# Innovations in the treatment of anemia in chronic kidney failure

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## ABSTRACT

Chronic kidney disease (CKD) is a chronic inflammatory process. Inflammation, uremic toxins, deficiency of erythropoietin production, iron deficiency, shortening of erythrocyte lifespan, gastrointestinal losses, etc. lead to anemia in CKD. The prevalence of anemia increases as the CKD stage increases. Hepcidin is an important molecule for the use of iron in anemia. Hypoxia-induced factors (HIF) maintain the continuity of erythropoiesis. This molecule is inactivated by prolyl hydroxylase (PH). HIF-PH inhibitors have come into use in the treatment of anemia due to CKD. This review describes anemia in CKD and the use of HIF PH inhibitors.

**Keywords:** Chronic kidney disease, anemia, hepcidin, HIF-PH inhibitors.

The prevalence of chronic kidney disease increase worldwide. Anemia in CKD may develop due to reasons such as decreased erythropoietin synthesis, inflammation, uremic toxins, iron deficiency, malnutrition, gastrointestinal losses, etc. The incidence of anemia increases as the CKD stage increases (especially after stage 3). In CKD, patients mostly die from cardiovascular causes. Anemia and secondary hyperparathyroidism in CKD associated with mortality. Therefore, anemia should be managed well in the course of the disease [1, 2].

The ARIC study compared patients with and without anemia in CKD patients. Mortality in CKD patients with anemia was 2 times higher than in CKD patients without anemia [3]. Weilner et al. analyzed 2423 CKD patients with and without anemia. All-cause mortality was increased by 65% in patients with anemia. Myocardial infarction (MI), stroke and all-cause mortality were 48% higher in the anemia group [4]. In the presence of anemia in CKD patients, the heart engages compensatory mechanisms to increase oxygen delivery. Left ventricular hypertrophy (LVH) develops. In the presence of anemia and LVH in CKD, the risk of MI, stroke and death increase 4 times, and all-cause mortality increases 3 times [5, 6].

Quality of life in CKD patients with anemia is adversely affected. In patients stage 4 and 5 CKD with anemia, fatigue 79%, respiratory distress 39%, fatigue and weakness 36% and gastrointestinal symptoms 18% were detected. Treating anemia in CKD improves quality of life and reduces mortality [7].

## HEPCIDIN and HYPOXIA INDUCIBLE FACTORS (HIF)

Hepcidin is the main regulator of iron metabolism. Hepcidin is an acute phase reactant with protein structure. Iron overload

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and inflammation stimulate hepcidin synthesis. Iron deficiency, hypoxia, blood loss, and stimulation of erythropoiesis inhibit hepcidin synthesis. Inflammation shortens erythrocyte lifespan and stimulates their phagocytosis.

Cells that produce erythropoietin (EPO) in hypoxic conditions increase renal EPO output. Hypoxia-inducible factors (HIF) increase gene transcription and erythropoiesis in EPO producing cells. In the presence of HIF (hypoxia, iron deficiency, blood loss, etc.), EPO production and hemoglobin (Hgb) synthesis increase. Hepcidin synthesis is also decreased, iron absorption from the small intestine and iron transport to the plasma and bone marrow for erythropoiesis increase [8, 9].

HIF consists of two structures, HIF α and β. The combination of these two structures (in condtions of hypoxia, anemia, blood loss, etc.) stimulate transcription factors for erythropoiesis. HIF is inhibited by prolyl hydroxylase at normal oxygen levels. Prolyl hydroxylase (PH) is involved in the degradation of HIF. There are three PHs, mainly HIF PH2. HIF PH is inactive in cases of hypoxia, anemia, blood loss, etc. HIF continues its activity and stimulates erythropoiesis [10, 11].

In addition to stimulating erythropoiesis, HIF affects more than 1000 genes such as stimulating angiogenesis, cell migration, glucose metabolism and availability, hormonal and vasomator regulation [12, 13].

## CURRENT TREATMENTS

Three treatment options are available for CKD anemia. CKD-associated anemia was described in 1836. Oral iron use is not recommended for CKD patients due to its effectiveness. Oral iron preparations are not recommended for treatment because they have poor gastrointestinal side effects and absorption, and because they interact primarily with phosphorus binders and antacids in CKD. The use of intravenous (IV) iron instead of oral iron preparations was found to be more beneficial and effective in terms of efficacy in CKD patients. IV iron drugs have better bioavailability and rapid action, increase hemoglobin levels and reduc the need for erythropoietin stimulating agents (ESA). The most important side effects of these drugs are anaphylaxis, cytotoxicity, hemosiderosis, bacterial infection, oxidative stress, etc [14-16].

Transfusion directly increases the erythrocyte level. The most important side effects are hemolysis, alloimmunization, anaphylaxis, infections (hepatitis, HIV etc.), fluid overload, hyperkalemia etc [17, 18].

EPO-producing genes identified in the 1950s. Using ESAs started in the 1980s. With the use of ESAs, a decrease in blood transfusions and improve in quality of life have been observed. The most important side effects of ESAs are cardiovascular events, thromboembolism, hypertension and malignancy [17].

High doses of ESA and high hemoglobin levels after using ESA are associated with stroke, MI, and death. The CREATE, CHOIR, and TREAT studies have observed stroke, MI, and cardiovascular events in patients with elevated Hgb following ESA treatment. In a cohort study conducted in Japan, the mortality rate was 13% higher in CKD patients using long-acting ESA. In another study in which stage 3b and 5 non-dialysis patients and patients undergoing dialysis were evaluated, major cardiovascular events was more found as the ESA dose increased, 36% in the non-dialysis group and 60% in the group that undergo dialysis [19-21].

When the effects and side effects of current treatments are evaluated, new searches have increased in the treatment of CKD anemia.

## HIF PROLYL HYDROXYLASE INHIBITORS

Since 2008, studies on HIF-PH inhibitors have intensified. The therapeutic use of these drugs started in China, Japan and Europe as of 2018 (Roxadustat and Daprodustat). Vadadustat, Molidustat, Desidustat ve Enarodustat ile ilgili klinik çalışmalar devam etmektedir. HIF-PH inhibitors inhibit HIF-PH reversibly. These drugs prevent HIF α from being hydroxylated by PH at normal oxygen levels, causing stabilization of HIF. As a result, Hepcidin levels decrease, EPO receptors and EPO production increase. The absorption of iron from the intestine and its mobilization from macrophages and transport to the bone marrow are stimulated. The most important advantage of this group of drugs is that they can be taken orally 3 days a week (22, 23).

In studies evaluating stage 3-5 CKD patients not receiving dialysis treatment, when HIF-PH inhibitors were compared with placebo for 52-104 weeks, change in Hgb level from baseline, reaching desired Hgb levels, and maintaining Hgb levels were more significant in those using HIF-PH inhibitors. The need for blood transfusion, IV iron and ESA use were lower in those taking HIF-PH inhibitors. LDL cholesterol

levels were lower in those using HIF-PH inhibitors as a secondary effect. CKD patients receiving ESA therapy who were not on dialysis were similar to achieving the desired Hgb response compared with those receiving HIF-PH inhibitors. IV iron requirement was less in those using HIF-PH inhibitors. LDL cholesterol level was also found to be lower in the same group [24-26].

Achieving and maintaining desired Hgb levels were similar in both groups when compared with patients on new onset (< 4 months) or stable dialysis patients (> 4 months) versus those using HIF-PH inhibitors (52 weeks to 4 years). The need for transfusion and IV iron were less in the group of HIF-PH inhibitors [27, 28].

When the side effect profiles were evaluated, the risk of cardiovascular events were similar in HIF-PH inhibitors compared to the ESA group. Advers effects that developed under treatment were similar to those of the ESA group. The incidences of sepsis, deep vein thrombosis, pulmonary embolism and epilepsy in those using HIF-PH inhibitors were the same as those using ESA [29].

In conclusion, HIF-PH inhibitors will take place as an alternative in the treatment of CKD anemia. It will reduce the need for transfusion and İV iron, and oral use will facilitate patient compliance.

## CONCLUSION

*Authors' Contribution*

Study Conception: YA,; Study Design: YA,; Supervision: YA,; Materials: YA,; Data Collection and/or Processing: YA,; Statistical Analysis and/or Data Interpretation: YA,; Literature Review: YA,; Manuscript Preparation: YA and Critical Review: YA.

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