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REVIEW

Erythropoietin Resistance in Patients with Chronic Kidney Disease: Current Perspectives

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Abstract: Anemia is a frequent complication of chronic kidney disease, and its primary cause is erythropoietin deficiency. After diagnosis, treatment begins with administration of an erythropoiesis-stimulating agent (ESA). However, some patients present with resistance to ESA, which needs to be reversed, as it can increase the risk of death in patients with kidney disease. Therefore, we provide a discussion of the current literature regarding the factors that can modify the response to this class of drugs and the strategies that can be considered to optimize the benefits of treating anemia.
Keywords: anemia, chronic kidney disease, erythropoietin, drug resistance

Introduction

Patients with chronic kidney disease (CKD) have a relatively deficient erythropoietin (EPO) production, and this is the main cause of anemia in this group.[1] In its severe form, anemia decreases quality of life and increases the risk of cardiovascular diseases and mortality in dialysis patients, so the implementation of prevention and control measures is recommended.[1,2]

Erythropoiesis-stimulating agents (ESAs) are generally used to control anemia and reduce the need for blood transfusions in patients with CKD.[1,3] Several ESAs are currently available, including epoetin alfa or beta, epoetin alfa biosimilars and longer-acting agents such as darbepoetin alfa and methoxy polyethylene glycol-epoetin beta.[4–6]

Clinical practice guidelines on the use of ESAs were developed and improved with a focus on evidence-based medicine[7,8] (Table 1). Currently, although ESAs are known to be effective for reversing the anemic state, the etiology of anemia is multifactorial; owing to other competing factors, the response capacity of patients with CKD vary widely.[9–11]

ESA resistance or hyporesponsiveness occurs when the patient does not reach the desired serum hemoglobin (Hb) concentration even with the use of ESA at doses higher than usual or when increasingly higher doses are necessary to maintain the recommended Hb concentration.[7,12] The pathophysiological mechanisms underlying this condition are not yet fully elucidated; however, the processes that cause anemia of chronic disease play a role.[8,10,13–16]

This fact is clinically important because resistance to EPO increases the risk of death in patients with CKD owing to its association with increased blood pressure (increased cardiovascular risk), increased blood viscosity (endothelial stress), and improved platelet function (prothrombotic effect).[4,16–18] Therefore, identification of

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Table 1 Current Recommendations on the Treatment of Anemia - KDIGO (2012)

				Stages of Chronic Renal Disease			
				3	**4**	**5**	**5D**
Investigation of Anemia				Complete blood count Absolute reticulocyte count Serum ferritin and transferrin saturation (TSAT) Serum vitamin B12 and folate levels			
Diagnosis of Anemia				Adults and children aged >15 years: Hb concentration of <13.0 g/dl for males and <12.0 g/dl for females Children: Hb concentration of <11.0 g/dl for ages 0.5–5 years, <11.5 g/dl for ages 5–12 years, and <12.0 g/dl for ages 12–15 years			
Monitoring	**Not anemic (**when clinically indicated and …)			Annually	Twice per year		Every 3 months
	Anemic but not on EAS (when clinically indicated and …)			Every 3 months			HD: Monthly PD: Every 3 months
Drug Treatment	**Iron agents**		**Initiation**	Adults: TSAT < 30% and ferritin < 500 mcg/l Children: TSAT <20% and ferritin <100 mcg/l			TSAT< 20% and ferritin < 100 μ/L
			Maintenance	Based on Hb responses to recent iron therapy and ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA-treated patients, trends in each parameter, and the patient's clinical status			
	EAS	**Initiation**		Adults with Hb concentrations of <10.0 g/dl and for all pediatric patients with consideration of potential benefits and harms			When the Hb concentration is between 9.0 and 10.0 g/dl
		Maintenance		Based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose, and clinical circumstances Pediatric: ESA therapy aimed at a range of 11.0 to 12.0 g/dl Use of iron indexes to help guide therapy, with considerations of infection risk from excess iron and suboptimal ESA responsiveness			
		Hyporesponsiveness	**Diagnosis (**Initial)	No increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing			
			Diagnosis (Subsequent)	After treatment with stable doses of ESA, patients require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable to maintain a stable Hb concentration			
			Management	Treatment for specific causes of poor ESA response Individualization of therapy, accounting for relative risks and benefits			
	Precautions			Administration of IV iron is avoided in patients with active systemic infections Monitoring for 60 minutes after IV iron infusion Addressing correctable causes of anemia prior to initiation ESA therapy ESA therapy not to be used to intentionally increase the Hb concentration to >13 g/dl ESAs are to be used with caution in patients with a history of malignancy, active malignancy, and a history of stroke			

Notes: Data from Kidney Disease Improving global outcomes Anemia work group.[8]

the factors that modify the response to the use of this class of drugs and development of strategies to optimize the benefits of treating anemia are essential.

ESA Response Conditioning Factors and Optimization Strategies

Iron Deficiency

The optimal management of iron deficiency in patients with CKD remains unclear.[19] However, Iron deficiency significantly increases the risk of anemia in CKD and is considered a causative factor of the resistance to EPO across CKD stages.[8,19,20]

This may be due to a true paucity of iron stores (absolute iron deficiency) or a relative (functional) deficiency, which prevents the use of available iron stores. Several risk factors contribute to absolute and functional iron deficiency in CKD, including blood losses, impaired iron absorption, and chronic inflammation.[8,19,20]

The consensus is that iron therapy can increase serum Hb levels, postpone the need for ESA therapy, and optimize the response to treatment.[1,8] Clinical practice guidelines recommend that oral iron will, in general, be sufficient to maintain and may be sufficient to attain the Hb within targets in ESA treated CKD patients not yet requiring dialysis and in those on peritoneal dialysis. However, in patients with resistance to ESA therapy on oral iron, or intolerant to oral iron, a therapeutic trial of IV iron trial seems reasonable. In contrast, most hemodialysis (HD) patients with iron deficiency will require IV iron.[1,8,19]

Dialysis clinics currently use dosage protocols that establish the prescription and intravenous (IV) administration of iron. These protocols consider the patient's iron index level and clinical progression to recommend the treatment, with the main objective of reaching a Hb target without exceeding the upper ferritin and transferrin saturation (TSAT) limits. Consequently, the dose, frequency, and duration of the treatment (dosing approach) are repeatedly adjusted when updated iron indexes and clinical features become available. These dosing protocols are known as dynamic administration strategies.[21]

The 2012 Kidney Disease Improving Global Outcomes guideline proposes two strategies for the routine administration of IV iron in hemodialysis patients as follows: the periodic strategy, serial administration to replenish iron reserves, or the maintenance strategy, administration of smaller doses at regular intervals to stabilize iron storage.[8]

Studies on the toxic effects associated with IV administration of higher doses of iron in hemodialysis patients are controversial. However, they are unanimous in showing that an IV regime of high iron doses results in the use of lower ESA doses.[16–19] Thus, in the absence of contraindications (Table 1), iron replacement may be a necessary strategy to reverse ESA resistance cases, although the negative iron toxicity effects should be considered, especially in older patients with high ferritin levels.[21]

Chronic Inflammation

Most CKD patients present a chronic inflammatory state with increased levels of inflammatory markers, such as C-reactive protein (CRP), interleukin (IL) −1, IL-6, Interferon-gamma (IFN-g), and tumor necrosis factor-alpha (TNF-α),[15] and increasing prevalence is associated with decreased renal function.[22,23]

Uremic syndrome, heart failure, persistent infections, biocompatibility of the dialyzer membrane, use of catheters, accumulation of advanced glycation products, and progressive decrease in the glomerular filtration rate (GFR) may contribute to the development of inflammation in CKD, with consequent production of inflammatory cytokines.[24]

Cytokines have a direct effect on cell differentiation from the erythrocyte pathway and mediate the induction of apoptosis. They also interfere with the EPO-mediated signaling pathway, inhibiting the expression and regulation of specific transcription factors involved in the control of erythrocyte differentiation.[25]

The responsiveness of erythrocytic progenitor cells to EPO appears to be inversely related to the severity of the chronic disease and the amount of circulating cytokines. The presence of high concentrations of IFN-g or TNF-α causes the need for higher amounts of EPO to restore the formation of erythrocyte colony forming units.[26]

In HD patients, inflammation has been associated with EPO resistance mainly because the inflammatory state decreases the bone marrow response to ESA, changing iron regulation through hepcidin upregulation and/or causing red blood cell/erythrocyte hemolysis.[14]

Recently, the Dialysis Outcomes and Practice Patterns Study, a prospective cohort study conducted between 2009 and 2018, evaluated 12,389 hemodialysis patients in 21 countries and reported that new inflammation, defined as an acute increase in C-reactive protein (CRP) level, decreased the Hb response to ESA treatment. Patients with increased CRP levels have rapidly decreased Hb levels and increased ESA doses, which result in an increase in the prevalence of ESA hyporesponsiveness.[18]

Thus, the measurement of circulating levels of immunoinflammatory mediators, as well as the investigation of polymorphisms of the genes that encode these immunoinflammatory mediators, show that patients with CKD present a pro-inflammatory state, according to the phenotype, which is more evident in the measure in which the kidney injury progresses to terminal stages.[27]

These evidences suggest that early recognition of inflammatory states can help identify the cause of EPO resistance and guide decisions on ESA and IV iron dose adjustments. In addition, frequent inflammation evaluation can help identify potential candidates for the use of new therapies for anemia that are less sensitive to the inflammatory state, such as hypoxia-induced prolyl hydroxylase inhibitors.[28]

Hypoxia-inducible factor (HIF)-prolyl hydroxylase plays the central role in oxygen sensing. In the presence of sufficient oxygen, prolyl hydroxylases (PHDs) degrade HIF. When hypoxia is present, HIF is stabilized and promotes the transcription of many genes responsible for cellular protection against hypoxia, including erythropoietin.[1]

HIF-2 appears to play an important role in regulating erythropoietin production and activating iron metabolism. Currently, PHD inhibitors which stabilize HIF-α, are being studied for the potential treatment of anemia in patients with CKD.[1]

Although these drugs are currently limited to the Chinese and Japanese markets, the establishment of clinical studies and the definition of their safety profiles will warrant their availability in other countries in the future.

Nutritional Status

Patients with CKD are at substantial risk of malnutrition, characterized by loss of protein energy (state of decreased body protein and energy fuel reserves).[13,29,30] Their nutritional status is affected by the general decrease in nutrient intake, dietary restrictions, intestinal malabsorption, inflammatory state, metabolic acidosis and dialysate losses (in dialysis patients). These situations increase the risk for micronutrient deficiencies (folic acid, vitamin B12, and iron)[31,32] and can favor the onset of anemia.[13]

Observational studies have shown that nutritional status is associated with EPO resistance in HD patients, mainly because of malnutrition-inflammation status.[10,30,33,34] For this reason, the nutritional status and body composition of these patients must be carefully evaluated to implement early interventions to support adequate EPO response and consequently, decrease the incidence of anemia.[30]

Individualized management of nutritional intake is a crucial aspect of care for individuals diagnosed with any stage of CKD, including those on maintenance dialysis. Therefore, it is essential that such individuals receive tailored nutrition assessment and counseling to prevent and treat protein-energy wasting, mineral and electrolyte disorders, and other metabolic co-morbidities associated with CKD.[35]

It is important to consider that malnutrition or protein energy waste is just one of the aspects related to CKD that can influence ESA resistance. However, further studies are needed to evaluate if the modulation of nutritional processes can improve the response to these drugs.

Secondary Hyperparathyroidism

CKD is associated with mineral and bone disorders (CKD-MBD) that start early in the course of the disease and worsen with its progression. In the final stages of CKD, parathyroid hormone (PTH) synthesis and secretion are continuously stimulated, causing secondary hyperparathyroidism (HPTS).[36]

Although CKD-MBD is the most widely recognized consequence of HPTS in these patients, consistent evidence shows that PTH and fibroblast growth factor 23 (FGF23), both with markedly elevated levels in HPTS, have multiple adverse effects on extraskeletal tissues, including the pathological development of anemia.[37]

The classical pathogenesis of anemia associated with HPTS in hemodialysis patients with CKD is established by excessive PTH secretion, which leads to bone marrow fibrosis and a consequent interference in erythropoiesis. Thus, HPTS severity and expanded bone marrow fibrosis increase the EPO dose required to obtain an adequate response. In addition to this pathway, PTH is identified as a uremic toxin that suppresses endogenous EPO synthesis, inhibits bone marrow erythroid progenitors and decreases red cell survival. High FGF23 levels cause chronic inflammation, which can also contribute to anemia and EPO resistance in these patients.[38]

Accumulated evidence supports the causal role of PTH in anemia in patients with CKD and provides an additional justification to control the secretion of this hormone in these patients.[38,39] Thus, HPTS control should be considered a strategy for EPO resistance reversal. Several treatment options are available, including vitamin D receptor activators, cinacalcet hydrochloride, and parathyroidectomy.[36]

However, the Mineral and Bone Disorders Outcomes Study for Japanese Chronic Kidney Disease Stage 5D Patients, a multicenter prospective cohort study conducted with hemodialysis patients with HPTS, showed that the use of a calcimimetic drug promoted a relatively small increase in Hb level and that further investigations are needed to define the role of calcimimetic drugs to control anemia.[39]

Other Important Factors

The interaction of ESAs with antihypertensive drugs of the class of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) can decrease the hematopoietic response to ESA. Renin-angiotensin system inhibition decreases erythropoiesis, and ACE inhibition can lead to a high level of negative erythropoiesis regulation.[40] Currently, ACE gene polymorphisms are known to largely influence ACE serum activity.[41] Thus, some patients may be more susceptible to ESA resistance when using ACE and ARB inhibitors. The exclusion of these therapeutic classes for the treatment of arterial hypertension in these patients can be an interesting strategy to optimize the treatment of anemia.

The treatment with ESA is well tolerated by most patients and anti-erythropoietin antibody associated pure red cell aplasia (PRCA) is a very rare cause of resistance. Nonetheless, pure red cell aplasia (PRCA) due to anti-erythropoietin antibodies should be suspected in an individual who has previously responded to EPO if the Hb level declines by >2 g/l per month or the reticulocyte count is <20,000/uL.[19] Anti-erythropoietin receptor autoantibodies have been detected in some HD patients and their presence was an independent and significant factor of resistance to ESAs.[37] Therefore, after excluding the most frequent causes of EPO resistance, it is important to investigate the presence of anti-erythropoietin receptor autoantibodies in serum.

In dialysis patients, inadequate dialysis can cause ESA resistance.[39] Although the mechanism that links dialysis to ESA resistance is not yet fully understood, therapy adequacy has been linked to the use of lower ESA doses in patients with CKD.[40,42] HD session duration has also been related to EPO response. A study conducted with 300 HD patients showed that the addition of 1 hour of treatment can reduce the EPO dose by approximately 2000 IU/week.[42]

ESA Adjuvant Therapies

Adjuvant therapies aimed at optimizing ESA response may be a promising strategy in the treatment of anemia in patients with CKD. Positive results on decreased ESA resistance with the use of L-carnitine,[43,44] ascorbic acid,[45,46] vitamin,[47,48] statins,[47,48] zinc[49] and ferric citrate[50] have been reported. However, the current international guidelines do not recommend adjuvant therapies, and iron, folic acid and vitamin B12 supplementation is only recommended when the need is diagnosed and not as a routine prescription for ESA optimization.[8,51]

Adjuvant therapies will only be recommended with consistent evidence of effective anemia treatments in ESA-resistant patients, which require controlled randomized studies to define the potential benefits of using these substances to treat ESA resistance.

Conclusion

Resistance to ESA treatment can increase the risk of negative outcomes in patients with CKD. Considering the weak evidence on the efficacy of ESA adjuvant drug therapies, reversing or controlling the potential causes of resistance seems to be the best strategy so far. It is important to individualize anemia management in these patients to identify the potential causes of resistance and apply the appropriate intervention for each patient before proposing an increased ESA dosage.

Disclosure

The authors report no conflicts of interest in this work.

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