Anaemia in chronic kidney disease- new treatment options

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ABSTRACT

In recent years anaemia has been recognized as one of the most specific and evident manifestations of chronic renal failure. In the majority of cases, renal anaemia is normocytic and normochromic with normal cellularity of bone marrow. Multiple factors contribute to the molecular origins of the anaemia of chronic kidney disease. Within those factors, the disturbances in the production of erythropoietin have the greatest impact on the disease pathogenesis. However, other components such as shortened erythrocyte survival, blood loss, iron or other nutritional deficiencies, hemolysis, the presence of uremic inhibitors of erythropoiesis among others can also significantly contribute to the occurrence of anaemia.

Key words: chronic kidney disease, anaemia, erythropoietin, hepcidin, iron

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INTRODUCTION

Iron is one of the most common elements in the Earth's crust and the most abundant metal in the human body. It is an essential element for survival, generation of hemoglobin in red blood cells and for growth. However, excess free iron is toxic to the cells due to its ability to form free radicals and induction of a pro-inflammatory state with subsequent dysfunction and peroxidation of lipid membranes [1]. Perturbation in physiologic iron concentrations may be a cause of cellular and organ damage that can directly lead to the disease state. A systemic iron balance needs to be tightly regulated through the mechanisms that specialize in the iron supply, utilization, recycling and its storage. Therefore, specialized transport systems and membrane carriers have been developed and serve to maintain effective iron in a non-toxic and soluble form that circulates in the blood and in this state can be transferred across cell membranes [2,3]. Iron absorption by the duodenal enterocytes and its efflux from macrophages after the phagocytosis, as well as the degradation of senescent erythrocytes and heme catabolism are the main processes that regulate iron homeostasis.

Iron deficiency contributes to the development of anaemia which is a frequent complication related to chronic kidney disease (CKD). Many patients suffered from CKD have notably reduced health-related quality of life associated with the progression of renal dysfunction and cardiovascular disease. As a consequence, those patients exhibit also a higher rate of hospitalizations and a significantly higher mortality level [4,5].

Historical milestones

This history was started a long time ago by Richard Bright and his first suggestion that the kidney might be involved in erythropoiesis. In 1835 he described the association between ‘anemia’ and ‘kidney dysfunction’. Then, in 1906 Carnot and Deflandre discovered, in the blood of anemic animals, a body to which they gave the name “hemopoietin”. They reported that serum from an anemic donor rabbit injected into a normal rabbit resulted in increased erythropoiesis [6]. Almost fifty years later, Allan Erslev proposed that plasma from anemic rabbits containing a factor able to stimulate erythropoiesis, could have a potential as a therapeutic approach. Next, in 1957 Jacobson and Goldwasser’s team showed that the kidney was the source of this substance [7]. Exactly 20 years later Miyake el. al isolated the hormone from urine of patients with aplastic anemia and named it erythropoietin [8,9]. Attributable to the advancement in biotechnology the gene of this agent was separated and cloned. It became clear that besides iron, erythropoietin would be a desirable approach to treat renal anemia. Fast-track of erythropoietin from bench to bedside became a milestone in the therapy of renal anemia enabling to avoid blood transfusion with secondary hemochromatosis and HLA sensitization.

New treatment options

HIF stabilizers

Deficiency of erythropoetin (EPO) is one of the predominant cause of anemia in CKD. EPO, the primary driver of erythropoiesis, is the hormone essential for maintaining the survival, proliferation and differentiation of erythroid progenitor cells in the bone marrow, acting by binding the EPO receptor (EPOR) homodimer on the cell surface of erythroblasts [10].

EPO is primarily produced by renal EPO-producing cells (REPs) in a hypoxia-inducible manner via the activation of hypoxia-inducible transcription factors (HIFs) [11]. It is has been recognized that the hypoxia-inducible expression of the gene encoding for EPO is the paradigm of oxygen-regulated gene expression. Unravelling the cellular oxygen sensing mechanisms and the central to this signalling cascade role of HIF-1 and HIF-2 factors enables higher organisms to compensate for changes in oxygen supply [12]. Inhibition of prolyl hydroxylation and as a consequence HIF stabilization paved a way for novel therapeutic approaches of anaemia, based on mimicking the hypoxia-driven expression of endogenous EPO in the kidney. The top new candidates for the antianemic drug include FG-2216, FG-4592 (roxadustat, Fibrogen), GSK1278863 (daprodustat, GSK) AKB-6548 (vadadustat, Akebia), BAY85-3934e (molidustat, Bayer), JTZ-951 (Akros Pharma Inc) and DS-1093a (Daiichi Sankyo Inc). All compounds belonging to the HIF stabilizers family and have entered the stage of clinical trials.

One of the first promising molecules of this class was tested by Fibrogen INC FG-2216. However, it was withdrawn after reaching an unfavorable hard endpoint - fatal hepatitis. Then the same company developed roxadustat (FG-4592). Data from phase 2 of clinical trials (roxadustat, molidustat, vadadustat and daprodustat) showed efficacy of these compounds with generally safety concerns.

Currently, FG-4592 is a phase III clinical trial in the treatment of secondary anemia to chronic kidney disease. Clinical or preliminary or available data confirm the enhanced production of hemoglobin and red blood cell by increasing the production of endogenous erythropoietin. FibroGen (collaborating with Astellas Pharma Inc. and AstraZeneca AB) anticipates filing a U.S. New Drug Application (NDA) for roxadustat for the treatment of anemia associated with CKD in 2018 [13-16].

Other HIF stabilizers such as were tested in clinical trials [17,18].

The benefits of prolyl hydroxylase inhibitors in the anaemia treatment in CKD are associated with its ability for modulation of the other genes functions that take part in erythropoiesis, depletion of hepcidin production and finally oral administration. Besides, HIF stabilizers are promising in the aspect of safety, efficacy, reimbursement and convenience over ESAs.

Additionally, the administration of HIF stabilizers is related to other effects as small decrease in blood pressure and cholesterol level. The elevation of platelet level was also not observed, while in other hand treatment with ESA seems to be associated with hypercoagulability and elevation of blood pressure. It is shown that the elevated level of endogenous EPO among patients treated with HIF stabilizers is mainly in the normal range or slightly above. And the height corresponds to the situation of high altitude or blood donation. Interestingly, there is no need for iron supplementation during the therapy. HIF stabilizers contribute also for lowering the level of hepcidin that could bring benefits to the therapy of anaemia with inflammation in the background. The mechanisms of the HIF-2 stabilization via inhibition of prolyl hydroxylase domain-containing protein 2 (PHD2) enzyme leads to erythropoiesis, suppress hepcidin, enhance circulating iron availability and hence bypass the main cause of EPO resistance. Thereby, different mechanisms of action that regulate the endogenous synthesis of EPO is an undoubted advantage, especially considering the development of potential resistance for the treatment. All those described aspects and, moreover simple chemical synthesis, not based on biotechnology, and good stability of the active components allow to consider HIF stabilizers for effective treatment of renal anaemia and may offer a future for novel therapies, even in patients with cancer [19].

Despite promising clinical data we have to be aware of unpredictable side effects and hence carefully evaluate the consequences of simultaneous upregulation of other hypoxia-sensitive genes and also those ones engaged in glucose and angiogenesis regulation. Stimulation of vascular endothelial growth factor might trigger tumor growth and leads to the progression of proliferative diabetic nephropathy. Therefore, special caution should be taken when ordering ESA to patients with a history of malignancy.

Epomimetics

New treatment approaches for the anaemia of CKD acting on the EPO receptor include the class of EPO mimetics molecules. Those are peptides such as Centocor R&D Inc. (a subsidiary of Johnson & Johnson) molecules, CNTO 530, CNTO 531, CNTO 528; AplaGen GmbH: AGEM400 (hydroxyethyl starch), AG-EM-0040; peginesatide; EPO fusion proteins such as EPO-EPO dimers, EPO-CTP (Carboxyl-Terminal Peptide), EPO-$(CTP)_3$, albumin-EPO, EPO-hyFc (Genexine Inc. GX-E2); antibodies agonists to EPO receptor such a as mouse monoclonal IgG, Ab12 and Ab12.6 (Abbott Laboratories ABT-007) molecule; EPO gene therapy (transducer autologous regenerative gene therapy EPO) – NCT02117427 and dimerization of EPO receptor intracellular domain with a chemical inducer of dimerization [20]. It has been shown that peginesatide (Omontys®, originally called Hematide™; Affymax/Takeda), was previously considered as one of the most advanced product with accepted safety surveillance. Nevertheless, the PEARL 1 and 2 study also recognized that it might increase the risk of safety clinical endpoints in non-dialyzed CKD patients [21]. After reporting the serious life-threatening allergic reactions the pharmaceutical company withdrew the drug from the market. Other promising drug candidates include activin ligand traps (sotatercept and luspatercept) and a group of new transcription factors - proteins - that bind to the GATA sequences in the regulatory regions of genes are under development and still require to carry out detailed research clinical trials in order to characterize the efficacy and safety profile. The FDA has issued warnings on the use of EPO analogs due to a greater risk of death and serious cardiovascular events [22].

Hepcidin and ferritin-ferroportin axis

A key regulator of iron transport and availability, hepcidin has been clearly associated in the CKD anaemia pathogenesis and have been considered as an important advance for its future treatment [23]. Many research pay attention and put a great impact in various therapeutic approaches that targeting hepcidin and ferroportin. Inhibition of hepcidin function (Direct Hepcidin Antagonists), prevention of its transcription (Hepcidin Production Inhibitors) and promotion of the resistance development of ferroportin to hepcidin action (Ferroportin agonists/stabilizers) are the main point of action of those new promising class of therapeutic.

Other hepcidin sequestering agents to be considered as a novel treatment options include mimicking soluble hemojuvelin; suppression of bone morphogenic protein (BMP) receptors as dorsomorphin; disruption IL-6 activation and there the action of tocilizumab, neutralizing antibody to IL-6, that has been already approved for rheumatoid arthritis and has been proved to ameliorate anaemia in Castleman's disease; and the inhibition of a transcription factor signal transducer and activator of transcription 3 (STAT3 inhibitor). Antisense oligonucleotides (ASOs) and RNA interference (RNAi) are the other therapeutic strategies for targeting transcription and translation of hepcidin

[24] and minihepcidins (small active peptides) - mimetics of iron-regulatory hormone hepcidin [25].

CONCLUSIONS

In the new era of advanced pharmaco-therapy, the nephrologists face to struggle not only with the end-stage kidney patients and many associated complications but also with the evaluation of the therapeutic possibilities that are given be the dynamic research conducted on new drug development.

Anaemia, one of the most frequent condition that CKD patients suffer from directly contributes to worsen quality of life and poor prognostic perspectives with the increasing rate of overall hospitalization incidents and mortality.

Therefore, several new strategies for treating the anemia of chronic kidney disease are currently being investigated in clinical trials, including prolyl hydroxylase inhibitors and modulators of hepcidin activity.

However, their role in the management of anaemia in CKD still remains to be better established.

Conflicts of interest

Not declared.

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