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Daprodustat in renal anaemia: changing the response to cellular hypoxia but is it a game-changer?

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Renal anaemia amongst people with chronic kidney disease (CKD) has been recognised for many years, but two recent clinical trials represent significant developments in its treatment.1,2 Patients with advanced CKD often required blood transfusions until the discovery of recombinant erythropoietin (EPO) which could stimulate patients’ own production of red blood cells. The development of erythropoiesis-stimulating agents (ESAs) revolutionised the management of renal anaemia by avoiding the need for transfusion and there was optimism that long-term outcomes would be improved.3 However, overcorrection of anaemia with ESAs has been linked to hypertension and increased stroke risk in people with CKD.4,5 Some patients such as those with chronic inflammation are more resistant to ESAs, requiring higher doses and potentially greater risks of off-target increase in cardiovascular risk.6 Patients with CKD are already at increased risk of cardiovascular events and in advanced CKD, heart failure is particularly problematic. CKD and anaemia are each associated with poor prognosis for patients with heart failure,7 so improving treatment of anaemia in the context of CKD and heart failure is likely to be of great benefit. The discovery of the hypoxia-inducible factor pathway (HIF-pathway) was a breakthrough in cellular physiology which earned a Nobel prize for Professors William G. Kaelin Jr., Sir Peter J. Ratcliffe, and Gregg L. Semenza in 2019.8 As a consequence of this work, Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-stabilisers) were developed as alternative therapeutic agents for treatment of renal anaemia (Figure 1).
Given previous associations of ESAs with increased cardiovascular risk, The ASCEND clinical trials\(^1,^2\) were designed to assess both the safety of the HIF-stabiliser daprodustat (particularly regarding cardiovascular events) as well as its efficacy to ensure it was at least non-inferior to an ESA for improving haemoglobin. Daprodustat was trialled in two distinct populations: patients on dialysis (ASCEND-D)\(^1\) and patients with CKD not on dialysis (ASCEND-ND).\(^2\) Before the results of these trials were published, there had been mixed results reported from other HIF-stabilisers: roxadustat was reported as non-inferior to ESAs,\(^9\) but more patients given vadadustat developed cardiovascular events than those given ESAs.\(^10\) The 6,836 patients enrolled in the ASCEND trials were randomised to an injectable ESA or oral daprodustat. Importantly, patients were anaemic but replete in iron with no evidence of recent cardiovascular events or cancer. Both groups of patients had their treatment titrated with a target haemoglobin of 10 to 11g/dL and efficacy was assessed between weeks 28 and 52. Patients were followed up for a median of 2.5 years in ASCEND-D and 1.9 years in ASCEND-ND, with a primary safety outcome of major adverse cardiovascular events (MACE: a composite of all-cause mortality, myocardial infarction and stroke). In both trials, daprodustat was non-inferior in terms of efficacy and safety. In ASCEND-D, the haemoglobin rose by a median of 0.18g/dL more in the daprodustat group than in the ESA group and the rates of MACE were similar (26.7% in the ESA group and 25.2% in the daprodustat group). In ASCEND-ND, the haemoglobin rose by a median of 0.08g/dL more in the daprodustat group than in the ESA group and the rates of MACE were similar (19.2% in the ESA group and 19.5% in the daprodustat group). However, in ASCEND-ND, the daprodustat group had higher rates of gastric erosions and cancer events than the ESA group. The trials therefore confirm findings from previous HIF-stabiliser trials that they can effectively treat renal anaemia but there is a suggestion of greater adverse effects compared to ESAs.

The kidneys play a key role in erythrocytosis. They detect cellular hypoxia and produce EPO, which binds to the EPO receptor in the bone marrow and stimulates red blood cell production. In CKD, nephron mass is reduced, decreasing EPO production, and this is accompanied by absolute and functional iron deficiency. By activating the HIF-pathway, HIF-stabilisers promote EPO production and enhance iron metabolism. They mimic intracellular hypoxia by down-regulating propyl-hydroxylase (PHD), preventing
the degradation of HIF-α. HIF-α dimerises with HIF-β and up-regulates the transcription of genes involved in EPO production in the kidneys and EPO receptors in the bone marrow. Activation of the HIF-pathway also ensures sufficient iron is available for effective erythropoiesis; hepcidin levels are reduced and divalent metal transporter-1 (DMT1) is activated, promoting iron absorption from the intestinal epithelium; transferrin and transferrin receptor genes are up-regulated which improves the transport of iron to the bone marrow. Each of the HIF-stabiliser medications inhibit different PHD isoenzymes: daprodustat inhibits PHD2 and PHD3, whereas roxadustat also inhibits PHD1. It is unclear whether these differences in action will influence the clinical effects of each drug.

The HIF-stabilisers were first approved for use in China and Japan in 2019. The European Medicines Agency have approved roxadustat, although at the time of writing the FDA in the US has not approved its use for treatment of renal anaemia. Clinicians must determine whether the safety profile of these agents is acceptable across the therapeutic class or if there are differences between the specific HIF-stabilisers. There are groups of patients where HIF-stabilisers are attractive including those with ESA-resistance who are receiving large doses of ESAs and/or blood transfusions. The oral route of administration is attractive in the non-haemodialysis population, particularly younger patients if they are at low risk of cardiovascular events and likely to require short-term treatment of renal anaemia before they receive a kidney transplant. Amongst the patients who are given HIF-stabilisers, clinicians should study the optimal use of iron supplementation and perhaps co-administration with ESAs. The PIVOTAL trial has described the optimal use of intravenous iron in people on haemodialysis treated with an ESAs, and similar work will be required for the HIF-stabilisers.

The discovery of the HIF-pathway and development of the HIF-stabilisers demonstrates how scientific breakthroughs lead to the development of new treatments. Scientific endeavour should continue to expand our understanding of the pathophysiology of anaemia, including iron metabolism in CKD. The HIF-stabilisers have advanced the treatment of renal anaemia beyond the administration of EPO and iron, but another potential pathway is the absorption and transport of iron. Medications targeting the hepcidin-ferroportin pathway have been through phase 1 trials, but further work is needed.
The HIF-stabilisers are therefore a significant development in the management of renal anaemia, but they are not a silver bullet. The discovery of the HIF-pathway is an exciting development for the scientific community and it opens up further opportunities for understanding pathophysiologic mechanisms of anaemia and pharmacotherapies.
Figure 1: HIF-stabilisers and the mechanism of action and potential side effects and targeted treatment.
Authors

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