Recommendations on the proper use of HIF-PH inhibitor by APSN

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1. Introduction

Hypoxia Inducible Factor (HIF) is a key transcription factor primarily involved in the cellular regulation and efficiency of oxygen delivery. Its preliminary state comprises a constitutively expressed, nucleus-bound ß-subunit and three isoforms of a cytoplasmic α-subunit (HIF-1α, HIF-2α, & HIF-3α). HIF-1α and HIF-2α are master regulator of defensive mechanisms against hypoxia and enhance oxygen delivery by stimulating a variety of genes. Representative target genes are erythropoietin (EPO) and those optimizing iron utilization.

When oxygen availability is normal, the α-subunit is sequentially destroyed: first by prolyl hydroxylation by HIF-prolyl hydroxylase (HIF-PH) and then ubiquitination by the Von-Hippel Lindau (VHL) gene and the E3 ubiquitin ligase complex, which facilitate proteosomal degradation. However, prolyl hydroxylation is oxygen-dependent; hence, during periods of hypoxia HIF-PH loses its activity, and the α-subunit stabilize subsequently before undergoing nuclear translocation and forming a heterodimer with the ß subunit.

As the oxygen sensing mechanism and the adaptive response against hypoxia is so important and essential, three great scientists who elucidated this mechanism, Peter Ratcliffe, Gregg Semenza, and William Kaelin Jr., were awarded the Nobel Prize in 2019. Previously we treated anemia in CKD by intravenous or

subcutaneous injection of human recombinant EPO or its derivatives, so-called erythropoiesis stimulating agents (ESA). ESA stimulates the hematopoietic system specifically. Now HIF-PH inhibitors (HIF-PHI) are approved and available at the bedside in some countries as an oral drug of a completely new mechanism to treat anemia in CKD. HIF-PHI work systemically and may have some effects outside the hematopoietic system. Although clinical evidence is not much at this moment, we decided that we should understand its potential benefits and harms when we prescribe this class of drug. This guideline summarizes expert opinions of the committee at this moment and will be updated when clinical evidence accumulates in the future.

2. Recommendations

- Strategy when replacing ESA with HIF-PH inhibitor and the other way around

<Recommendation>

Physicians can HIF-PHI as alternatives to ESA in correcting and maintaining hemoglobin for renal anemia both in dialysis and non-dialysis CKD patients based on new information concerning the efficacy and safety.

- Opinion on supplement of iron and monitoring of iron status

<Recommendation>

Iron status should be evaluated before HIF-PHI are used. We suggest correcting iron deficiency before initiation of HIF-PHI (ferritin>100ng/ml and TSAT>20%) for all CKD patients.

- Types of patients who should be treated with HIF-PH inhibitor

<Recommendation>

Anemia in CKD should be controlled using ESA or HIF-PHI after sufficient iron supplementation. A combination therapy of ESA and HIF-PHI should not be performed.

If patients with good drug adherence desire oral treatment because of various reasons such as frequency of hospital visits and

invasiveness of injections in case of non-HD patients, HIF-PHI may be preferable than ESAs. In case of treatment with HIF-PHI, an issue of polypharmacy should be acceptable.

If target Hb cannot be achieved with the recommended dose of ESA, the first priority is to search for the cause of ESA hyporesponsiveness and consultation with a nephrologist/specialized medical institution should be considered. If the cause of ESA hyporesponsiveness is unknown or difficult to manage due to defective iron utilization or some other reasons, conversion to HIF-PHI should be considered.

3. Potential concerns (some are evidence based, some are theoretical)

- Malignancy

<Recommendation>

Before using HIF-PHI, malignancy should be checked. In light of current limited follow-up, prescribing HIF-PH inhibitors in patients with known malignancy should be undertaken only with great caution. It will be essential to maintain post-marketing surveillance for a substantive period—at least five years—given the theoretical and experimental concerns associated with increased HIF activity, as well as the long-term malignancy risk posed by related genetic diseases.

- Retinopathy

<Recommendation>

Retinopathy is a theoretical concern of HIF-PHI in CKD patients. Early referral for ophthalmologic assessment is warranted in patients who report visual disturbance after drug initiation.

- Liver dysfunction

Recommendation: Liver dysfunction is relatively uncommon in CKD patients receiving HIF-PHI. Regular monitoring of liver function may facilitate early detection of HIF-PHI -related hepatic dysfunction.

- Hyperkalemia

<Recommendation>

The data about hyperkalemia as an adverse effect of HIF-PHI are inconclusive. However, considering hyperkalemia can be a medical emergency, we suggest serum potassium being monitored.

- Hypertension

<Recommendation>

Clinical studies have no signals that suggest a hypertensive effect of HIF-PHI, but as ESA use is associated with hypertension or compromised blood pressure control, one should pay attention to blood pressure control in patients treated with HIF-PHI.

- Pulmonary hypertension / Heart failure

<Recommendation>

Clinical studies have no signals that suggest aggravation of pulmonary hypertension or heart failure by HIF-PHI, but one should pay attention to changes of cardiac function in patients treated with HIF-PHI.

- Thrombotic events and Vascular calcification

<Recommendation>

Clinical data and basic studies raise the concerns of thrombotic events in HIF-PHI treatment. We suggest a limited use of HIF-PH inhibitors in patients with any history of thrombotic events or a careful use of HIF-PHI in patients with cardiovascular disease. Large studies with unbiased reports and long-term follow-up are required.

- Cyst growth

<Recommendation>

One should follow sizes of cysts up when HIF-PHI are used in patients with polycystic kidney disease.

- Seizure

<Recommendation>

Clinical studies have no signals that suggest seizure as an adverse event by HIF-PHI.

4. Potential benefits of HIF-PHI in addition to improvement of anemia (all theoretical, not proven in clinical studies)

<Summary>

Potential benefits include an increase in circulating EPO levels within a physiological range, preservation of kidney function, and protection against ischemic disease such as ischemia heart disease, brain stroke, peripheral arterial disease, and acute kidney injury. Metabolic effects may remain elusive as HIF-PHI decrease both LDL and HDL cholesterol

Disclosure of COI

Masaomi Nangaku got honorarium, advisory fees, and research grants from KyowaKirin, GSK, Astellas, AstraZeneca, Akebia, Mitsubishi-Tanabe, JT, and Bayer.

Lawrence McMahon (ANZSN) is National PI in Clinical Trial with Akebia and received advisory fees from Pfizer & AstraZeneca, research funding from Amgen and Roche

Chuan-ming Hao (CSN) got honorarium from Fibrogen and AstraZeneca.

Nan Hu (CSN) got research grant from CAMS Innovation Fund for Medical Sciences.

Desmond Yap (HKSN) got research grants and advisory fees from GSK and AstraZeneca.

Hirokazu Okada (JSN) got honorarium, advisory fees, and research grants from Kyowa Kirin, Daiichi Sankyo, Mitsubishi Tanabe, Takeda, Chugai, Torii, Astellas, and MSD.

Yusuke Suzuki (JSN) got honorarium, advisory fees, and research grants from Kyowa Kirin, Mitsubishi-Tanabe, Daiichi-Sankyo, Novartis, Chugai.

Sung Gyun Kim (KSN) got honorarium, advisory fees, and research grants from Fibrogen, GSK, Akebia, JW Pharmaceutical and KyowaKirin.

Soo Kun Lim (MSN) got honorarium from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Fresenius Kabi, Baxter and

Sanofi.

Kriengsak Vareesangthip (NST) got honorarium and advisory fee from AstraZeneca, Fresenius Kabi, Siam Bioscience, and Novo Nordisk.

Chi-Chih Hung (TSN) has no conflicts of interest to disclose.