb lowers risk for graft loss 0.91 0.89–0,93 *P* = 0.003	
Vanrenterghem *et al.* [63]	1160 KTx, graft > 1 year yearly evaluation 7.7 years mean	Hct 50% vs. 38.2% 1.75 1.03–2.46 <0.05		
Heinze *et al.* [57]	1794 Ktx Yearly evaluation 5.6 years median	Hb 14.0 vs. 12.5 g/dL ESA treated 2.8 (CI 1.0–7.9) Not ESA treated 0.7 (CI 0.4–1.5)		ESA treated 1.4 events/100 person years Not ESA treated 0.8 events/100 person years
Ott *et al.* [60]	207 KTx – 3 years	Anemia vs. normal 96.7% vs. 99.5% – *P* < 0.001	Anemia versus normal 95.7% vs. 100% – *P* < 0.001	

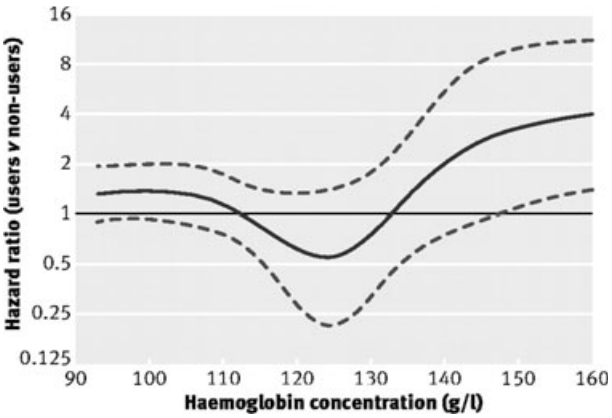

Figure 1 Adjusted hazard ratio at various haemoglobin concentrations for patients who did and did not use erythropoietins. Hazard ratios >1 indicate higher risk for those who received erythropoietins. Results were obtained by multivariable Cox regression with restricted cubic splines with five knots for haemoglobin concentration, adjusted for dialysis status, cerebrovascular disease, peripheral vascular disease, coronary heart disease, heart failure, cholesterol concentration, immunosuppressive regimen, diabetes status, age at transplantation, and cold ischaemia time (Reprint from Heinze *et al.*, *BMJ* 2009 Oct 23; **339**: b4018. doi: 10.1136/bmj.b4018).

in transplant patients with failing grafts before returning to dialysis [75]. Hb-stability can be achieved and maintained after correction or conversion to once-monthly methoxy-polyethylene-glycol-Epoetin-beta [76]. Intra- or peritransplant application of high doses of ESA's did not affect graft histology or function in cadaveric allograft kidney transplants [77], did not decrease the incidence of delayed graft function [78], did not change GFR after one month, nor the number of blood transfusions during the first month or patient's quality of life [79]. Very high doses (250 IU/kg/week) of short-acting epoetin (alfa or beta) within the first months after kidney transplantation had no effect on anemia or renal function by 1 month post-transplant [80].

Recent studies in non transplant populations suggested that in EPO treated patients the Hb-target should be lower, than initially thought [81–83]. Heinze *et al.* [57], retrospectively, investigated the effect of anemia treatment with ESAs on mortality in Austrian transplant recipients. Patients treated with ESAs were more likely to be females, recipients of older donor kidneys, and treated with induction therapy. They were more likely to be anemic and hypertensive, had a higher prevalence of biopsy proven rejection and chronic allograft nephropathy. By an elaborate statistical analysis the authors showed that raising the Hb-concentration to above 14 g/dl with ESAs was associated with an increase in mortality (Fig. 1). Even though a causal relation could not be proven it was suggested that kidney transplant recipients with Hb-values >12.5 g/dl should not be treated with ESAs. In another retrospective analysis the same group reported that Hb-variability did not influence graft loss but was associated with an increased mortality [84].

Data from the CAPRIT study reported by Choukroun *et al.* [85] now show in a small controlled study ($n = 63$ and 62, respectively), that normalization of anemia with epoetin beta (Hb-target, 13.0–15.0 g/dl), is associated with higher GFR, improved death-censored graft survival and less patients reaching endstage renal disease than partial correction (Hb-target, 10.5–11.5 g/dl). The incidence of adverse effects (including cardiovascular events) was similar between the groups. While these results are in contrast to findings in CKD-populations, recent experimental data support a beneficial effect of EPO for the protection from chronic renal allograft injury and suggest that this effect goes beyond the correction of anemia [86].

Post-transplant erythrocytosis (PTE)

Definition of PTE

PTE is defined as Hb-values >17 g/dl (or hematocrit >51%) that occur after engraftment.

Epidemiology of PTE

Most often PTE occurs within the first 8–24 months after transplantation. Its prevalence varies from 8% to 15% [2,87–90] but was reported as a high as 22.2% in one study [91].

Pathogenesis of PTE

The pathogenesis of PTE is multifactorial. In many cases erythropoiesis appears to be stimulated by excess EPO-release from the native kidneys [92,93]. However, plasma EPO-levels do not seem to be a reliably measure of the contribution of EPO to the development of PTE, as levels were similar between patients with and without PTE in the study of Brox *et al.* [94]. Unidentified factors not related to EPO appear to contribute to PTE, supported by the finding of normal or even appropriately suppressed plasma EPO levels in patients with PTE [95–97]. The non-EPO factors may either enhance the sensitivity to EPO or directly promote erythropoiesis [88]. As an example, an anomaly in IGF-1 and its binding proteins-1 and 3 have been accused to induce PTE [87,94]. The observation, that stimulation of marrow CFU-E growth by serum from hemodialysis-patients with erythrocytosis can be partially blocked by anti-IGF-I antibodies, suggests that IGF-I is physiologically active in this particular setting [98].

It has also been suggested that activation of the Angiotensin-II-receptor may enhance erythropoietin production

in the graft or increase sensitivity of red cell precursors to erythropoietin [93,99,100]. A role for renal artery stenosis and subsequent renal ischemia leading to increased erythropoietin production has been postulated [101,102].

Risk factors for PTE

PTE appears predominantly in patients without native kidney nephrectomy and in those, who had an adequate erythropoiesis prior to transplantation, as evidenced by no or limited use of ESA while on dialysis [89]. Male gender is one important factor predisposing to PTE [2,88]. Other factors include smoking, transplant renal artery stenosis and a rejection-free post-transplant course [88,90,102,103]. Other causes for an increased erythropoiesis, e.g. due to renal interstitial ischemia or a compensatory increased endogeneous EPO-production in patients with chronic obstructive pulmonary, renal cell carcinoma, hepatocellular carcinoma, hemangioblastomas, pheochromocytoma, uterine myomata and polycystic kidney disease, must be equally considered.

PTE as a predictor of outcome

Erythrocytosis can increase plasma viscosity and may cause thromboembolic events. Wickre *et al.* reported an increase in thromboembolic events (18.9%) in patients with PTE, despite therapeutic phlebotomy, when compared to non-PTE patients (0%) [103]. Others, however, did not find an association between PTE and increases of thromboembolisms [104,105]. Similarly, the role of PTE on graft loss remains unclear. In a recent study by Kolonko *et al.* [23] PTE did not affect the risk of graft loss or patient death. Kiberd [2] found that patients with erythrocytosis had superior overall survival but a trend for worse death censored graft loss.

Treatment of PTE

The treatment goal in patients with PTE is to lower Hb-level below 17.5 g/dl in normotensive patients [106]. As PTE can have a relapsing course, it is suggested that PTE therapy should be pursued indefinitely [87]. Several drugs have shown efficacy in reducing the red blood cell count in transplant patients.

Inhibitors of the renin-angiotensin-system

ACEi and ARBs decrease Hb-levels in kidney allograft recipients by 0.2–0.3 g/dl [107–109]. The effect of ACEi may be mediated by Ac-SDKP (goralatide), a tetrapeptide that inhibits erythropoiesis [110,111].

Theophylline

Theophylline acts as an adenosine antagonist. Adenosine facilitates the release and perhaps the bone marrow response to EPO. The effectiveness of theophylline cannot be predicted as reliable as for ACEi [112,113]. Aminophylline was not associated with lowering of Hb-levels in patients with PTE [114].

Summary

Anemia is more prevalent in kidney transplant patients than in GFR-matched CKD-patients [1]. Post-transplant anemia, PTA, shows a biphasic pattern with an early peak immediately after transplantation and a late rise associated with a decrease in allograft function. As of today open questions concerning PTA remain unanswered. It is still unclear whether correction of low Hb-levels is beneficial in transplant patients, and which Hb-values should be targeted when treatment is initiated. Registry data suggest that the use of ESAs in patients with Hb-values <10 g/dl and >14 g/dl is associated with an increase in mortality. Thus, and in analogy to controlled trials in non-transplanted patients [81–83], Hb-values higher than 11 or 12 g/dl should probably not be targeted and ESA treatment in patients with Hb-values >12.5 g/dl cannot be recommended.

Post-transplant erythrocytosis, PTE, may have adverse consequences and should be treated in order to reduce Hb-values to below 17.5 g/dl. The prevalence of PTE, however, has seen a steady decline over the years, probably due to the increased prescription of ACEi/ARBs and/or due to the more intensive use of antiproliferative immunosuppressants.

Randomized controlled studies are urgently needed in PTA as well as in PTE. As it is unlikely that results from these studies will be available in the near future, physicians treating renal transplant patients will have to continue to use their critical, clinical judgment before initiating therapy and for the decision to choose respective treatment target.

Authorship

JM: collected and analyzed data and contributed in writing the paper. RO: collected and analyzed data and contributed in writing the paper. BW: collected and analyzed data and contributed in writing the paper.

Funding

None.

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