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## Advancing the Science of Anemia Due to CKD

### ReachMD Announcer:

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This medical industry feature, titled "Burden of Anemia Due to CKD" is sponsored by Akebia Therapeutics Medical Affairs. This program is intended for Healthcare Professionals.

### Announcer:

Anemia due to chronic kidney disease, or CKD, is a condition that affects close to 5 million people in the United States and is defined as hemoglobin levels <12 g/dL in women and <13 g/dL in men.

Anemia is more than two times as likely to be present in patients with CKD than in patients without CKD. And within the CKD population, the prevalence of anemia increases to over 50% in later stages of the disease. Anemia can impose a significant clinical burden on patients with CKD, including increased risk of kidney failure, hospitalization, cardiovascular disease, metabolic imbalance, and cognitive impairment.

In addition, anemia can increase the mortality rate in patients with CKD. Severity of anemia is also associated with hospitalization. In one study, as hemoglobin levels increased in patients with CKD, both hospitalization and mortality rates decreased.

Finally, studies have shown that anemia may worsen quality of life for patients with CKD, as shown by measures of physical symptoms, fatigue, and depression. Anemia due to CKD places a significant burden on millions of patients, which may affect clinical outcomes and quality of life.

Anemia due to chronic kidney disease, or CKD, has a complex, multifactorial pathogenesis. A key factor in its pathogenesis is insufficiency in the hormone erythropoietin, or EPO. EPO, along with iron, are vital components for the production of red blood cells.

To increase red blood cell production during hypoxia, the number of renal erythropoietin-producing cells, or REPCs, increases. Within these cells, hypoxia-inducible factor, or HIF, is upregulated, and activates genes associated with EPO production and iron availability. This leads to increased red blood cell production in the bone marrow. Diseases like CKD, in which the kidneys are affected by abnormalities of structure and function, can affect red blood cell production. In CKD, the number of REPCs is decreased because of trans-differentiation to myofibroblasts. This decreased number of REPCs results in lower levels of EPO production.

Additionally, in CKD, chronic inflammation is a common feature, which can contribute to anemia. When inflammation is present, hepcidin production is stimulated in the liver. Hepcidin promotes iron sequestration and decreases iron absorption via the gut, which leads to decreased red blood cell production. Activation of HIF indirectly reduces hepcidin production.

Overall, anemia due to CKD has a complex pathogenesis that involves dysregulation of oxygen sensing, insufficient EPO production, impaired iron availability, and hepcidin upregulation.

Anemia is associated with chronic kidney disease progression. For example, in a cohort of patients followed up for 3 years, patients progressed from stage 3 to stage 4 or 5 within 28 months on average. In contrast, patients with anemia due to CKD in the same group progressed faster than those with CKD alone. One of the criteria used to diagnose and stage CKD is glomerular filtration rate, or GFR. Anemia is associated with an accelerated decline of GFR in patients with CKD.

In addition to its impact on clinical measures, anemia is associated with reduced quality of life in patients with CKD. Based on kidney disease questionnaire analysis, increases in hemoglobin, were correlated with quality of life improvements. Anemia due to CKD may

lead to faster disease progression and a worsening of quality of life.

Current therapies available for anemia due to chronic kidney disease, or CKD, include iron supplementation, erythropoiesis-stimulating agents, or ESAs, and red blood cell transfusion. Iron supplementation has been shown to decrease the use of ESA rescue, and treating with ESAs may reduce the need for transfusions. Clinical guidelines recommend that a balance between potential benefits and associated risks be considered when treating patients with either iron supplementation or ESA therapy. Red blood cell transfusion may provide benefits for patients who suffer severe blood loss or who are hyporesponsive to ESA therapy. Guidelines recommend avoiding red blood cell transfusions to minimize general risk related to their use.

These treatments improve clinical measures by addressing specific components of the mechanism of anemia due to CKD. There are efforts underway to leverage recent scientific advancements that the underlying mechanism. Stabilization of hypoxia-inducible factor, or HIF, is a recent scientific advancement that may address the underlying mechanism of anemia due to CKD and regulate red blood cell production. In normoxia, oxygen-dependent prolyl hydroxylase domain enzymes, or PHD, hydroxylate HIF- $\alpha$ .

The hydroxylated HIF- $\alpha$  binds to the von Hippel-Lindau tumor-suppressor protein, or VHL, and becomes polyubiquitinated. This leads to degradation of HIF- $\alpha$  by the proteasome. As a downstream effect, HIF- $\alpha$  is unable to initiate gene activation. In hypoxia, or when oxygen is too low for PHD to be active, HIF- $\alpha$  is not degraded.

As a result, HIF- $\alpha$  translocates to the nucleus, where it dimerizes with HIF- $\beta$ . This complex initiates gene activation related to EPO production, iron availability, and hepcidin regulation. The inhibition of PHD may mimic the body's response to hypoxia and is currently under clinical investigation. By doing so, HIF- $\alpha$  stabilization has been shown to increase red blood cell production.

In closing, anemia due to CKD is a multifaceted disease, and there are efforts underway to leverage recent scientific advancements that address the underlying mechanisms.

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