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Pioneering Experience: Physiological Mechanisms and Real-World Evidence from Japan

Masaomi Nangaku

The University of Tokyo Graduate School of Medicine, Japan

Erythropoiesis-stimulating agents (ESAs) together with iron supplementation had been the standard treatment for anemia in chronic kidney disease (CKD) for the past decades. Although ESAs are well-established and highly efficacious treatment, clinical trials demonstrated that the use of ESAs with a high hemoglobin (Hb) target was associated with increased risk of cardiovascular events. This safety concern raised considerable interest in developing an alternative therapeutic strategy. Recently, hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors have attracted attention as a novel treatment option. HIF-PH inhibitors are a new class of oral drugs designed to treat anemia associated with CKD. This class of medication is based directly on the research that won the 2019 Nobel Prize in Physiology or Medicine, awarded to William G. Kaelin Jr., Sir Peter J. Ratcliffe, and Gregg L. Semenza for discovering how cells sense and adapt to oxygen availability. HIF-PH inhibitors activate HIF and promote the production of endogenous erythropoietin. Because HIF-PH inhibitors improve both erythropoietin production and iron metabolism, they are expected to be effective in treating ESA hyporesponsiveness and solve the inconvenience of injectable preparations. On the other hand, its effects are systemic and multifaceted, and long-term effects must be closely monitored. In Japan, five HIF-PH inhibitors were approved and are available at bedside. While theoretical concerns include adverse events such as cardiovascular outcomes, thrombotic events, and tumor progression, we have not observed significant adverse events in the real world. Potential benefits of HIF-PH inhibitors against ischemic diseases and progression of kidney disease should be studied in the future.

Keywords: anemia, chronic kidney disease, end stage kidney disease, HIF, HIF-PH