Global Science. Local Change.

KDIGO Controversies Conference on Novel Anemia Therapies in CKD - Scope of Work -

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and ask what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline updating efforts and other times they highlight areas for which additional research is needed.

BACKGROUND

In patients with kidney disease, anemia is a multifactorial disorder resulting from a combination of low erythropoietin production, abnormal iron metabolism (e.g., absolute/functional iron deficiency, impaired absorption of dietary iron through the gut), blood loss, inflammation, nutritional deficiencies, and oxidative stress.[1] Current treatment of anemia includes oral or intravenous iron and the use of erythropoiesis stimulating agents (ESAs).

Clinical trial data have indicated that ESAs, when used to target the low-normal hemoglobin range, do not improve survival[2] and actually confer worsen cardiovascular outcomes such as stroke[3] and cardiovascular events[4, 5] in chronic kidney disease (CKD) patients, including those treated with dialysis. As a result, current KDIGO guideline suggests that ESA may be considered when Hb is below 10 and ESA should not be used to maintain Hb concentration above 11.5. There have also been concerns about the safety of intravenous iron, specifically in relation to purported increased risk of infections but the recent PIVOTAL trial demonstrated that proactive iron replenishment

reduces cardiovascular risk compared to a reactive approach.[6] Oral iron, on the other hand, is poorly absorbed in patients with CKD G4-G5 at least in part due to elevated levels of hepcidin.[1] Hepcidin regulates ferroportin, an iron channel on the surface of enterocytes, hepatocytes, and macrophages, and inhibits iron absorption from the gut,[7] and hepcidin is upregulated when there are increased levels of iron in the plasma and suppressed in the setting of iron deficiency.[8] Hepcidin is also upregulated in states of chronic inflammation, including CKD.[9]

Hypoxia-inducible factor (HIF) is a master switch that coordinates response to hypoxia, stimulating erythropoietin production in the liver and kidneys. The HIF pathway is also linked to iron metabolism in as yet incompletely understood manner but it is known that HIF is downregulated by prolyl hydroxylase domain enzymes (PHDs), which serve as cellular oxygen sensors. In the presence of oxygen, PHDs hydroxylate HIF, thereby targeting it for subsequent proteasomal degradation. When oxygen levels decrease, prolyl hydroxylation or degradation of HIF is inhibited.[1, 10]

HIF accumulation thus induces the transcription of several hundred target genes with various effects on erythropoiesis. During hypoxia, HIF-PH activity is reduced and HIF accumulates and upregulates the following: (1) divalent metal transporter 1 and duodenal cytochrome B, which increases intestinal iron absorption; (2) EPO receptors and endogenous EPO production; and (3) transferrin receptors, increasing iron uptake by proerythrocytes and promoting maturation of erythrocytes.[11] The effect of HIF on hepcidin appears to be indirect; during erythropoiesis, erythroblasts produce erythroferrone (ERFE), a hormone that acts directly on the liver to downregulate hepcidin anticmicrobial peptide transcription, inhibiting hepcidin production.

Prolyl hydroxylation can be pharmacologically inhibited by HIF-PH inhibitors (HIF-PHI),[12, 13] thereby stimulating erythropoiesis and increasing iron absorption and mobilization. HIF-PHIs (also referred to as HIF stabilizers) are orally active and may enhance erythropoiesis through several mechanisms.[14] HIF-PHIs have already been approved in some countries such as China and Japan, and the Asian Pacific Society of Nephrology has recently published recommendations on their proper use.[15] However, since HIF activation results in a broad physiologic response, pleiotropic effects have been widely reported. It is currently unknown whether these effects might be beneficial, harmful, or neutral, and hence further careful investigations are required.[16, 17]

CONFERENCE OVERVIEW

The objective of the December 2021 KDIGO conference is to gather a global panel of individuals with multidisciplinary clinical and scientific expertise (i.e., nephrology, cardiology, pediatrics, pharmacology, hematology etc.) to identify key issues relevant to the novel anemia therapies in CKD. The goal of this KDIGO conference is to determine best practice and areas of uncertainty in the treatment of anemia, review key relevant literature published since the 2012 KDIGO Anemia Guideline, address ongoing controversial issues, identify new topics or issues to be revisited in the next iteration of the KDIGO guideline, and outline research needed to improve anemia management in CKD. One key question this conference will address is whether there is a specific population in which HIF-PHI should be preferred or avoided.

Drs. Elaine Ku (University of California San Francisco, San Francisco, CA, USA) and David C. Wheeler (Centre for Nephrology, University College London, London, UK) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a summary report that will help guide KDIGO and others in the therapeutic management and future research in anemia and CKD.

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APPENDIX: SCOPE OF COVERAGE

Group 1: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients not on dialysis treatment

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients with CKD not on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment?
2. What should the hemoglobin target be in relation to HIF-PHI use? Do higher hemoglobin levels remain an area for concern and should there still be an upper limit that is below normal?
3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESA to HIF-PHI?
4. Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, improve cardiovascular endpoints (MACE) or physical function and health-related quality of life compared with iron/ESAs?
5. What is the current evidence-based data surrounding differences between HIF-PHI agents in patients with CKD not on dialysis?
6. Are there particular advantages to the use of oral HIF-PHIs in the non-dialysis CKD population as compared to the dialysis population? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations?
7. What is the role of iron and EPO in the era of HIF-PHIs for patients with CKD not on dialysis treatment? What is the comparative advantage of HIF-PHIs relative to iron and EPO?

Group 2: Therapeutic use of HIF-PHIs vs. current therapies in anemia management: CKD patients treated with dialysis (patients incident and prevalent to dialysis)

1. What is the efficacy of HIF-PHIs in the treatment of anemia in patients on dialysis therapy and the mean hemoglobin change that we can expect under standard treatment? Does this differ from patients with CKD not on dialysis treatment?
2. What should the hemoglobin target be in relation to HIF-PHI use? Do higher hemoglobin levels remain an area for concern and should there still be an upper limit that is below normal?
3. What is the appropriate dose for HIF-PHIs and how should dosing be adjusted (based on what parameters)? How do we manage a patient converting from the use of ESA to HIF-PHI?
4. Is there any evidence that the use of HIF-PHIs slow down the progression of CKD, improve cardiovascular endpoints (MACE) or physical function and health-related quality of life compared with iron/ESAs? Are there any differences between the incident vs prevalent dialysis populations?
5. What is the current evidence-based data surrounding differences between HIF-PHI agents in patients on dialysis?
6. What is the role of iron and EPO in the era of HIF-PHIs for patients on dialysis therapy? Are there advantages or disadvantages to the use of oral HIF-PHIs as opposed to current therapeutic options in the dialysis population? What should be the optimal strategy to treat anemia in the hemodialysis population, including the incorporation or prioritization of currently available therapies and novel therapies?
7. Are there advantages to HIF-PHI use in patients who are hyporesponsive to ESA or iron? Cost-savings, resource utilization, or COVID-19 pandemic-related considerations? Do HIF-PHIs reduce iron requirements among patients receiving dialysis?
8. Are there subgroups for which HIF-PHIs might be particularly beneficial, such as patients receiving home dialysis therapies?

Group 3: Safety profile of HIF-PHIs in CKD anemia management

1. What are the currently available safety data surrounding use of HIF-PHIs in different populations: patients not on dialysis; patients who are incident or prevalent to dialysis? Is there any evidence that safety differs by level of GFR or inflammatory states?
2. Does the use of HIF-PHIs apply to anemia of CKD in kidney transplant populations with low eGFR and anemia? Pediatric populations? Older adults? Patients with underlying liver disease, polycystic kidney disease, or diabetic retinopathy? Immunosuppressed patients (e.g., due to underlying GN)? Patients with AKI?
3. What parameters should be monitored during the treatment of anemia when using HIF-PHIs? Are there novel biomarkers or testing that should be made available to ensure safety? What toxicities should be monitored for?
4. Are there theoretical or known safety differences between various HIF-PHI agents that are available or being developed in phase II/III trials?
5. What long-term post-marketing data may be needed given the numerous potential actions of HIF-PHIs that may not be intended? Theoretical risks that may be of concern (e.g., oncologic)?
6. Are there drug-drug interactions that should be considered with the use of HIF-PHIs? Do we have safety data on patients who are simultaneously on ESA and HIF-PHI therapies?

Group 4: Pathophysiology of HIF-PHIs and pleiotropic effects beyond hemoglobin

1. What is the physiologic role of HIF-PHIs and their interaction with EPO and iron and effects on their metabolism?
2. What is the pathophysiologic mechanism by which use of HIF-PHIs may require special consideration as it relates to AKI, other kidney diseases including cystic disease, immune-mediated kidney diseases, etc.?
3. What are the theoretical off-target effects that warrant considerations as we begin to assess the impact of HIF-PHIs on major adverse cardiovascular events as mediated by effects on BP, cholesterol, etc.? Do these benefits seem to be agent specific or common across the HIF-PHI class?
4. Do HIF-PHIs affect BP or dyslipidemia differentially among patients not on dialysis therapy or on dialysis? Electrolytes or acid-base disturbances?
5. What are the benefits, risks, and differences of the current ESAs that are available (short-acting, long-acting [CERA], biosimilars/biogenerics)? How may or may not HIF-PHIs address the shortcomings of ESAs?
6. What data are available for HIF-PHIs surrounding symptoms and quality of life? Patient-centered outcomes? Patient preferences?
7. Are there other novel therapeutic agents (non-HIFs such as ziltivekimab, SGLT2i) for the treatment of anemia that need to be considered or are on the horizon? How might they compare to HIFs or ESAs?
8. Is there evidentiary support to the suggestion that HIF-PHIs are associated with lower (or slower?) increases in EPO than ESA , thus explaining the elevated CV risk/mortality in the latter? Has this purported benefit in HIF-PHI been substantiated?