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THERAPY

PHD inhibitors correct anaemia in CKD

New findings from two phase II trials suggest that oral hypoxia-inducible factor prolyl hydroxylase (PHD) inhibitors might be effective therapies for anaemia in patients with chronic kidney disease (CKD). Both of the novel agents tested—GSK1278863 and roxadustat—were well tolerated by the study participants.

"Current therapies for anaemia of CKD include recombinant human erythropoietin (rhEPO) and IV iron, both of which carry considerable safety concerns," explains Louis Holdstock, lead author of the GSK1278863 trial. "PHD inhibitors produce effects in the body that are similar to those that occur at high altitude in response to hypoxia, essentially causing the body to make more red blood cells." In addition to stimulating erythropoesis, PHD inhibitors have been shown to reduce circulating levels of hepcidin, which is upregulated in CKD and limits iron absorption in the gut.

Holdstock *et al.* showed that 4 weeks of once-daily GSK1278863 therapy dose-dependently increased haemoglobin levels in 73 nondialysis-dependent patients with CKD and anaemia who were not receiving rhEPO. Moreover, the highest dose of the drug administered in the study (5 mg daily) maintained haemoglobin levels in 20 patients on haemodialysis who switched from rhEPO therapy.

In their study, Anatole Besarab and colleagues found that 12 weeks of roxadustat treatment with or without oral or IV iron, increased haemoglobin levels in 60 anaemic patients on incident haemodialysis or peritoneal dialysis who had never received EPO analogues. Roxadustat treatment also significantly reduced mean serum hepcidin levels in all patient groups. "Our study shows that hepcidin is reduced by roxadustat with no iron as well as with oral iron, but the effect is blunted by IV iron supplementation," says Besarab.

Future studies of GSK1278863 will assess whether this agent has a better cardiovascular risk profile than rhEPO. Phase III global safety and efficacy studies of roxadustat in anaemic patients with CKD, starting dialysis or already on dialysis are underway.

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ORIGINAL ARTICLES Holdstock, L. *et al.* Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anaemia. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2014111139 | Besarab, A. *et al.* Roxadustat (FG-4592): Correction of anemia in incident dialysis patients. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2015030241