Journal of Population Therapeutics & Clinical Pharmacology

An Effective Adjuvant Therapy In Treatment Of Anemic Hemodialysis Patient With Hypozencemia: A review article

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ABSTRACT

Anemia of chronic renal disease is of multifactorial origin, the widely accepted etiology being decreased renal production of erythropoietin (EPO), the hormone responsible for stimulating red blood cell production. Decreased erythropoietin has recently been linked with the downregulation of hypoxia-inducible factor (HIF), a transcription factor that regulates gene expression of erythropoietin. Other mechanisms include uremia (leading to RBC deformity responsible for hemolysis), folate and vitamin B12 deficiency, iron deficiency, bleeding due to dysfunctional platelets, and rarely blood loss from hemodialysis.Treatment of end-stage renal disease involves correcting parameters at the level of the patient's presentation Interventions aimed at slowing the rate of kidney disease. Zinc is one of the most valuable trace elements in the body, and the symptoms caused by zinc deficiency may not be limited to anemia but may also include systemic symptoms, such as hair loss, dermatitis, and dysgeusia. Zinc deficiency is also an important cause of renal anemia in CKD, but reports on this are scarce. However, anemia is very common in CHF. The aim of this article to review an effective adjuvant therapy in treatment of anemic hemodialysis patient with hypozencemia.

Keywords: Hypozencemia; Hemodialysis Patients; Anemia; Zinc Supplementation

Introduction

More than 500,000 people in the United States live with end-stage renal disease (ESRD). The development of chronic kidney disease (CKD) and its progression to this terminal disease remains a significant cause of reduced quality of life and premature mortality. Chronic kidney disease (CKD) is a debilitating disease, and standards of medical care involve aggressive monitoring for signs of disease progression and early referral to specialists for dialysis or possible renal transplant. The Kidney Disease Improving Global Outcomes (KDIGO) foundation guidelines define CKD using kidney damage markers, specifically markers that determine proteinuria and glomerular filtration rate. By definition, the presence of both factors (glomerular filtration rate [GFR] less than 60 mL/min and albumin greater than 30 mg per gram of creatinine) along with abnormalities of kidney structure or function for greater than three months signifies chronic kidney disease. End-stage renal disease is defined as a GFR of less than 15 mL/min **(1)**.

According to KDIGO 2012 clinical practice guideline, CKD is classified into five stages considering the GFR level **(2)**.

Treatment of end-stage renal disease involves correcting parameters at the level of the patient's presentation Interventions aimed at slowing the rate of kidney disease should be initiated and can include: treating the underlying cause and managing blood pressure and proteinuria. Blood pressure should be targeted to a systolic blood pressure of less than 130 mmHg, and diastolic blood pressure of less than 80 mmHg in adults with or without diabetes mellitus whose urine albumin excretion exceeds 30 mg for 24 hours. For diabetic patients with proteinuria, an angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin 2 receptor blocker (ARB) should be started in cases where urine albumin values range between 30 and 300 mg in 24 hours and greater than 300 mg in 24 hours. These drugs slow the disease progression, particularly when initiated before the GFR decreases to less than 60 mL/min or before plasma creatinine concentration exceeds 1.2 and 1.5 in women and men, respectively **(3,4)**.

Waiting for uremic symptoms to set in before commencing RRT had added risks of the patient being malnourished with increased mortality risk. Asking patients to compare their current eating habits and physical activity levels with those 6 to 12 months back helps avoid the lack of awareness. The concept of a 'healthy start,' with dialysis commencing before the onset of severe uremia symptoms, is associated with prolonged survival. An early start will prepone the need for a change of modality or further procedures without any improvement in the quality of life while adding to healthcare costs. The Renal Physicians Association's (RPA) criteria for identifying dialysis patients with a poor prognosis beyond 75 years of age **(5)**.

Epidemiology

The condition usually develops following a greater than 50 percent loss of kidney function, typically when the glomerular filtration rate (GFR) decreases to less than 60 mL/min/1.73 m^2. The severity of anemia tends to worsen as chronic kidney disease (CKD) progresses. The deficiency in renal production of erythropoietin and the severity of anemia do not always tend to correlate with the severity of renal dysfunction. At least 90% of patients who end up on dialysis will eventually develop anemia of chronic disease **(5).**

Anemia is a common complication in chronic kidney disease (CKD), and is associated with a reduced quality of life, a worse renal survival, an increase in morbidity and mortality, and higher costs. Several studies focused on prevalence of anemia on CKD non-dialysis dependent (NDD) report variable anemia rates up to 60% **(6)**. Regarding new onset of anemia, the observational study NADIR-3 followed CKD stage 3 patients without anemia during 3 years. The authors estimated an annual rate of onset of anemia of 11% in the first year, 20% in the second year and 26% in the third year. In addition, the study revealed that those that had developed anemia significantly progressed more rapidly to CKD stages 4–5, had higher rates of hospitalizations (31.4 vs. 16.1%), major cardiovascular events (16.4 vs. 7.2%) and mortality (10.3 vs. 6.6%) **(7).**

Pathophysiology

The mechanisms of anemia in CKD are multifactorial. The progressive reduction of endogenous erythropoietin (EPO) levels has classically been considered to play a preeminent role. However, other factors have also been described to contribute to anemia in CKD patients, such as an absolute iron deficiency due to blood losses or an impaired iron absorption, an ineffective use of iron stores due to increased hepcidin levels, systemic

inflammation due to CKD and associated comorbidities, a reduced bone marrow response to EPO due to uremic toxins, a reduced red cell life span, or vitamin B12 or folic acid deficiencies **(8)**.

EPO is a glycoprotein (30.4 kDa) that binds to its receptor on the surface of erythroid progenitor cells mainly in the bone marrow, and serves as a key stimulus for red cell survival, proliferation and differentiation. EPO is produced predominantly by the fibroblast-like interstitial peritubular cells of the kidneys, and in a much lesser proportion, by the perisinusoidal cells in the liver, in response to changes in tissue oxygen tension. The production of EPO is controlled at the level of the EPO gene transcription. One of the most important factors that regulate its expression is the hypoxia-inducible factor (HIF) system, whose activity depends on the tissue oxygen levels **(9)**.

Recent work has shown that the HIF transcription factors are key elements in the control of cell metabolism and function. An effect of HIF on total and LDL-cholesterol levels has also been described, probably in part by the effects of HIF on degradation of the rate-limiting enzyme, 3-hydroxy-3-methylglutaryl-CoA reductase , similar to what has been observed in high altitude settings **(10)**.

In CKD patients, EPO levels are inadequately low with respect to the degree of anemia. EPO deficiency starts early in the course of CKD, but it appears that when eGFR falls below 30 ml/min per 1.73 m^2 this deficiency becomes more severe. This absolute EPO deficiency can be caused by a decrease in the EPO production and/or by errors in EPO-sensing. CKD associates an alteration in oxygen delivery to the kidneys due to a reduced blood flow. This results in an adaptation of renal tissue to consume less oxygen and the subsequent maintenance of a normal tissue oxygen gradient. As a consequence, PHD enzymes remain active, the HIF heterodimer is not formed and the EPO gene is not activated **(11)**.

Furthermore, it has been demonstrated experimentally that hypoxia-induced EPO production is inhibited by some inflammatory cytokines such as interleukin-la (IL-la), IL-l beta, transforming growth factor-beta (TGF-beta), and tumor necrosis factor-a (TNF-a). It is well-known that CKD itself leads to an increase of inflammation and immune activation molecules, which would inhibit hypoxia-induced EPO production **(12)**. However, this mechanism of EPO production seems to be blunted rather than abolished in some CKD patients, as they are able to produce additional endogenous EPO in their kidneys and liver under certain circumstances **(Fig. 1)**. For instance, when exposed to high altitude or bleeding. Apparently, augmentation of HIF signaling can revert quiescent EPO-producing and oxygen-sensing (REPOS) cells back to EPO production **(13)**. This has been confirmed in observational studies, where hemodialysis patients living in higher altitude require lower doses of recombinant human EPO (rhuEPO) **(14)**.

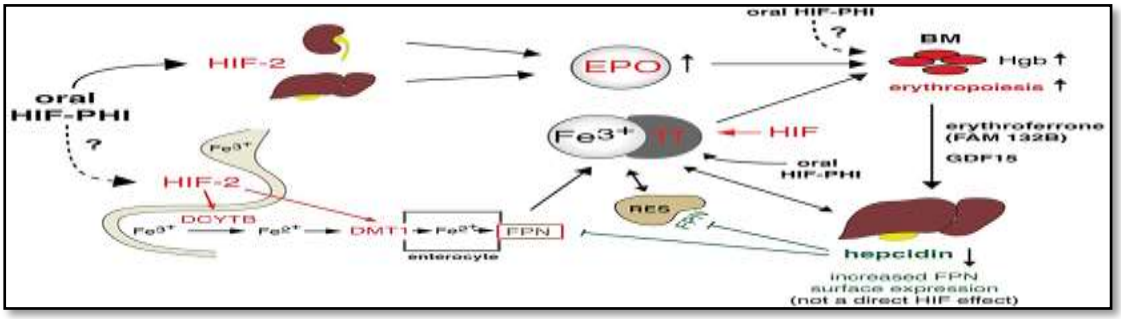

Figure (1): Integrated model for CKD-anemia physiology and actual and potential treatments. HIF, hypoxia-inducible factor; Fe, iron; HIF-PHI, hypoxia inducible factor prolyl hydroxylase inhibitor; EPO, Erytrhopoietin; Tf, transferrin; DCYTB, duodenal cytochromeb; DMT1, divalent metal

transporter 1; BM, Bone marrow; FPN, ferroportin; GDF15, Growth differentiation factor 15; Hgb, hemoglobin; RES, Reticuloendothelial system; FAM132B, Gene that codes for erythroferrone **(13).**

Erythropoiesis-Stimulating Agents (ESAs)

The first EPO analog available was epoetin α and short time later epoetin β. It is produced by recombinant DNA technology in cell cultures. Darbepoetin alfa (DA) and methoxy polyethylene glycol-epoetin beta where developed thereafter and presented a prolonged half-life. More recently, biosimilars of the original epoetin have been introduced in the market **(12)**.

Not all ESAs are equal. They have different pharmacokinetic and pharmacodynamic properties, such as different half-lives and EPO receptor affinity, allowing a less frequent dosing and ease of administration for NDD CKD patients with long-acting ESAs. In addition, it is important to point out the fact that the conversion factor between short-acting and long-acting ESAs is likely not linear. In fact, at higher doses, long-acting ESAs are more dose-effective . However, based on efficacy and safety data, various Cochrane metaanalysis advocate for insufficient evidence to suggest the superiority of any ESA formulation or any ESA administration pattern **(15)**.

Some observational studies have shown conflicting results regarding such outcomes. For instance, the Study of the Japanese Registry of Dialysis that showed a 20% higher risk of mortality from any cause in patients treated with long-acting ESAs compared to those treated with short-acting ESAs. On the contrary, an Italian observational study in ND-CKD that showed a higher risk of progression to ESKD and mortality in patients receiving short-acting ESAs at high doses **(16)**. These results should be taken cautiously due to the study design and the risk of bias. In contrast, a recent randomized controlled trial (RCT) comparing monthly administration of CERA with reference shorter-acting agents epoetin alfa/beta and DA, showed non-inferiority regarding Hb target achievement, major adverse cardiovascular events or all-cause mortality in NDD and DD-CKD. It was however observed that patients who did not achieve levels of Hb above 10 g/dL or those at the highest quartile of ESA dose, had a higher risk of CV events or death, independent of the assigned treatment. More RCTs are needed to assess the differences between different ESA formulations and administration patterns, particularly in patients requiring higher doses of ESA **(17).**

Anemia in CKD-Key Points

The pathophysiology of CKD-anemia is multifactorial, thus requiring a holistic approach. Not all ESA are equal and whether their different pharmacokinetics and pharmacodynamics is associated with different outcomes in CKD patients remains to be elucidated. Iron is essential for other physiologic process beyond erythropoiesis. Observational studies in NDD-CKD patients suggest that iron deficiency is associated with worse outcomes, paving the way to randomized controlled trials that demonstrate the benefit of correcting iron deficiency beyond anemia. The upper limits of ferritin and TSAT indicating iron overload and risk of developing adverse events are still not clear, especially in the long-term. HIF prolyl hydroxylase inhibitors are new drugs under clinical evaluation. The available data suggest that they are efficacious and safe alternatives to ESA for the treatment of anemia in NDD and DD-CKD patients with several potential advantages over current therapies. However, more data is required to confirm these findings **(14-18)**.

Individualizing Hb Target According to the Patient Profile

The target Hb concentration during ESA therapy is still controversial. Studies early after the appearance of rhuEPO demonstrated its efficacy in reducing the need for blood transfusions, the symptoms related to anemia and an improved quality of life. Various landmark trials have dwelt on the convenience of a complete correction of anemia. Indeed, in the CHOIR trial the use of a target Hb level of 13,5 g/dl was associated with increased risk of suffering a composite of death, myocardial infarction, hospitalization for congestive heart failure and stroke, and no incremental improvement in the quality of life **(19)**.

Guidelines acknowledge that the optimal strategy to manage iron metabolism remains unclear, and advocate for balancing the potential benefits and risks of iron supplementation. In recent years some good quality pre-clinical studies, clinical trials and epidemiological studies have shed some light on the therapeutic approach regarding iron deficiency in CKD and will surely change clinical practice **(20)**.

Intravenous (IV) iron has shown benefits both in DD-CKD and more recently in NDD-CKD, as it has proved to be more efficacious in rising ferritin and Hb levels, while reducing ESA and transfusion requirements. Specifically, in hemodialysis patients, oral preparations seem to be useless, maybe except for the phosphate binder ferric citrate. In addition, gastrointestinal intolerance and constipation reduce tolerance and compliance of oral iron formulations **(21)**. However, some concerns raised about IV iron formulation such as enhanced oxidative stress, endothelial dysfunction or the potential role in favoring infection. Further, IV iron administration has been associated with an increased risk of hypotension, headaches or hypersensitivity reactions. Labile iron, which is the iron that is freed into the circulation after administration and non-bound to transferrin, is an important cause of such adverse reactions **(22).**

IV iron supplements are non-biologic complex drugs. An iron core, covered by a complex structure of polysaccharides forms them. Indeed, the differences in the structure of the molecule among different IV iron formulations may be responsible for the differences in outcomes of each IV iron formulation. Some studies have even demonstrated differences in the attainment of Hb levels between the "original" brand and its generic form of iron sucrose **(23).** On the other hand, there is growing evidence that oral compound can have a deleterious effect on gut microbiota which may worsen uremic dysbiosis . Whether oral iron induced changes in gut microbiota, increases uremic toxins production and/or inflammation in CKD remain to be elucidated **(24).**

Dosing Patterns: The "Iron First-Approach" and the "High Dose-Low Frequency Approach"

Iron is essential for an adequate erythropoesis. In this sense, several trials have demonstrated that the correction of iron deficiency lessens the need for ESA in CKD patients (FIND: CKD). Hence, results from TREAT study demonstrate that control group receiving only IV iron but no ESAs may increase Hb by 1 g/dl. The so called "iron fist approach" suggested by guidelines (CITA) is based in his efficacy for anemia correction. Unfortunately, we have no evidence of the effect on hard end-points. Moreover, the risk of Hb overshooting depends on high levels of EPO but no IV iron use, since iron is not a growth factor **(25)**.

In addition, various studies carried out in patients with heart failure (HF) with reduced ejection fraction and iron deficiency demonstrated that IV iron supplementation have shown an improvement outcomes, HF symptoms, functional class and quality of life, Large registry data show that CKD is present in 12 to 74% of HF cases and that its prevalence increases as renal function declines **(26)**.

The Anemia Working Group of the Spanish Society of Nephrology published a review advocating for this "iron first-approach" and recommending the administration of IV ferric carboxymaltose in patients with CKD, HF with reduced ejection fraction and iron deficiency, even in the absence of anemia, extrapolating the recommendations of the Heart Failure Guidelines of the European Society of Cardiology **(22).**

Moreover, newer IV iron formulations are more stable and have safer profiles that allows the administration of higher doses of iron per session. The recent PIVOTAL trial has confirmed the efficacy and safety of high-dose IV iron sucrose: it is a UK open label, randomized controlled trial among 2,141 incident hemodialysis patients, that compared a proactively administered high-dose IV iron regimen with a reactively administered low-dose regimen **(27).**

The trial demonstrated that a proactive high-dose schema reduced the death of all causes or an aggregated of non-fatal cardiovascular events. In addition, the high-dose regimen was not associated with higher risks of death, major adverse cardiovascular events, or infection. These findings should lead to a change in clinical guidelines **(18).**

Iron overload is a condition of elevated body iron content associated with signs of organ dysfunction that is presumably caused by excess iron. Some studies have demonstrated an increase in the liver iron content in hemodialysis patients, and an association between hepatic iron overload and hepatic steatosis has been recently described. However, its clinical relevance is still not known, and no deposits have been observed in other territories, such as cardiac or pancreatic **(28).**

Patients that received higher doses of IV iron did not show a higher risk of mortality, infections or cardiovascular events. Nonetheless, the strength of the findings is limited by the small number of patients and of events in the clinical trials, and by the statistical heterogeneity in the observational studies included **(29).**

A recent epidemiological study has shown a slight higher mortality risk in patients with NDD-CKD and ferritin levels above 500 ng/ml, compared to patients with no iron deficiency, and patients with absolute or relative iron deficiency. These findings should be taken cautiously due to the presence of possible confounding factors. On the contrary, incident hemodialysis patients in the proactive high dose iron regimen in the PIVOTAL study showed a reduced risk in the primary end point (composite of death, MI, stroke, hospitalization and HF), as mentioned above in this article, and achieved higher mean ferritin levels (without exceeding 700 ng/ml, as per protocol). The upper limits of iron targets and the long-term safety of high doses of IV iron supplementation, specially of the accumulated high iron doses in hemodialysis patients, still needs to be clarified **(30)**.

Efficacy of HIF Prolyl Hydroxylase Inhibitors

Roxadustat is the most advanced HIF-PHI under clinical development, which has already been approved in China and Japan. Two phase 3 studies were published in 2019 comparing roxadustat with placebo in NDD, and with epoetin alfa in DD-CKD patients in China. These studies had a relative small sample size a study population and of short duration. The former compared roxadustat with placebo, without adjuvant iron supplements, and demonstrated its efficacy in rising hemoglobin levels after 9 weeks. The latter compared roxadustat with epoetin alfa, with iron supplement only as a rescue therapy. After 26 weeks of follow up, the attained hemoglobin levels in the roxadustat group were non-inferior to those in the epoetin alfa-arm, and both groups had a similar safety profile. These results were

similar to those found by a phase 3 study comparing roxadustat to ESAs in hemodialysis and peritoneal dialysis patients in Japan **(31).**

The results of several phase III clinical trials were presented in the past 2019 and 2020 Annual Meetings of the American Association of Nephrology. The ROCKIES, PYRENES and SIERRAS studies compared roxadustat vs. epoetin alpha in prevalent HD patients. In prevalent DD patients the risk of major cardiovascular events (MACE) was comparable between the two treatment arms, whereas there was a 16% reduction in the risk of MACE plus [HR = 0.84 (0.73, 0.97); p = 0.02] in the roxadustat group. (MACE+: Mace plus heart failure and thromboembolic events). Interestingly, patients receiving roxadustat had reduced iron needs, and those on roxadustat and an elevated C-reactive protein were able to increase Hb levels **(32).**

The results of the DOLOMITES trial were presented i in the past ERA-EDTA congress in June 2020 and in the 2020 ASN Annual Meeting. This phase 3, randomized, open-label, active-controlled study evaluated the efficacy and safety of roxadustat compared to DA in the treatment of anemia in NDD- CKD patients. The median time of follow up was 104 weeks and the study enrolled 616 adult anemic patients with CKD stages 3-5 **(33)**.

Roxadustat was non-inferior to DA in the primary endpoint, which was the achievement of Hb response during the first 24 weeks of treatment. Regarding secondary efficacy endpoints, roxadustat was superior in decreasing low-density lipoprotein cholesterol and in time to first IV iron use. Roxadustat was non-inferior in blood pressure control and time to first occurrence of hypertension, in changes in Quality of life scores, and in Hb change. The occurrence of treatment-emergent adverse events (TEAEs) was similar between the two groups, and the TEAEs leading to withdrawal of treatment were more frequent in the roxadustat group. They reported no significant differences between groups in adjudicated cardiovascular events. In all the Roxadustat studies the roxadustat patients presented an early and sustained LDL-reduction as a pleiotropic effect **(34).**

Roles of Zinc in the Process of Red Blood Cell Hematopoiesis

In the early stage of erythropoiesis, erythropoietin and IGF-1 act together to initiate hematopoiesis. IGF-1 is a hormone that is mainly produced in the liver by the action of GH. GH and IGF-1 are also related to zinc; the liver stores a small amount of systemic zinc,[35] along with considerable amounts of copper and iron. Plasma GH levels are increased during intravenous zinc administration, and IGF-1 and IGF-binding protein 3 levels are increased after oral zinc supplementation. Therefore, GH and IGF-1 levels decrease when zinc is deficient and increase with zinc supplementation. Zinc supplementation in older men significantly increases hematocrit levels, RBCs, and testosterone levels. Therefore, an increase in RBCs because of zinc supplementation may occur via androgen metabolism. Erythropoietin then regulates erythrocyte production by delaying deoxyribonucleic acid (DNA) degradation and preventing apoptosis (programmed cell death) of erythroid progenitor cells **(35).**

Safe Zinc Supplementation

With regard to the balance of zinc, copper, and iron, zinc and iron have a competitive antagonistic effect during absorption. Oral iron supplementation inhibits zinc absorption, but not copper. Notably, zinc antagonizes divalent cations, such as iron and copper, in the process of absorption by DMT1 . In addition to iron, DMT1 in the gastrointestinal mucosa transports divalent cations, such as zinc and copper, and is a common pathway for absorption in the

gastrointestinal tract. When iron is absorbed and ferritin increases, hepcidin binds to ferroportin, and ferroportin is internalized and degraded, leading to decreased export of cellular iron **(36).**

When a patient on hemodialysis is unable to maintain a target hemoglobin value (hemoglobin level of 100-120 g/ L), despite erythropoiesis-stimulating agent treatment, if the patient has a serum ferritin level of, 100 ng/mL (,224.7 pmol/L) and a transferrin saturation of ,20%, iron supplement therapy is recommended. Mean corpuscular hemoglobin is controlled to 30-35 pg, and if it is, 30 pg, iron is replenished. The RBC count is controlled in the range of 300-350 (10^{12}/L), and if it is 300 (10^{12}/L), erythropoietin is considered to be insufficient and use of an erythropoiesis-stimulating agent is increased **(37).**

After iron has been pumped from ferroportin, hephaestin requires copper (Fig. 4, left). Iron is converted from the divalent to trivalent form by hephaestin and is carried by transferrin. Copper is a divalent copper ion, which has a pathway that competes with iron and zinc (mentioned above); it also has a pathway that involves reduction from the divalent to monovalent form, followed by absorption in the duodenum **(38)**.

CONCLUSION:

The lack of developments in the treatment of renal anemia may accelerate the vicious cycle of cardiorenal anemia syndrome. Regular monitoring for renal anemia, especially ESA-resistant anemia, is vital.

The possibility of renal anemia due to zinc deficiency should be monitored beginning with the stage of conservative renal failure. Renal anemia and malnutrition are important disorders to monitor in patients with conservative renal failure undergoing dialysis. Furthermore, in the patients from this group who develop hypozincemia, the side effects of zinc preparations should be carefully considered.

Successful treatment is associated with a significant improvement in cardiac function, functional class, and renal function. Furthermore, a marked fall in the need for diuretics and hospitalization has been noted.

No conflict of interest.

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