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Managing Anemia with Desidustat in a Hyporesponsiveness to Erythropoietin-Stimulating Agents among CKD Patients

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ABSTRACT

Patients with chronic kidney disease (CKD) frequently experience anemia, which frequently calls for erythropoiesis-stimulating agent (ESA) treatment to maintain appropriate haemoglobin levels. However, a significant subset of CKD patients develops hyporesponse to ESAs, requiring escalating doses to achieve target haemoglobin levels. This occurrence is linked to higher rates of morbidity and mortality, especially in dialysis patients. In recent years, Desidustat, a novel prolyl hydroxylase inhibitor, has emerged as a promising therapeutic option for managing anemia in patients with CKD, particularly in those who don't respond well to conventional ESA therapy. By targeting the hypoxia-inducible factor pathway, Desidustat stimulates endogenous erythropoiesis, potentially reducing the dependence on exogenous erythropoietin and overcoming ESA resistance. This abstract outline the current approaches to managing anaemia in CKD patients, with a specific examination of desidustat effectiveness in addressing hyporesponsiveness to erythropoietin-stimulating agents. Through meticulous scrutiny of both existing literature and ongoing clinical trials, an in-depth evaluation of desidustat efficacy and safety profile is conducted, providing invaluable insights into its prospective role as a therapeutic option for optimizing haemoglobin levels and enhancing clinical outcomes in CKD patients experiencing ESA hyporesponse.

INTRODUCTION

Anemia in CKD

A glomerular filtration rate (GFR) < 60 ml/min/1.73 $m^2$for minimum of three months is indicative of chronic kidney disease (CKD), which affects 10% of adult patients. While the effects of CKD stages 1-3 are usually not significant on health, stage 4 symptoms become more prominent and may have an influence on Health-Related Quality of Life (HRQoL). A GFR of less than 15 ml/min/1.73 m^2 is associated with CKD stage 5, which is also known as renal failure (1).

Anemia, a commonly recognized consequence of CKD, is intricately associated with deteriorating quality of life, elevated morbidity and mortality rates, and the progression of CKD. A multitude of factors, including iron and nutritional deficiencies, erythropoietin (EPO) deficiency resulting from reduced renal mass, and other pro-inflammatory mediators that are frequently elevated in CKD and may influence erythropoiesis, all contribute to the complex process of anemia in CKD (2).Fatigue, depleted energy levels, and decreased physical functionality are prevalent indicators of anaemia linked to CKD, posing a significant threat to a patient's health-related quality of life. While clinical laboratory measurements such as haemoglobin have been employed to track anemia in patients, they are not sensitive to the psychological and functional aspects of the patients (3).

Causes of anemia in CKD

Inadequate EPO synthesis, abnormalities of iron metabolism, and extra variables including inflammation, infection, and malignancy that inhibit erythropoiesis are the main causes of anemia in CKD (4).

Mechanism of anemia in CKD

In the bone marrow, EPO and iron are necessary for the production of red blood cells (RBC). By affecting iron absorption from the food and iron recycling by macrophages from senescent RBCs, the liver hormone hepcidin controls the availability of iron. Hepcidin levels are controlled through iron and EPO feedback loops. Hepcidin synthesis is produced by inflammation and is commonly high in patients with CKD, particularly those receiving Hemodialysis, because of poor renal clearance (Figure 1). Consequently, erythropoiesis is limited by iron. Moreover, decreased lifespan of RBC, increased blood loss, and decreased

kidney production of EPO are all consequences of chronic kidney disease. Circulating uremic-induced inhibitors of erythropoiesis can also occur (5).

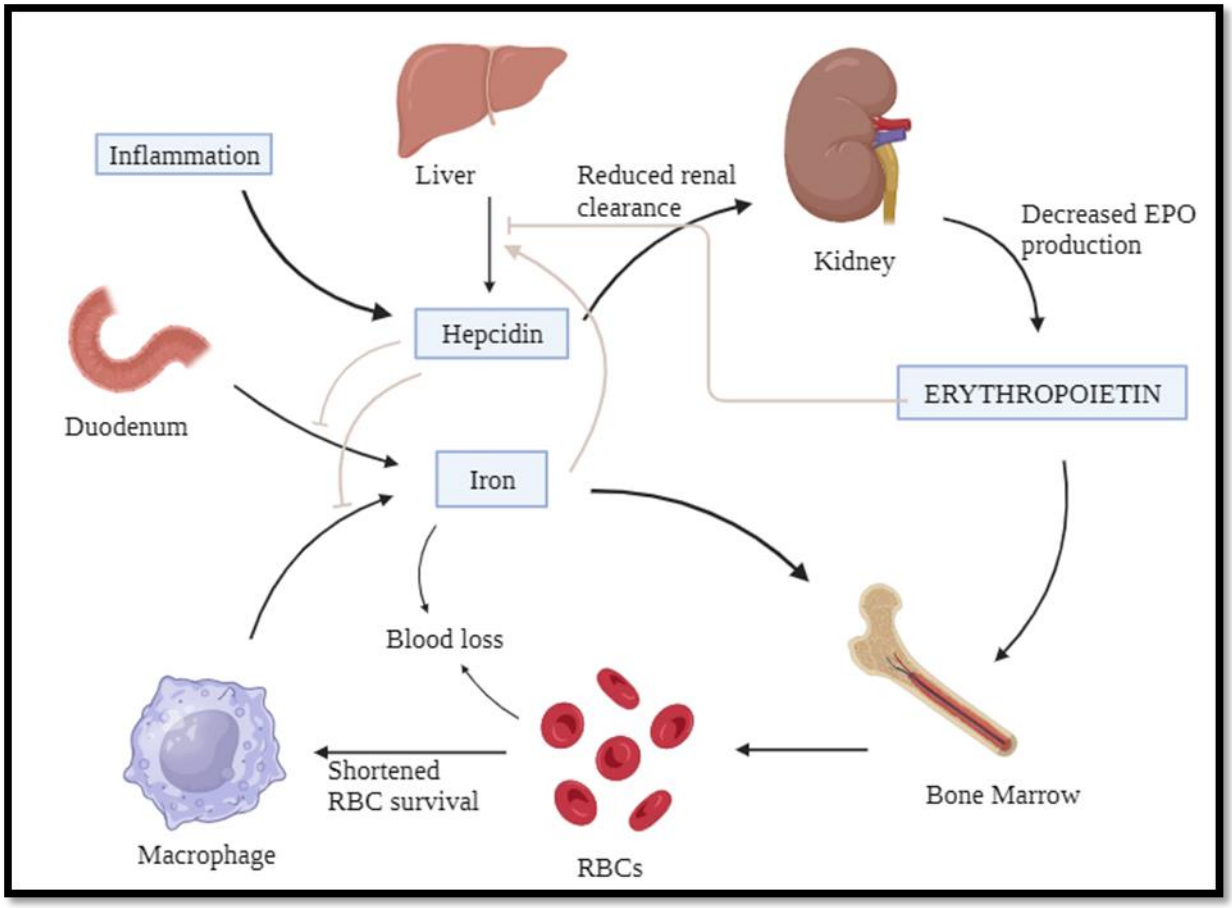

Figure 1: Mechanism of anemia

Management of anemia

Kidney Disease Improving Global Outcomes guidelines advocate red cell transfusions, erythropoiesis-stimulating agents (ESAs), and iron compounds as therapies for anemia in CKD (6).

Erythropoietin

EPO, a glycoprotein hormone weighing approximately 30 kDa, primarily originates from the kidneys during adulthood, while its synthesis in the developing embryo is largely limited to the liver. One important illustration of oxygen-dependent gene expression regulation is EPO production (7).

Erythropoietin stimulating agents

The approval of recombinant human EPO by the US Food and Drug Administration in 1989 sparked optimism for a safe and effective treatment for anemia associated with CKD, potentially leading to a global reduction in the condition's morbidity and mortality rates(8).When determining the initial dose of an ESA, consider various factors such as the patient's weight, baseline haemoglobin concentration, laboratory findings, and the rate of decline in haemoglobin concentration (9). According to the Renal Association Clinical Practice Guidelines, the recommended target haemoglobin levels for patients with CKD on ESA therapy are as follows:

- Adults and children aged 2 years and older: Target Hb levels should be between 100 and 120 g/L.

- Children age less than 2 years: Target Hb levels should be between 95 and 115 g/L, reflecting the less than normal range for that particular age group (10).

Presently available ESAs are epoetin alfa and beta (first-generation), darbepoetin (second-generation) and continuous erythropoietin receptor activators (third-generation) (11).EPO directly interacts with their receptor on the surface of RBCs to initiate a number of signal transduction pathways that promote the growth and terminal differentiation of erythroid precursor cells and shield them from RBC precursor apoptosis(12).

ESA HYPORESPONSIVENESS

ESA resistance, sometimes referred to as hyporesponsiveness, is a condition in which the patient uses ESA at higher-than-usual dosages but is unable to attain the desired serum haemoglobin concentration, or in which ever greater doses are needed to maintain the recommended Hb value (13). Resistance to ESAs has been associated with an increased risk of cardiovascular morbidity and all-cause mortality, and it has been observed in a considerable proportion of patients with CKD (14). Patients often experience reduced responsiveness to ESA therapy due to either the emergence of an inflammatory state, which diminishes ESA effectiveness, or the occurrence of genuine iron deficiency an occurrence that is increasingly rare due to the widespread adoption of aggressive iron supplementation practices (15).

Causes of ESA hyporesponsiveness

There are several factors causing resistance or hyporesponsiveness of ESAs that are presented in the following figure (2).

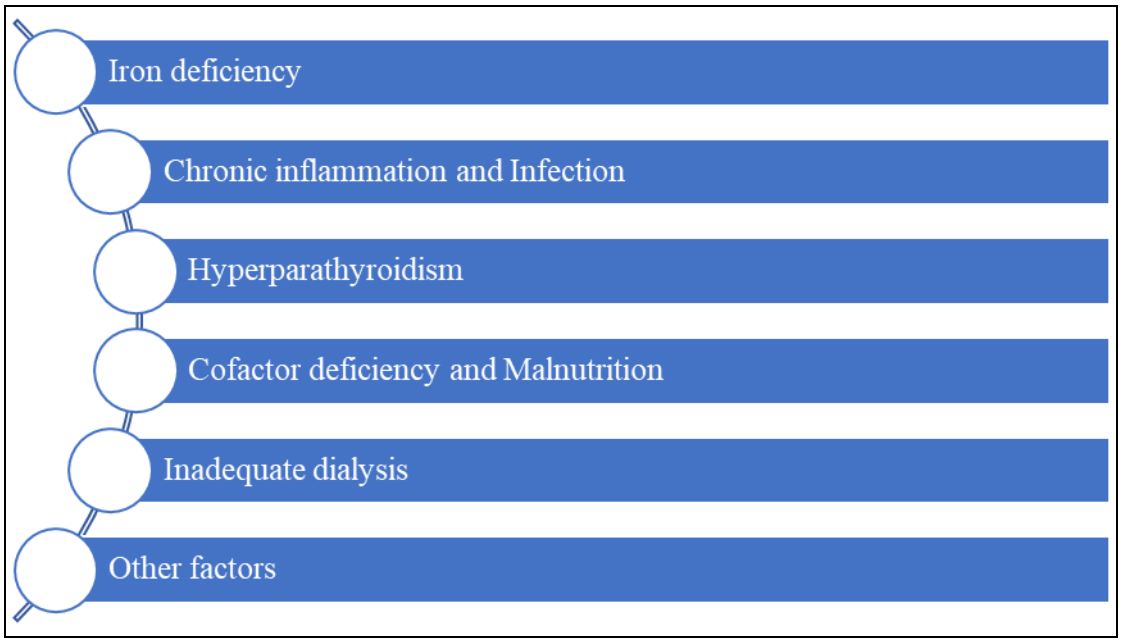

Figure 2: Causes of ESA hyporesponsiveness

Iron deficiency. Iron deficiency is a major contributing factor to the development of anemia and ESA resistance in individuals with chronic kidney disease. There are numerous reasons why people are iron deficient. Some patients have a genuine iron deficiency, whereas 10% to 20% of CKD patients have "functional" iron shortage, which results in ESA resistance (14).

Inflammation -ESA hyporesponsiveness is becoming more and more linked to inflammation, which may be caused by oxidative stress, reduced renal clearance of pro-inflammatory cytokines, advanced glycation end product build-up, and other variables like infections and medications.

Hyperparathyroidism - Secondary hyperparathyroidism has been linked to ESA hyporesponsiveness, potentially due to various mechanisms including heightened RBC fragility and direct inhibition of EPO synthesis (16).

Cofactor deficiency and Malnutrition - Insulin resistance, increased protein catabolism and decreased muscle synthesis, oxidative stress, dialysis-induced nutritional loss, and inadequate food intake are the main causes of protein energy shortage in individuals undergoing dialysis.

Inadequate dialysis - An inadequate dialysis is a primary contributing reason to anemia in patients receiving the treatment. Uremic toxins can cause harm to erythrocytes in people with chronic kidney disease. These toxins can prevent the synthesis of EPO and erythropoiesis. Moreover, the dialysis process results in blood loss and mechanical harm to erythrocytes (17).

Other factors- Antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) can lessen the haematological response to ESAs when taken together (13)**.**

Table 1: Studies related hyporesponse to erythropoietin-stimulating agents

S.NO	AUTHOR	STUDY POPULATION	STUDY DESIGN	CONCLUSION
1	Kristina Petruliene et al (2017) (14).	173 adult patients on maintenance hemodialysis.	Stratified Randomization	Study revealed that a positive correlation between serum hepcidin and erythropoietin. Erythropoietin resistance index and ferritin were found to be significant determinants of hepcidin in maintenance hemodialysis patients.
2	Shiva Samavat et al. (2017) (18).	1224 patients from 22 dialysis centres in Tehran, Iran	A multicentre cross-sectional study	Iron deficiency, dialysis inadequacy, poorly controlled serum phosphate level and treatment with ACEI/ARBs might be responsible for ESA hyporesponsiveness.
3	Luo J et al (2016) (19).	98,972 hemodialysis (HD) patients between 2012 and 2013.	Retrospective observational study.	ESA hyporesponsiveness was consistently and potentially associated with lower haemoglobin levels, higher iron and ESA consumption, and higher mortality than non-ESA hyporesponsiveness.
4	Okazaki M et al (2014) (20).	248 patients	A prospective cohort research	Greater levels of resistance to ESA are associated with a greater death rate in people with chronic HD.
5	Suttorp M M et al (2013) (21).	1013 HD and 461 Peritoneal dialysis (PD) patients	Dutch multi-centre prospective	Both HD and PD patients have higher mortality rates when they exhibit ESA

			cohort study	resistance, as shown by their ESA and Hb categories. Although the precise mechanism is yet unknown, there is a tight relationship between haemoglobin, ESA dose, and ESA resistance.
6	Minutolo Ret al (2012) (22).	There were 194 CKD patients	A Prospective cohort study	Erythropoietin stimulating agent resistance predicts renal prognosis in patients with CKD, where end stage renal disease is the most common outcome and low-dose ESA is commonly treated.
7	Kalantar-Zadeh Ket al (2009) (23).	38,328 prevalent HD patients	A retrospective cohort studies.	Significant ESA hyporesponsiveness has been linked to poor iron reserves, hyperparathyroidism, and high-turnover bone disease in long-term HD patients.
8	MacdougallICet al (2002) (24).	47 HD patients	Prospective interventional study	Increased pro-inflammatory cytokine production by activated T cells could contribute to a poor response to recombinant human EPO.

DESIDUSTAT IN A HYPORESPONSIVENESS TO ERYTHROPOIETIN-STIMULATING AGENTS

Desidustat

In recent times, the spotlight in the field of renal anaemia has focused sharply on hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), representing a promising avenue for therapeutic intervention (25). The isoforms of prolyl hydroxylase domains (PHD) are PHD1, PHD2, and PHD3 that may differ in how they function in oxygen sensing. Notably, in human cell lines, silencing PHD2 specifically causes HIF-1α to stabilize and activate under normoxic conditions; in contrast, silencing PHD1 and PHD3 genes has no effect, indicating that PHD2 functions as the main oxygen sensor controlling HIF-1α regulation under normoxic conditions (26). Inhibiting PHD enzymes to stabilize hypoxia-inducible factor (HIF) emerges as a groundbreaking approach for managing CKD, as it fosters increased EPO synthesis and optimizes iron utilization by lowering hepcidin production (27).

In this mechanism, under normoxic conditions, the HIF-α transcription factor subunit undergoes ubiquitination and subsequent proteasomal degradation after prolyl hydroxylation. However, exposure to hypoxic environments or pharmacological inhibition of HIF prolyl-hydroxylase stabilizes HIF-α. Upon heterodimerization with HIF-β, it augments the transcription of hypoxia-responsive genes, including those involved in EPO synthesis and iron metabolism regulation (28).

Role of desidustat in a hyporesponsive state to erythropoietin-stimulating agents

The introduction of HIF-PHIs marks a notable advancement in addressing the treatment challenges faced by patients who do not respond well to rHuEpo therapy with several orally active compounds demonstrating varied structures and successfully completing clinical trials, HIF-PHIs have demonstrated their effectiveness in managing anemia in CKD patients (29).

Desidustat a prolyl hydroxylase inhibitor is used to treat anemia with EPO resistance by increasing EPO synthesis and lowering hepcidin levels. This could decrease the requirement for EPO and stop haemoglobin from declining following EPO treatment (Joharapurkar AA et al) (30).

Desidustat is being a well-tolerated and non-inferior treatment for anemia in patients with CKD undergoing dialysis. Based on comparable effectiveness and tolerability levels, desidustat could be a feasible substitute for epoetin in the therapy of anemia among CKD patients receiving dialysis (Sishir Gang et al and Kurata et al) (31, 32). HIF-PHIs showed significant improvements in iron biomarkers compared to ESAs, increasing serum iron levels and reducing the need for intravenous iron therapy, suggesting their potential as a valuable option for anaemia in dialysis-dependent patients with hyporesponsive ESAs due to iron deficiency and inflammation (Zheng Qet al) (33).

CONCLUSION

The occurrence of hyporesponse to erythropoiesis-stimulating agents presents considerable difficulties in the treatment of anemia, especially in individuals suffering from CKD. This hyporesponse has a complex relationship with increased cardiovascular morbidity and mortality risks as well as reduced quality of life. Iron deficiency and inflammation appear to be the main causes of the complex etiology of ESA hyporesponse.

Addressing this complex interplay of factors necessitates innovative therapeutic approaches. Desidustat, a prolyl hydroxylase inhibitor, emerges as a promising agent in this regard. By targeting the hypoxia-inducible factor pathway, desidustat offers a novel mechanism to stimulate endogenous erythropoiesis, thereby reducing the reliance on exogenous erythropoietin and potentially mitigating the risks associated with ESA therapy.

The promising potential of desidustat suggests a paradigm shift in the management of ESA-resistant or hyporesponsive conditions, suggesting that future combination therapies could offer superior efficacy and safety compared to monotherapy for optimizing anemia management in CKD patients.

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ABBREVIATIONS

1. ACEI - Angiotensin-Converting Enzyme Inhibitors
2. ARB - Angiotensin Receptor Blockers
3. CKD - chronic kidney disease
4. EPO - Erythropoietin
5. ESA - Erythropoiesis-Stimulating Agent
6. GFR - Glomerular Filtration Rate
7. HD - Haemodialysis
8. HIF - Hypoxia-Inducible Factor
9. HIF-PHIs - Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors
10. HRQoL - Health-Related Quality of Life
11. PD - Peritoneal Dialysis
12. PHD - Prolyl Hydroxylase Domains
13. RBC - Red Blood Cells