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Editorial

A new approach for anemia in kidney disease

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Anemia represents an almost obligatory complication in patients with chronic kidney disease (CKD) and, if ineffectively treated, is associated with increased cardiovascular (CV) mortality, a reduced quality of life and the well know clinical consequences secondary to the need of an exceedingly high number of iron infusions and red blood cell (RBC) transfusions, which have been the only available therapy until the end of 1980s [1,2].

Three decades ago, the introduction of recombinant erythropoietin (rEPO) in the pharmaceutical market represented a great breakthrough in the field of CKD treatment, greatly improving the effectiveness of the control of anemia in CKD patients [3].

However, the results of three large interventional trials [4–6], although confirming the effectiveness of rEPO in improving the control of anemia in CKD and the reduced need for RBC transfusions, have raised safety concerns due to the observation of an increased rate of CV events and stroke, particularly in the case when trying to reach Hb levels close to normality.

Furthermore, the correction of CKD anemia with rEPO is often partial, with far from rare cases of true resistance to its action. In addition, rEPO treatment frequently leads to an increased need for iron administration, with the clinical consequences caused by iron overload.

At the same time, nephrologists gained more and more awareness that, though the reduced production of erythropoietin by the failing kidneys plays a primary role in causing the anemia of CKD patients, many other additional factors can actually contribute to anemia development. Among them, the role of the functional iron deficiency (FID), mainly secondary to the increased levels of hepcidin, an acute-phase reactant protein, responsible for a reduced bioavailability of iron (reduction of iron intestinal absorption and of its release from cellular stores) gained a more and more relevant weight.

On this background, in the search for new drugs which could satisfy the unmet needs of rEPO-based therapy, the emergent role of the small-molecule inhibitors of prolyl hydroxylase domain (PHD) dioxygenases has recently gained particular attention due to some promising peculiarities.

The PHD proteins are a group of enzymes which, in the presence of normoxic conditions and in cooperation with the Von Hippel Lindau protein (pVHL), inactivate the oxygen-sensitive subunits of hypoxia-inducible factor (HIF), namely HIF-2α and HIF-1α, by an ubiquitin-proteasome mediated process [7,8]. Hypoxia strongly inhibits PHD dioxygenase activity, stabilizing the HIFα molecules which, after dimerizing with the constitutively expressed HIFβ, behave as transcription factors (TFs) activating a number of target genes, among which EPO gene and many genes involved in iron metabolism. So, the major final effects of PHD inhibition and HIF stabilization are the increased production of EPO, the increased iron bioavailability (mediated also by the reduction of hepcidin, an inflammation related protein, which inhibits the release of iron from macrophages and the intestinal iron absorption), and the direct bone marrow stem cell stimulation.

For these reasons, a number of compounds with inhibitory action on PHD dioxygenases have now become object of intense clinical investigation [8]. Among these products, Roxadustat (FG 4592), an orally active compound, with a half-life around 12–15 h, has been demonstrated by some phase-II trials [9–11] to be effective, when given thrice weekly, in the correction of anemia in CKD patients, either those on HD treatment or those not on HD treatment. Based on these results, Roxadustat has been the first PHD dioxygenase inhibitor which achieved a formal approval for clinical use, at the present time limited to the treatment of anemia in hemodialysis (HD) and peritoneal dialysis (PD) patients in China.

Very recently, the results of two phase-III RCTs which evaluated the efficacy and safety of Roxadustat, used for correcting anemia in dialysis [12] and in CKD stage 3–5 not on dialysis [13] patients, respectively, have been reported in two papers published in the same issue of the New England Journal of Medicine (N Engl J Med. 2019 Jul 24).

Both studies confirmed the efficacy of Roxadustat in the achievement of anemia correction which was not inferior to the correction observed with rEPO (epoietin alfa) in CKD patients on HD and superior to anemia control that was even worsened in CKD patients not on HD treated with placebo. Furthermore, Roxadustat better preserved iron balance, evaluated as the transferrin saturation levels and the need for iron infusions, as compared to rEPO and even more to placebo.

In addition to these expected positive effects, both studies demonstrated that Roxadustat significantly reduces the levels of both total cholesterol and hepcidin, in comparison with either the rEPO and placebo treated patients. Since both high hepcidin and cholesterol levels are considered two among the main drivers of the increased inflammatory status and hence of the exceedingly high CV morbidity and

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Table 1
Off-target potentially positive or negative effects of PHD deoxygenase inhibitors.

Reference	Potential positive e effects	Potential negative effects
Jain IH et al. Science 2016 [14]	Therapeutic potential in mitochondrial diseases	
Besarab A et al. JASN 2016 [15]	Improved hypertension	
Tang D et al. Cell Physiol Biochem 2018 [16]	Improved wound healing	
Zhang P et al. J cell Mol Med 2019 [17]	Radioprotective effects	
Li X et al. Front Aging Neurosci 2018 [18]	Therapeutic potential in Parkinson's Diseases	
Xie RY et al. Biomed Pharmather 2019 [19]	Protection from glucose-induced glomerular endothelial injury	
Mokas S et al. Kidney Internat 2016 [20]		Vascular calcification
Cygulska K et al. Pol Arch Int med [21]		Pulmonary hypertension
Groenendaal van de Meent D et al. Clin Drug invest 2016 [22]		Possible difference in PK and PD in condition of severe liver impairment
Lucia Del Vecchio Expert Opin Invest Drug 2018 [23]		Potential hepatic toxicity
Li W et al. Front Med 2018 [24] Schley G et al. Kidney Internat 2019 [25]	Contradictory effects on renal fibrosis and on inflammation	
Krock BL et al. Genes Cancer 2011 [26] Price C et al. Cancer Res 2019 [27] Fujimoto TN et al. Cancer Res 2019 [28]	Contradictory results on risk of cancer	

mortality rate in CKD patients, these results could suggest an additional beneficial effect in the use of Roxadustat and possibly of all the other compounds of this new class of drugs in the clinical set of CKD patients.

On the other hand, in both trials Roxadustat was shown to induce an increase in serum potassium levels, which might represent a critical limitation in the use of this drug, in particular in CKD patients not as yet on HD, who are often treated with other drugs which often induced hyperkalemia (e.g. ace-inhibitors, angiotensin receptor blockers, anti-aldosterone drugs).

Other undesired effects of Roxadustat, reported in these two clinical trials, were the increased incidence of upper respiratory tract infections (URTI) in CKD patients on HD [12] and increased occurrence of metabolic acidosis (MA) in CKD patients not on HD [13]. The induction or worsening of MA represents a concern in the use of this drug in patients with CKD patients, given the recognized role of this metabolic alteration in CKD progression. At the same time, given the increasing age of CKD population and the increased susceptibility of older CKD patients to infections, if confirmed in larger study also this observed higher incidence of URTI might be reason of concern.

Overall, while these two RCTs might represent a potential first step towards a radical shift of the therapeutic approach to anemia in CKD, there are some critical limitation and consequently as yet unanswered questions which deserve attention.

First, these studies included relatively small number of patients with an unequal distribution of the enrolled subjects in the treatment and comparator groups (2:1). We need larger studies, possibly based on a 1:1 enrollment design, to achieve more robust and informative evidence.

Second, the enrolled patients were all of Chinese ethnicity: future studies should enroll more patients from different Countries, to exclude that some ethnic specificities can have affected some of the positive or of the negative results.

Third, these trials do not face one of the most critical open questions: could be Roxadustat able to achieve a full correction of CKD anemia without any major adverse effect, at variance with what observed with rEPO? This is a key point for assessing whether CKD patients can really benefit or not by a complete correction of the hemoglobin levels.

Fourth, the short duration of these two studies do not allow to draw any definitive conclusion on the efficacy and, more important, on the safety in the use of this new drug in the long run. This point is of particular relevance at the light of the large series of either positive or negative off-target effects which have been reported in small clinical and/or experimental studies (Table 1) with the use of this new class of drugs.

A potential further point to be explored is the possible reduction of the adherence to the treatment with an oral drug in patients who are usually burdened by a huge number of pills as compared with a therapy which, at least in dialysis, is directly managed by the health workers.

Finally, the cost-effectiveness of these new drugs in comparison with the already available therapeutic tools need to be explored, also considering the considerable reduction in the costs of the therapy of anemia in CKD after the introduction in the market of biosimilar rEPOs.

In conclusion, although Roxadustat can represent an innovative and promising opportunity for the cure of anemia in CKD patients, we still need more evidence from larger and longer studies, preferably performed in different ethnic groups.

It would be desirable that these additional studies will not limit themselves to report on the secondary endpoints associated with the anemia control, but they also give information on many additional clinical and metabolic parameter, which can be potentially affected by the purported off-target effects: these studies will reassure the medical community on the safety issues linked to potential long-term effects of these new promising class of drugs.

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Piergiorgio Messa[a], Maria Domenica Cappellini[b,*]
[a] *Nephrology, Dialysis and Renal transplant Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[b] *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
E-mail address: maria.cappellini@unimi.it (M.D. Cappellini).

* Corresponding author.