South African Nephrology Society:

consensus statement on the use of hypoxia-inducible factor-prolyl hydroxylase inhibitors

Background

Hypoxia-inducible factors (HIFs) are heterodimeric transcription factors which, in the presence of tissue hypoxia, increase hepatic and renal erythropoietin (EPO) production to stimulate erythropoiesis. They also have a suppressive effect on hepatic production of hepcidin, increasing gastrointestinal absorption of iron and liberating it from stores.[1] Inhibition of oxygen-regulated degradation of HIF by prolyl hydroxylase inhibitors (HIF-PHIs) results in sustained EPO stimulating effect, allowing use of the HIF-PHIs as erythropoiesis-stimulating agents (ESAs).[1]

Potential benefits of HIF-PHIs over conventional ESAs are shown in Table 1.

Table 1. Potential benefit of HIF-PHIs over conventional ESAs

Oral formulation	• Reduced discomfort over subcutaneous ESA • Ease of administration for non-dialysis requiring patients living with CKD on an outpatient basis • Ease of administration in peritoneal dialysis patients • Does not require refrigeration
Improved iron absorption and distribution	• Better absorption of oral iron, potentially reducing need for use for intravenous formulation • Reduced dose of iron required
Suppression of hepcidin production	• Improved erythropoiesis in chronic inflammatory states with resistance to conventional ESA

ESA; erythropoiesis-stimulating agents

Adoption of the HIF-PHI class in clinical practice requires appreciation of the efficacy and side-effect profile of these novel agents relative to conventional ESAs. Current data on these parameters relies on trials that assessed the superiority of the HIF-PHIs over placebo or their non-inferiority to existing ESAs. HIF-PHIs have therefore not been assessed for superiority over available ESAs.

This document considers available literature on the efficacy of the HIF-PHIs in the treatment of anaemia of chronic kidney disease and the side-effect profile of these drugs. Recommendations are provided for the prescription of HIF-PHIs based on current data.

Efficacy of HIF-PHIs in the treatment of anaemia of chronic kidney disease

Current literature suggests that HIF-PHIs are superior to placebo and non-inferior to conventional ESA in treating anaemia in patients living with chronic kidney disease (CKD) (Table 2).

It should be noted that trials evaluating the efficacy of HIF-PHIs in anaemia have used established KDIGO targets. The safety of using HIF-PHIs to target normalized haemoglobin concentrations in CKD is therefore not known, and it should be noted that increased risk of thrombosis has been reported with treatment with HIF-PHIs (see below).

Trials of HIF-PHI efficacy have also not been designed to specifically evaluate iron parameters and use. At present, therefore, the need to adjust iron treatment protocols in patients receiving HIF-PHIs remains uncertain.

Table 2. Efficacy of HIF-PHI in the treatment of anaemia of chronic kidney disease

Trial	HIF-PHI	Comparator	n	Change in haemoglobin from baseline to evaluation period*	Haemoglobin response rate**
Non-dialysis dependant CKD					
ASCEND-ND[2]	Daprodustat	Darbepoetin alfa	3872	0.08 g/dL greater (non-inferior)	Not reported
DREAM-ND[3]	Desidustat	Darbepoetin alfa	588	0.11 g/dL greater (non-inferior)	77.8% vs. 68.5%
ALPS[4]	Roxadustat	Placebo	594	1.69 g/dL greater	79.2% vs. 9.9%
ANDES[5]		Placebo	922	1.8 g/dL greater	86% vs. 6.6%
OLYMPUS[6]		Placebo	2781	1.35 g/dL greater	77% vs. 8.5%
DOLOMITES[7]		Darbepoetin alfa	616	Not reported	89.5% vs. 78%
PRO_2TECT[8]	Vadadustat	Darbepoetin alfa	1751	0.05 g/dL greater^{+}	50.4% vs. 50.2%$^{+}$
PRO_2TECT[8]			1725	0.01 g/dL less^{++}	60.1% vs. 60.7%$^{++}$
Dialysis-dependent CKD					
ASCEND-D[9]	Daprodustat	Epoetin or Darbepoetin alfa	2964	0.18 g/dL greater	Not reported
HIMALAYAS[10]	Roxadustat	Epoetin alfa	1043	1.18 g/dL greater	84.3% vs. 79.5%
PYRENEES[11]		Epoetin or Darbepoetin alfa	838	0.23 g/dL greater	84.2% vs. 82.4%
ROCKIES[12]		Epoetin alfa	2133	0.09 g/dL greater	79% vs. 76%
SIERRAS[13]		Epoetin alfa	741	0.48 g/dL greater	66.1% vs. 58.6%
$INNO_2VATE$[14]	Vadadustat	Darbepoetin alfa	3554	0.17 g/dL less	49.2% vs. 53.2%

**mean Hb in HIF-PHI group less mean Hb in control group; **% of participants reaching trial Hb target*
$^{+}$ESA naïve; $^{++}$ESA-treated

Improvement in haemoglobin and reductions in invasive therapies may reasonably be expected to improve quality-of-life scores in patients prescribed HIF-PHIs. Whilst such improvements have been evaluated in some trials,[4-6,11] the effect of these drugs on this outcome parameter remains inconclusive at present.

Side-effect profile of HIF-PHIs

Cardiovascular events

Cardiovascular safety of HIF-PHIs in non-dialysis dependent CKD has not been definitively established (Table 3). In contrast, with regards to cardiovascular events HIF-PHIs appear to be non-inferior to conventional ESA in CKD patients on dialysis.

Table 3. Cardiovascular safety of HIF-PHI

Trial	HIF-PHI	Comparator	MACE HR*
Non-dialysis dependent CKD			
ASCEND-ND[2]	Daprodustat	Darbepoetin alfa	1.03 (0.89–1.19)
Pooled analysis[15]: ALPS[4] ANDES[5] OLYMPUS[6]	Roxadustat	Placebo	1.10 (0.96–1.27)
PRO$_2$TECT[8]	Vadadustat	Darbepoetin alfa	1.17 (1.01–1.36)
Dialysis dependent CKD			
ASCEND-D[9]	Daprodustat	Darbepoetin alfa	0.93 (0.81–1.07)
Pooled analysis[15]: HIMALAYAS PYRINEES ROCKIES SIERRAS	Roxadustat	Epoetin or Darbepoetin alfa	1.09 (0.95–1.26)
INNO$_2$VATE	Vadadustat	Darbepoetin alfa	0.96 (0.83–1.11)

**HR of major adverse cardiovascular (MACE) event for HIF-PHI referenced to Comparator*

Thromboembolic events

HIF-PHI, particularly roxadustat, have been associated with increased risk of thrombotic events.[16] It remains unclear whether this risk relates to rate of haemoglobin correction and whether dose adjustments to curtail the rate of raise of the haemoglobin concentration might reduce this risk.

Progression of kidney disease

Limited and contradictory data is available on the effect of HIF-PHI on CKD progression. No effect on GFR decline has been observed in trials involving daprodustat[3] and vadadustat[8], but accelerated rate of decline has been reported in a single phase 3 trial of roxadustat.[12] Particular concern exists over the safety of HIF-PHI in CKD due to polycystic kidney disease, given the overexpression of HIF in animal models of the disease.[17]

Hypertension and hyperkalaemia

Higher rates of hyperkalaemia have been reported for HIF PIHs in some studies.[18] These results have, however, not been confirmed by larger trials. With regards to hypertension, so far, no significant blood pressure effects have been reported in any HIF-PHI phase 3 trials. Results from a dedicated blood pressure study with daprodustat (ASCEND-BP) are awaited.

Malignancy

The HIF pathway is an important mediator of malignancy progression through angiogenesis and cancer cell proliferation and survival,[19] and a significant contributor to tumour growth in von Hippel-Lindau syndrome.[20] As a result, HIF-PHIs may theoretically increase the risk of malignancy in at-risk patients; however, at present there exists limited data addressing the safety of these drugs in this patient group.

Retinopathy

Increased expression of VEGF by the HIF pathway has been associated with progression of diabetic retinopathy in murine models.[21] Despite the theoretical risk posed to human patients living with diabetic kidney disease, no acceleration of retinopathy has been reported in human subjects living with diabetic kidney disease.

Patient considerations in the prescription of HIF-PHIs

Patients hyporesponsive to conventional ESA due to chronic inflammation or iron deficiency may benefit from HIF-PHIs due to resultant decrease in hepcidin with improvement in iron absorption and mobilization from stores. Since efficacy trials have not specifically included patients with significantly increased C-reactive protein, this potential role for HIF-PHIs is not currently supported by substantial evidence. Prescription of HIF-PHI should not be used to circumvent workup of chronic inflammation or evaluation of ESA resistance.

Children may represent a special patient group in which an oral formulation of ESA may be particularly desirable. Lack of specific data in this regard means that this potential indication remains theoretical at this time.

In view of potential adverse effects, HIF-PHI are probably best avoided in patients with recent or active malignancy, and patients with CKD due to polycystic kidney disease.

Placental HIF-1α expression is increased in the setting of preeclampsia,[22] and increased spontaneous abortion has been reported in murine preclinical drug trials. HIF-PHI metabolites have been detected in breastmilk in animal subjects. The HIF-PHIs are therefore currently contraindicated in pregnancy and in breastfeeding.

Conclusions

Current data suggests that HIF-PHIs are non-inferior to conventional ESA in maintaining haemoglobin concentration in both non-dialysis and dialysis dependent CKD. The cardiovascular safety of HIF-PHI over conventional ESA has not definitively been established, and the class may be associated with increased risk of thrombosis. Patients with active or recent malignancy, and those living with polycystic kidney diseases, should probably not be prescribed HIF-PHI until the effect of this class on these disease categories is better established; patients with retinopathy are an additional group of concern. Patients refractory to conventional ESA due to chronic inflammation may constitute a group in whom prescription of HIF-PHI may facilitate haemoglobin correction, should overt contraindication be excluded. Prescription of the HIF-PHI should however not substitute thorough investigation for the aetiology of ESA resistance nor appropriate management thereof. Lack of overt benefit of the HIF-PHI should not preclude prescription in preference to conventional ESA in consideration of possible advantages for individual patients such as ease of administration.

Disclosure

This consensus statement aims to provide information and assist decision making. It is not intended to define a standard of care, nor dictate an absolute course of management. Health-care professionals utilising this consensus statement are responsible for evaluating the appropriateness of the application to any clinical situation, by taking into account the individual needs and preferences of each patient, available resources, and institution/ practice limitations.

Appendix: suggested prescription approach

		Transferrin saturation %		
		< 20%	20-30%	> 30%
Hb	> 10g.dl	Replace iron (IV > Oral) No ESA/HIF-PHI	Replace iron (IV = Oral) No ESA/HIF-PHI	No iron No ESA/HIF-PHI
	< 10g.dl	Replace iron (IV >> Oral) Give ESA/HIF-PHI	Replace iron (IV = Oral) Give ESA/HIF-PHI	No iron Give ESA/HIF-PHI

		Ferritin		
		< 200ng.ml	200 - 500ng.ml	> 500ng.ml
Hb	> 10g.dl	Replace iron (IV > Oral) No ESA/HIF-PHI	No iron No ESA/HIF-PHI	Search for inflammation and infection. Avoid iron. Consider an ESA/HIF-PHI if Hb < 10g.dl
	< 10g.dl	Replace iron (IV >> Oral) Give ESA/HIF-PHI	No iron Give ESA/HIF-PHI	

References

1. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anaemia of chronic kidney disease. Kidney Int Suppl 2021;11(1):8-25 doi 10.1016/j.kisu.2020.12.002
2. Singh AK, Carroll K, McMurray JJV Solomon S, Jha V, Johansen KL, et al. Daprodustat for the treatment of anemia in patients not undergoing dialysis. New Eng J Med 2021;385(25):2313-2324 doi 10.1056/NEJMoa2113380
3. Agrawal D, Varade D, Shah H, Nazar A, Krishnan J, Shukla V, et al. Desidustat in anaemia due to non-dialysis-dependent chronic kidney disease: a phase 3 study (DREAM-ND). Am J Nephrol 2022;53(5):352-360 doi 10.1159/000523961
4. Shutov E, Sulowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a phase 3,randomized, double-blind, placebo controlled study (ALPS). Nephrol Dial Transplant. 2021;36:1629–1639
5. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. Kidney Int Rep. 2021;6:624–635
6. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. J Am Soc Nephrol. 2021;32:737–755
7. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant. 2021;36:1616–1628
8. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. N Engl J Med. 2021;384:1589–1600

9. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the treatment of anemia in patients undergoing dialysis. N Engl J Med. 2021;385:2325–2335
10. Provenzano R, Shutov E, Eremeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant. 2021;36:1717–1730
11. Csiky B, Schomig M, Esposito C, et al. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: a European phase 3, randomized, open-label, active controlled study (PYRENEES). Adv Ther. 2021;38:5361–5380
12. Fishbane S, Pollock CA, El-Shahawy M, et al. Roxadustat versus epoetin alfa for treating anemia in patients with chronic kidney disease on dialysis: results from the randomized phase 3 ROCKIES study. J Am Soc Nephrol. 2022;33:850–866
13. Charytan C, Manllo-Karim R, Martin ER, et al. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. Kidney Int Rep. 2021;6:1829–1839
14. Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. N Engl J Med. 2021;384:1601–1612
15. Ku E, del Vecchio L, Eckardt K-U, Haase VH, Johansen KL, Nangaku M, et al. Novel anemic therapis in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney In 2023 doi 10.1016/j.kint.2023.05.009 [preprint accessed online 10/6/2023]
16. US Food and Drug Administration. Roxadustat for the treatment of anemia due to chronic kidney disease in adult patients not on dialysis and on dialysis. FDA Presentation: Cardiovascular and Renal Drugs Advisory Committee Meeting, July 15, 2021. Available from https://www.fda.gov/media/150756/download [accessed online 10/6/2023]
17. Buchholz B, Eckardt K-U. Role of oxygen and the HIF-pathway in polycystic kidney disease. Cell Signal 2020;69:109524 doi 10.1016/j.cellsig.2020.109524
18. Zheng Q, Wang Y, Yang H, Sun L, Zhang P, Zhang X, et al. Cardiac and kidney adverse effects of HIF Prolyl-Hydroxylase Inhibitors for anemia in patients with CKD not receiving dialysis: a systematic review and meta-analysis. Am J Kidney Dis 2023;81(4):434-445.e1 doi 10.1053/j.ajkd.2022.09.014
19. Rashid M, Zadeh LR, Baradaran B, Molavi O, Ghesmati Z, Sabzichi M, et al. Up-down regulation of HIF-1α in cancer progression. Gene 2021;25(798):145796 doi 10.1016/j.gene.2021.145796
20. Haase VH. The VHL tumour suppressor: master regulator of HIF. Curr Pharm Des. 2009;15(33):3895-3903 doi 10.2174/138161209789649394
21. Zhang D, Lv F-L, Wang G-H. Effects of HIF-1α on diabetic retinopathy angiogenesis and VEGF expression. Eur Rev Med Pharmacol Sci 2018;22(16):5071-5076 doi 10.26355/eurrev_201808_15699
22. Rath G, Aggarwal R, Jawanjal P, Tripathi R, Batra A. HIF-1 alpha and placental growth factor in pregnancies complicated with preeclampsia: a qualitative and quantitative analysis. J Clin Lab Anal 2016;30(1):75-83 doi 10.1002/jcla.2819