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REVIEW
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From iron to HIF-PH inhibitors: rethinking anemia management after kidney transplant

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ABSTRACT

Anemia is one of the most common complications in patients undergoing kidney transplantation, with an estimated prevalence between 30% and 50%, especially in the first six months after transplantation. The pathogenesis of anemia in these patients is multifactorial, related to chronic inflammation, disorders of iron metabolism, myelosuppression from several immunosuppressive drugs, and hormonal and metabolic alterations. The clinical implications of anemia in kidney transplants are significant: it is a negative prognostic factor for patient and transplant survival, significantly affecting cardiovascular risk and quality of life.

This review analyzes in detail the pathogenic mechanisms of anemia in the post-transplant context, illustrating their clinical impact and providing an updated overview of currently available therapeutic strategies, with a focus on new molecules belonging to the class of prolyl-hydroxylase inhibitors (HIF-PHi), which are revolutionizing the therapeutic approach to anemia secondary to renal failure.

Keywords: Kidney Transplantation, Anemia, HIF-PH inhibitors

Introduction

Kidney transplantation is the gold standard in the treatment of chronic end-stage renal failure (ESRD), offering better long-term survival than dialysis and a better quality of life (1). Thanks to the optimization of pre-transplant immunological study techniques and a better clinical management of infectious, immunological and cardiovascular risks, the long-term survival rate of both patients and the transplant itself has greatly increased over the years. The death rate of patients with a functioning transplant at 10 years has been reduced from 33.7% to 26.2%. In addition, in 2006, patients transplanted from a living donor had a transplant failure rate of 34.2% at 10 years, regardless of the cause, while the death rate with a functioning transplant was only 18% (2). Data from our experience at the Transplantation Centre show that out of approximately 1000 patients transplanted between 2004 and 2022, graft failure rates were 12%, while mortality with a functioning kidney was 10%. These results are particularly encouraging, especially given the many prognostically negative factors, such as the increase in the average age and the increased incidence of obesity, metabolic and cardiovascular diseases of the donor and receiving populations. However, successful transplantation requires careful and prolonged clinical and laboratory follow-up to identify and manage the many complications that may arise, including post-transplant anemia. It is not a condition limited to the pre-transplant phase but persists—or arises de novo—after transplantation, representing an important clinical problem that negatively affects the recovery of renal function, graft function in the long term, the patient's physical and cognitive performance, cardiovascular risk and overall survival. This review analyzes in detail the pathogenic mechanisms of anemia in the post-transplant context, illustrating their clinical impact and providing an updated overview of currently available therapeutic strategies, with a focus on new molecules belonging to the class of prolyl-hydroxylase inhibitors (HIF-PHi), which are revolutionizing the therapeutic approach to anemia secondary to renal failure.

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Classification of post-transplant anemia

Post-transplant anemia is a common condition, with a prevalence that varies according to the definition used and the time since transplantation. Studies report the prevalence

of anemia in CKD is 14% in the USA, 39.36% in India, 51.5% in China, 43.18% in South Africa, and 79% in Cameroon, with prevalence increasing as CKD severity progresses. As in patients with chronic kidney disease, it is typically normocytic, normochromic and hypo-proliferative. (1)

Classically distinguished in:

- Early anemia: occurring within the first 6 months after transplantation; frequently associated with multifactorial causes (infections, drugs, acute dysfunction or delayed recovery of graft function).
- Late anemia: develops after 6 months; often related to chronic dysfunction of the transplanted organ, persistent EPO deficiency and chronic alterations in iron metabolism.

Pathogenic mechanisms of anemia in the kidney transplant

Erythropoietin deficiency (EPO)

Even in the presence of an apparently functioning transplant, the production of erythropoietin (EPO) may remain inadequate, especially if the eGFR is suboptimal or if there is a persistent increase in creatinine. This deficit can be attributed to chronic tubulo-interstitial damage and loss of EPO-producing peritubular cells (4).

Chronic inflammation and iron metabolism dysregulation

A chronic inflammation, frequent in transplanted patients, involves an increase of pro-inflammatory cytokines (among which: IL-1, TNF-α, IL-6) that interfere with the production and efficacy of EPO and induce an increase in hepatic production of hepcidin, a negative iron absorption and release regulator hormone. Hepcidin inhibits the intestinal absorption of iron and its release from ferritin deposits. For this, we assume a functional deficit, since iron is present in the body but cannot be used in normal erythropoiesis (5).

Uremia toxins

Molecules such as indoyl sulfate (IS), derived from protein metabolism and poorly eliminated due to renal dysfunction, directly inhibit the transcription of the EPO gene and contribute to an increase in hepcidin. IS has also been observed to play a role in the apoptosis of red blood cells typical of renal failure (6).

Myelotoxic effects of drugs

Numerous drugs prescribed in post-transplant follow-up can impair bone marrow function. First, drugs such as mycophenolate mofetil and azathioprine, used long-term in the immunosuppressive regimen, may cause myelosuppression, which inhibits lymphocyte proliferation by inhibiting the enzyme IMPDH, regulating guanine synthesis and DNA replication. However, the bone marrow effect of these drugs is not only to suppress the immune system, but also an obstacle to normal erythropoiesis.

Secondly, ACE inhibitors and ARBs, which are prescribed for blood pressure control, reduce angiotensin-mediated erythropoietic stimulation. In the study conducted by Mohanram and colleagues, it is clearly pointed out that long-term use of the drug Losartan (50–100 mg/day) in diabetic and albuminuric patients results in an average decrease of 1 g/dL of hemoglobin. Fortunately, this effect does not compromise the nephroprotection (7).

Secondary hyperparathyroidism

In the vicious circle that feeds anemia, hyperparathyroidism also plays a crucial role. This correlation has been studied both in patients diagnosed with secondary hyperparathyroidism in the presence of chronic kidney disease and in subjects with normal function with primitive abnormalities of the parathyroid gland. In these cases, it is assumed that anemia is caused by the direct action that parathormone has on erythropoiesis, which is going to inhibit the erythroid progenitors and the synthesis of endogenous EPO. This hormone has an additional indirect negative effect, inducing bone marrow fibrosis (8,9).

Clinical impact of anemia in the transplanted patient

Anemia is an important determinant of outcome in the transplanted patient and should be considered a therapeutic target. In fact, if not treated, it becomes an important risk factor for much more serious pathologies, which not only reduces the quality of the graft but also reduces the patient's quality of life and survival. The main clinical consequences include left ventricular hypertrophy and progression of heart failure, a higher rate of hospitalization, and reduced physical and cognitive function (10). The increased risk of mortality, hospitalization, cardiovascular events and progression of chronic kidney disease follows the same pattern: the lower the hemoglobin level, the higher the risk (2). For these reasons, it is necessary to treat early anemia in patients with renal failure, slowing its progression and the possible start of replacement therapies, such as hemodialysis (3,4).

Therapeutic strategies

In the first place, any nutritional deficits must be corrected, as pointed out by KDIGO guidelines, while the subsequent therapy will be based on the administration of iron, agents stimulating erythropoiesis (ESA) and possibly, in patients with severe and symptomatic anemia, blood transfusions (14).

Supplementation of iron

Martial therapy, where necessary, is the first step in correcting anemia. Most patients are prescribed oral iron supplementation, especially if they have good gastrointestinal tolerance. Given the difficult intestinal absorption, it is recommended to use its most bioavailable form, namely ferrous salt, away from meals, to avoid interactions with food such as milk. Instead, if the patient was found to be intolerant, it might be useful to take iron complex and muco-protease, to be taken with a full stomach. In cases where there is severe anemia and the need for rapid correction, it is possible to administer iron supplementation intravenously, with formulations that also allow a single dose (e.g., carboxymethylcellulose) (15).

Iron intake is crucial even in patients already treated with ESA, since it is necessary to support the supply of the molecule, especially at the time when erythropoiesis is stimulated. In patients on dual therapy (ESA + iron), however, the iron overload represented by ferritin values > 500 ng/mL must be considered, especially if associated with an adequate level of transferrin saturation.

Erythropoiesis stimulating agents (ESA)

ESAs are the therapeutic standard for the correction of CKD anemia. The aim of this pharmacological treatment is to obtain an increase in hemoglobin above 11 g/dL, the cut-off for the use of this therapeutic scheme, with the idea of stopping treatment when the target level of 12 g/dL is reached, since above this threshold, there is a clear reduction in benefits in terms of cardiovascular risk (16).

However, the administration of ESA in patients with ongoing cancer has been shown to be associated with a worse outcome than observed in neoplastic patients not treated with ESA. For this reason, in these patients, other pharmacological interventions are recommended, although the relationship between the expression of EPO-R at the level of neoplastic cells and the administration of ESA has not yet been well defined. In addition, it should be taken into account that some patients may be hypo-responsive—or even non-responsive—to this therapy; therefore, instead of increasing the dosage, it would be advisable to opt for another therapeutic line.

Their possible limits are hypo-responsiveness, cardiovascular adverse events, contraindications in oncology patients, or high risk of thromboembolic events. In addition, it should be considered that they are drugs administered intravenously or subcutaneously.

New perspectives for the treatment of anemia in transplantation: prolyl-hydroxylase inhibitors HIF (HIF-PHi)

In recent years, new drugs have been studied to improve anemia, reducing not only the side effects associated with long-term use of erythropoietic stimulants but also the need for transfusion and thus improving patient compliance with therapy. For this purpose, and specifically to be able to extend the therapeutic possibilities in the case of patients who have a non-optimal response to ESAs, it was essential to study new therapeutic targets. Inhibitors of the prolyl-hydroxylase enzyme that inhibits the action of hypoxia-inducing factor (HIF-PHi), also known as HIF-stabilizers, are among these and are an important alternative to ESAs in the treatment of anemia (17,18).

Mechanism of action

HIF-PHi acts by inhibiting the degradation of the hypoxic-inducible complex (HIF) through inhibition of proline hydroxylation inhibitory enzymes (PHD). Under normal conditions, the latter are activated, promoting the inactivation of the HIF complex; whereas in the case of hypoxia or use of HIF-PHi, HIF is activated by nuclear translocation and induces transcription of relevant genes in erythropoiesis. It stimulates the increase of endogenous EPO production at the renal and hepatic level, reduces hepcidin levels, improves intestinal iron absorption, reduces the production of pro-inflammatory cytokines such as TNF-alpha and TGF-beta and stimulates the production of VEGF. In addition, as a pleiotropic effect, it has an inhibitory action on HMG-CoA-reductase, reducing the endogenous production of cholesterol. For all the reasons mentioned above, HIF-PHis are valid molecules because they act upstream on inflammation, giving benefit not only to erythropoiesis (19,20).

Effectiveness and safety

The molecules currently available are: Roxadustat, Vadadustat, Daprodustat, Molidustat, Desidustat and Enarodustat. In Italy, only Roxadustat is currently available, while Daprodustat and Vadadustat are being evaluated by the EMA. All HIF stabilizers share the same mechanism of action but differ because of molecular structure and selectivity for the PHD subunit. For example, while Roxadustat inhibits all three forms of PHD equivalently (1,2,3), Daprodustat inhibits PHD 1 and PHD 3, Vadadustat PHD3 and Molidustat PHD2. All these drugs are administered orally, unlike ESAs, which are administered intravenously or subcutaneously. The frequency of intake varies according to their half-life: Roxadustat is taken three times a week, every other day, while others are active once a day. After intake, they are rapidly absorbed and undergo the effect of first passage at the hepatic level. Elimination occurs with urine and faeces mostly as metabolites and only minimally as unmetabolized substances. Research has focused on assessing the safety profile of HIF-PHi in patients with CKD, both in dialysis and pre-dialysis. General mortality, cardiovascular mortality, the occurrence of cardiovascular and thrombotic events, the development of neoplasms, ocular complications, and the onset of arterial hypertension were analyzed. In studies comparing the use of HIF-PHi to placebo, the frequency of adverse events was substantially similar between groups, with a higher rate of discontinuation of therapy in placebo patients (21). In comparison with ESA, the number of adverse events was similar, but it was pointed out that subjects taking HIF-PHi had more gastrointestinal disorders and a higher rate of interruption for clinical reasons (22,23).

Some publications have pointed out that there is a possible increased risk of thromboembolic and cerebrovascular complications in patients with polycythemia due to mutations in the HIF system. But phase 3 clinical trials have generally shown a non-inferiority of HIF-PHi compared to placebo or ESAs (24-26).

To date, the available studies have not shown whether the therapeutic use of HIF-PHi results in an increased risk of adverse events compared with ESA therapy. It should also be noted that there are currently few studies investigating the action of HIF-PHi in the kidney transplanted population. What's more, these studies were conducted with a limited number of patients. However, research has demonstrated that roxadustat was well-tolerated and effectively elevated Hb levels. Future studies need to find a more balanced and optimized dosing regimen (27-29).

In addition, there is one study conducted by Ishiyama and others that brings together and compares anemia in

transplant and non-transplant patients. Their research points out that roxadustat and daprodustat are effective in both groups, by increasing Hb in 1, 3, and 6 months of treatment. However, in the transplanted cohort, there's a higher incidence of thrombotic events in comparison to the other studied group (30).

An important meta-analysis of 3839 dialysis and 4406 non-dialysis patients with CKD highlighted a reduction in major cardiovascular events (MACE) in subjects treated with HIF-PHi compared to ESA. However, this difference was not significant in the non-dialysis cohort. Whereas in the PRO2TECT study, non-dialysis patients treated with HIF-PHi had a higher risk of MACE than those treated with Darbepoetin Alfa. These results could be caused by a significant difference in the hemoglobin levels, set as targets in the studies (10-12 g/dL versus 10-11 g/dL in the meta-analysis study and 11-13 g/dL in the PRO2TECT study). In any case, this suggests the need to better clarify the cardiovascular risk depending on the prescribed therapy, the patient's history, and their blood tests (31). Regarding the action of HIF-PHi in the stimulation of pro-angiogenic factors such as VEGF, the possible increase in the incidence of tumors has been studied. Two meta-analyses, one on non-dialyzed patients treated with HIF-PHi vs placebo, and the other on dialyzed and non-dialyzed patients treated with HIF-PHi vs ESA, didn't find an increase in the neoplastic risk associated with the use of the new class of drugs.

In addition, it has been hypothesized that the angiogenic effect mediated by VEGF can worsen eye diseases such as diabetic retinopathy. The data, however, are discordant because the SYMPHONY-HD study found an increase in adverse ocular events in patients treated with HIF-PHi, while other analyses didn't show significant differences, nor in the risk of new eye diseases, nor in the aggravation of pre-existing retinal conditions.

Finally, as already observed for ESAs, the use of HIF-PHi was also associated with an increased incidence of hypertension compared to placebo, according to the meta-analysis by Provenzano et al. However, comparisons between HIF-PHi and ESA do not show substantial differences in the appearance of hypertension, both in dialysis patients and those under conservative treatment. Some evidence even suggests that the use of HIF-PHi may reduce the need to intensify antihypertensive therapy, indicating a potential benefit on blood pressure.

In Table 1, we added a table aimed to summarize all the points focused on in the present review.

TABLE 1 - At-a-glance summary of post-transplant anemia and emerging therapeutic strategies

Domain	Main points discussed in the review	Relevant data/evidence summarized	Clinical message
Burden and definition	Post-transplant anemia is a frequent complication and may persist after transplantation or occur de novo.	Estimated prevalence is approximately 30-50%, particularly within the first six months after kidney transplantation; anemia is usually normocytic, normochromic and hypoproliferative (3).	It should not be regarded as a marginal laboratory abnormality, but as a clinically meaningful condition requiring structured assessment.
Timing/classification	Early anemia occurs within the first 6 months; late anemia develops after 6 months.	Early anemia is linked to infections, drugs, acute graft dysfunction or delayed graft function; late anemia is often associated with chronic graft dysfunction, persistent EPO deficiency and altered iron metabolism (3,4).	The timing of onset helps guide the diagnostic work-up and prioritization of reversible causes.
Erythropoietin deficiency	EPO production may remain insufficient even after successful transplantation, particularly with suboptimal graft function.	Chronic tubulo-interstitial injury and loss/dysfunction of peritubular EPO-producing cells are key mechanisms (4).	Assessment of graft function is central when investigating persistent or late post-transplant anemia.
Inflammation and iron dysregulation	Chronic inflammation promotes functional iron deficiency through hepcidin-mediated iron sequestration.	IL-1, TNF-alpha and IL-6 may impair EPO production/effectiveness and increase hepatic hepcidin synthesis, reducing intestinal iron absorption and iron release from stores (5).	Ferritin alone may be misleading; iron status should be interpreted in the context of inflammation and transferrin saturation.
Uremic toxins	Residual renal dysfunction may expose patients to uremic toxins that directly interfere with erythropoiesis.	Indoxyl sulfate can inhibit EPO gene transcription, increase hepcidin and contribute to red blood cell apoptosis (6).	Persistent anemia can reflect ongoing metabolic consequences of impaired graft function.
Drug-related mechanisms	Several post-transplant drugs may contribute to anemia through bone marrow suppression or reduced erythropoietic stimulation.	Mycophenolate mofetil and azathioprine may induce myelosuppression; ACE inhibitors and ARBs can reduce angiotensin-mediated erythropoietic stimulation; Losartan was associated with an average Hb decrease of about 1 g/dL (7).	Medication review is mandatory before escalating anemia-specific therapy.

Domain	Main points discussed in the review	Relevant data/evidence summarized	Clinical message
Secondary hyperparathyroidism	Persistent hyperparathyroidism may worsen anemia through direct and indirect effects on erythropoiesis.	PTH may inhibit erythroid progenitors and endogenous EPO synthesis and may contribute to bone marrow fibrosis (8,9).	CKD-MBD evaluation remains relevant after transplantation in the anemia work-up.
Clinical impact	Anemia is associated with worse patient-centered and graft-related outcomes.	Reported consequences include left ventricular hypertrophy, heart failure progression, hospitalization, reduced physical/cognitive function, higher cardiovascular risk and increased mortality (10-13).	Post-transplant anemia should be considered a therapeutic target, not only a descriptive finding.
Iron supplementation	Correction of iron deficiency is the first therapeutic step when indicated.	Oral iron may be used when tolerated; intravenous iron can be considered in severe anemia or when rapid correction is needed. In patients receiving ESA, adequate iron availability is essential; ferritin >500 ng/mL may suggest iron overload when TSAT is adequate (14,15).	Iron therapy should be individualized according to severity, tolerance, inflammatory status and concomitant ESA use.
ESA therapy	ESAs remain the therapeutic standard for CKD-related anemia but have important limitations.	The review discusses Hb targets around 11-12 g/dL and highlights ESA hyporesponsiveness, cardiovascular/thromboembolic concerns, injectable administration and caution in oncology patients (16).	Failure to respond should trigger reassessment of causes rather than automatic dose escalation.
HIF-PH inhibitors: mechanism	HIF-PHi stabilizes HIF and stimulates a coordinated erythropoietic and iron-metabolism response.	They increase endogenous renal/hepatic EPO production, reduce hepcidin, improve intestinal iron absorption, modulate inflammatory cytokines and may reduce cholesterol through HMG-CoA reductase-related effects (17-20).	Their upstream mechanism may be particularly attractive in inflammation-driven or ESA-hyporesponsive anemia.
HIF-PH inhibitors: available agents	Available/under-investigation molecules include roxadustat, vadadustat, daprodustat, molidustat, desidustat and enarodustat.	They differ in molecular structure, PHD isoform selectivity and dosing schedule; roxadustat is taken three times weekly, whereas other agents may require daily administration (18-20).	Oral administration may improve treatment acceptability compared with intravenous/subcutaneous ESA therapy.
HIF-PH inhibitors: efficacy and safety	Evidence in CKD suggests effective Hb correction, but the transplant-specific evidence base remains limited.	Available studies in kidney transplant recipients suggest roxadustat can increase Hb and is generally tolerated; however, transplant cohorts are small, and one real-world comparison reported a higher incidence of thrombotic events in transplant recipients than in non-transplant individuals (21-31).	Larger transplant-specific studies are needed to define optimal dosing, cardiovascular safety, thrombotic risk, ocular/neoplastic safety and long-term graft outcomes.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHi, hypoxia-inducible factor prolyl-hydroxylase inhibitor; PTH, parathyroid hormone; TSAT, transferrin saturation.
Note: Reference numbers follow the current manuscript reference list.

Conclusions

Anemia in kidney transplant patients is a clinically relevant condition, often underestimated, but associated with a significant impact on prognosis and quality of life. While iron therapy and ESA remain the mainstay of treatment, the advent of HIF-PHi inhibitors opens up new therapeutic scenarios, particularly useful in patients who are hyporesponsive to ESA or with contraindications to their use. It will be important in the long term to evaluate the action of HIF-PHi and possible adverse events with new studies on the transplant population, as Dr. Maaz points out in his letter to International Urology and Nephrology, Roxadustat could be a unified solution for many anemic patients with different renal pathologies (32).

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