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# A Modern Approach to the Treatment of Anemia in Patients with Chronic Kidney Disease

**Naimov Dilshod Qayim o'g'li**

Bukhara State Medical Institute, Assistant of the Department of Internal Medicine,

Uzbekistan, Bukhara

***Abstarct:*** Anemia is one of the most common complications of chronic kidney disease. Current potential of hypoxia-inducible factor prolyl hydroxylase inhibitors in the treatment of anemia in patients with CKD.

***Key points:*** disease, anemia, iron supplements, roxadustat.

Anemia is one of the most common complications of chronic kidney disease. Current potential of hypoxia-inducible factor prolyl hydroxylase inhibitors in the treatment of anemia in patients with CKD.

Unresolved issues in the treatment of anemia in patients with CKD.As noted by the head of the Interdistrict Nephrology Center of the State Clinical Hospital (GKB) named after. S.P. Botkina, Head of the Department of Nephrology and Hemodialysis of the Russian Medical Academy of Continuing Professional Education, Doctor of Medical Sciences, Professor Evgeniy Viktorovich SHUTOV, anemia in chronic kidney disease (CKD) has a complex multifactorial pathophysiology, however, existing treatment options only affect one specific aspect of it1 . The main options for correcting anemia in CKD remain iron supplements, erythropoiesis-stimulating agents (ESS), and blood transfusions. However, the use of most of them is limited by inflammation, elevated hepcidin levels, and the need to visit the hospital and undergo injections. Therefore, as DOPPS data show, treatment of renal anemia is still a pressing problem not only in our country, but also in the USA, Europe, and Japan2.

The difficulties in treating renal anemia are due, firstly, to the lack of a clear understanding in the medical community of the algorithms for the use of iron and ESA preparations, and secondly, resistance to therapy in patients, especially in the presence of inflammatory conditions. According to research, in patients with pre-dialysis stage CKD, resistance to ESA3 is observed in 34% of cases. About 10–20% of patients with end-stage chronic renal failure did not achieve the target hemoglobin level of 100 g/L despite ESA use.

Iron deficiency is one of the most common complications in patients with CKD and is found in more than half of them and in 20–25% of dialysis patients. The use of iron supplements, although it helps to improve the control of anemia in this severe category of patients, does not completely solve the problem. First of all, this is due to the unequal practice of using iron supplements in different countries, which is due to discrepancies in national clinical guidelines and the lack of a clear position on this issue in the international clinical guidelines KDIGO. For example, the 2012 KDIGO recommendations suggested starting treatment with iron supplements at ferritin levels <500 ng/ml and transferrin iron saturation (TIS) <30% and stopping treatment when these same levels are reached, which is not possible or logical. The NICE recommendations (UK, 2017) indicate stopping

treatment with iron supplements when ferritin levels reach 500–800 ng/ml, and the KDOQI recommendations (USA, 2013) do not limit the use of iron supplements in patients at all.

The problem is that there is no consensus on what doses and at what ferritin level it is safe to use iron to treat anemia. Meanwhile, today there is a clear connection between serum ferritin levels and mortality from all causes and hospitalization due to cardiovascular diseases4. Hospitalization and mortality rates have been shown to nearly double when ferritin levels rise above 200 ng/mL.

In a study by G. Rostoker et al. It has been demonstrated that the era of iron supplementation in hemodialysis patients contributed to the development of hemosiderosis in the vast majority of patients.

Intravenous iron is routinely administered to patients with CKD to treat anemia. In a study by K. Kalantar-Zadeh et al. (2005) found an association between the dose of intravenously administered iron and levels of general and cardiovascular mortality5. A reasonable dose of intravenous iron supplementation was considered to be no more than 300 mg per month.

What are the mechanisms of the negative effects of high doses of iron? The administration of iron further increases the level of hepcidin and prevents the recycling of iron from aging erythrocytes, reducing the supply of iron to erythrocytes. The increase in reactive oxygen species caused by bone marrow iron overload may contribute to decreased proliferation potential of erythroid progenitors and impaired differentiation of bone marrow mesenchymal stem cells.

Hepcidin is a key regulator of iron metabolism in the body.

According to the World Health Organization (WHO), risks of iron overload occur when serum ferritin concentrations are more than 200 ng/ml in men and more than 150 ng/ml in women.

Most countries, with the exception of Japan, agree that iron levels should be higher in patients with CKD. The situation is similar to that with diabetes mellitus (DM), where it was believed that patients with DM should have significantly higher glucose levels.

A Japanese study found that low-dose oral iron therapy was effective for patients with C-reactive protein (CRP) <0.1 mg/dL on hemodialysis6. It has been shown that when hematopoiesis is stable, a serum ferritin level of approximately 60 ng/ml may be sufficient to prevent negative consequences.

Another study demonstrated better survival in patients who had ferritin levels of 30–80 ng/mL and IFG >20%.

Resistance to treatment for anemia may be due to iron overload, high hepcidin levels, inflammation, infection, and other risk factors. According to Professor E.V. Shutov, overcoming resistance due to a significant increase in doses of ESA and iron preparations leads to negative results, and this complex problem requires an early solution. To date, target levels of ferritin and NT, and optimal routes of iron administration have not been established. Certain hopes are associated with the introduction of new classes of drugs for the treatment of anemia7.

In this regard, it is difficult to overestimate the emergence of a new class of drugs - Hypoxia-Inducible Factor Prolilhydroxylase Inhibitors (HIF-PHI), or HIF prolyl hydroxylase inhibitors.

Professor E.V. Shutov made a brief excursion into the history of studying the HIF-PHI class. In 1991, scientists discovered that in the kidney and liver, hypoxic or ischemic conditions induce the production of nuclear factors that promote the expression of erythropoietin (EPO) by binding to elements located at the third end of the human EPO gene, first described as HIF. In 1993, the widespread distribution of this oxygen-sensitive system in mammals was revealed. In 1995, HIF-1 was isolated and purified, and it was confirmed that HIF-1 contains two subunits, HIF-1α and HIF-1β.

Activation of HIF occurs when oxygen levels decrease8,9. Under normal oxygen levels, HIF-PH (HIF prolyl hydroxylase) is present in sufficient quantities and causes continuous destruction of HIF-1α, preventing activation of the hypoxia response. When oxygen levels are low, HIF-PH is inactive because oxygen is needed for the enzymatic reaction, so HIF-1α accumulates. HIF-1α

dimerizes with HIF-1β and enters the nucleus, stimulating transcription of the gene responsible for erythropoiesis.

The protective role of HIF-PHI (HIF prolyl hydroxylase inhibitors) in cardiovascular diseases is also being studied. According to in vitro studies, HIF-PHI contributed to the reduction of ischemic and reperfusion damage to the myocardium, reduction of hypertension, and regression of atherosclerosis10. HIF-PHI class drugs have shown a protective role in acute kidney injury (AKI), as well as in diabetic nephropathy. The neuroprotective effects of HIF prolyl hydroxylase inhibitors include potential protection against ischemic cerebral injury, spinal cord injury, and improvement in Parkinson's disease. The effects of HIF-PHI related to organ protection (heart, kidney, liver, lung) are being studied in several clinical studies.

The drug roxadustat is a class of HIF prolyl hydroxylase inhibitors that stimulates the production of hemoglobin and red blood cells. Roxadustat is the first oral drug approved for patients with anemia from chronic kidney disease. What is the mechanism of action of the drug? Roxadustat inhibits HIF prolyl hydroxylase, which leads to the accumulation of HIF-α. HIF-α translocates to the nucleus, where it forms a transcriptional complex with HIF-β. The HIF-α/β complex induces transcription of erythropoiesis and iron metabolism genes.

Evrenzo (roxadustat) is the first of a new class of drugs to treat anemia in CKD in almost 30 years since the introduction of ESAs. The drug is approved for the treatment of anemia in CKD in more than 40 countries. In 2022, Evrenzo was approved in Russia for the treatment of anemia in CKD.

Activation of the HIF pathway by Evrenzo (roxadustat) triggers a coordinated erythropoietic response. The drug has a positive effect not only on erythropoiesis due to an increase in the synthesis of endogenous erythropoietin, but also on iron absorption and reduces the production of hepcidin. This makes it possible to use it in patients with ESA-resistant anemia.

A phase III clinical trial program has been conducted involving more than 9600 patients from around the world 7 , 10 - 18 . The efficacy and safety of roxadustat were studied in patients not receiving dialysis, as well as in patients on incident and stable dialysis.

In a multicenter randomized study involving pre-dialysis patients, including those from the City Clinical Hospital named after. S.P. Botkin, a higher effectiveness of roxadustat in the treatment of anemia was demonstrated compared to placebo7. Roxadustat was effective in achieving and maintaining hemoglobin levels regardless of the use of salvage therapy. Roxadustat reduced low-density lipoprotein levels. Roxadustat has been shown in studies to reduce serum hepcidin and ferritin levels and increase transferrin levels.

The results of three double-blind, placebo-controlled phase III studies comparing roxadustat with placebo in patients with anemia of CKD not receiving dialysis were pooled and compared with the results of an open-label study comparing roxadustat with darbepoetin alfa in the same population15. Analysis of regional pooled results (n = 4886) showed that roxadustat was more effective than placebo and as effective as darbepoetin alfa in correcting hemoglobin. However, roxadustat was more effective than darbepoetin alfa in achieving target hemoglobin levels without rescue therapy.

A randomized trial of incident dialysis patients (n = 1043) demonstrated non-inferiority of roxadustat compared with epoetin alfa in correcting hemoglobin levels.

The phase III HIMALAYAS clinical trial showed that roxadustat therapy resulted in a greater reduction in intravenous iron use compared with epoetin alfa. Importantly, the dosage of roxadustat was the same in patients with elevated CRP levels and in patients with normal CRP levels. In contrast, mean doses of epoetin alfa were higher in patients with initially elevated CRP levels compared with patients with normal CRP levels. The difference between subgroups was 15.1 IU/kg ($p = 0.0088$).

Evrenzo (roxadustat) demonstrated comparable efficacy to ESA in achieving and maintaining target hemoglobin levels in patients on incident and stable dialysis. In several phase III studies, Evrenzo was shown to consistently reduce hepcidin levels compared with placebo and ESA in patients

regardless of dialysis status. Studies have confirmed the ability of Evrenzo to reduce the need for intravenous iron in incident dialysis patients compared to ESA.

A prospective study by Y. Zhou et al. (China, 2021) studied the effectiveness of roxadustat in dialysis patients with treatment-resistant anemia in CKD19. After roxadustat therapy, transferrin levels and total iron-binding capacity increased, whereas TG and cholesterol levels decreased. In 48.39% of cases, target hemoglobin levels were achieved.

Phase III studies provided data on the cardiac safety of Evrenzo. Evrenzo has been shown to be comparable to ESA in terms of MACE, MACE+ and all-cause death in both nondialysis and dialysis patients 15 , 16 .

In a meta-analysis of 110 articles (11 randomized trials in non-dialysis patients), roxadustat increased serum hemoglobin levels more significantly than placebo and comparable to ESA. It was concluded that roxadustat is an effective and safe drug for the treatment of anemia in patients with predialysis CKD.

A systematic review and meta-analysis of 133 papers (21 studies) published in April 2023 confirmed that roxadustat is more effective and safe than standard ESAs in the treatment of anemia in Chinese hemodialysis patients20.

At the end of the speech, Professor E.V. Shutov stated that anemia is considered an important complication of CKD and without adequate treatment can have serious consequences for patients. In this regard, HIF prolyl hydroxylase inhibitors (roxadustat), a new class of oral drugs with a simple dosing method for the treatment of anemia in patients with CKD, deserve special attention. HIF prolyl hydroxylase inhibitors, of which roxadustat is the first representative, have the following advantages:

- decreased hepcidin levels;
- increased mobilization of internal iron reserves;
- good effectiveness, regardless of inflammation;
- decrease in LDL levels.

**Treatment of anemia in CKD. The view of a clinical pharmacologist**

Chronic kidney disease is a common disease that affects 10–15% of the adult population. According to the head of the Department of General and Clinical Pharmacology of the Medical Institute of the Russian Peoples' Friendship University, Deputy Chief Physician for Therapy of City Clinical Hospital No. 24 (Moscow), Doctor of Medical Sciences, Professor Sergei Kensarinovich ZYRYANOV, the relevance of the problem also lies in the fact that in CKD it is significant the risk of developing systemic complications, including anemia, increases.

The prevalence of anemia increases with increasing stage of CKD. According to available data, more than 83% of patients with stage 5 CKD are anemic. Importantly, CKD-associated anemia significantly increases the risk of cardiovascular events as well as death from all causes. A study of 2,423 patients with CKD found that anemia increased the risk of all-cause death by 65% and the risk of heart attack, stroke and mortality by 48%.

Today, specialists have several therapeutic options at their disposal to correct anemia in CKD - iron supplements, erythropoietin preparations, blood transfusions, as well as activators of the HIF mechanism. Undoubtedly, a promising new class of oral drugs are hypoxia-inducible factor prolyl hydroxylase inhibitors. Of great importance in the creation of a new class of drugs was the description of the mechanism of the cellular response to hypoxia and the role of HIF made by William Kelin, Greg Sementzi and Sir Peter Ratcliffe. In 2019, scientists were awarded the Nobel Prize for their research into how cells respond to oxygen and its absence.

There are several main reasons for the development of anemia in CKD: decreased sensitivity of the kidneys to oxygen; chronic inflammation, which increases the concentration of hepcidin; decreased

production of erythropoietin; iron deficiency. HIF prolyl hydroxylase inhibitors, imitating the body's natural response to hypoxia, trigger a coordinated erythropoietic response, taking into account the multifactorial nature of anemia.

Roxadustat is the first HIF prolyl hydroxylase inhibitor registered in Russia, which opens up new possibilities in the treatment of anemia in patients with CKD.

Professor S.K. Zyryanov briefly described the method of using the drug. Roxadustat should be taken three times a week, every other day. After the third day of admission, a two-day break is taken. The tablets are taken regardless of meals, swallowed whole. The tablets should be taken at least one hour before or one hour after taking phosphate binders (except lanthanum) or other (drugs) containing polyvalent cations such as calcium, iron, magnesium or aluminum. If a patient already taking the lowest dose (20 mg three times a week) requires further dose reduction, the dosing frequency should simply be reduced to twice a week, and if further reductions are necessary, to once a week21.

Assessing the clinical and pharmacological characteristics of roxadustat, the expert noted the drug's ability to maintain the achieved hemoglobin level for a long time. Phase III studies (ROCKIES, SIERRAS, PYRENEES) showed that roxadustat maintained stable hemoglobin levels in dialysis patients without dose escalation compared with ESA dose escalation over two years16.

The use of roxadustat allows one to maintain a stable hemoglobin level regardless of the presence of inflammation in patients with anemia in CKD. According to the ROCKIES study, roxadustat in dialysis patients, regardless of CRP levels, was more effective in increasing and maintaining stable hemoglobin levels compared with epoetin alfa12.

The use of roxadustat leads to a decrease in the use of intravenously administered iron. Studies have confirmed that roxadustat maintained iron levels with less use of intravenous iron supplementation compared with ESA in nondialysis and dialysis patients15,22.

Of course, the safety profile of the drug is important. In studies, roxadustat showed a safety profile comparable to ESA in terms of cardiovascular events and all-cause mortality in both non-dialysis and incident dialysis patients.

To summarize the above, Professor S.K. Zyryanov formulated the following conclusions:

- HIF prolyl hydroxylase inhibitors, particularly roxadustat, are comparable in efficacy to current standard of care ESA therapy, as measured by mean hemoglobin levels over 104 weeks in non-dialysis patients with CKD and over 52 weeks in dialysis patients;
- in patients receiving roxadustat, there was a decrease in hepcidin, the frequency of intravenous iron supplementation, and rescue therapy compared with the placebo and ESA groups;
- roxadustat did not increase the risk of cardiac events and death compared with ESA in non-dialysis patients and in patients on incident dialysis;
- The overall safety profile of roxadustat was comparable to ESA for most safety endpoints assessed.

"An important feature of the drug is the oral route of administration, which distinguishes roxadustat from erythropoiesis-stimulating drugs that are widely used today," the expert emphasized.

Unfortunately, not all patients with anemia in CKD receive adequate therapy and, accordingly, are exposed to the risks associated with anemia. How can I get medicine for free? According to Professor S.K. Zyryanova, in most cases medicines are provided free of charge. The prescription of a medicinal product not included in the list of Vital and Essential Drugs/clinical recommendations is determined by Federal Law No. 323 of November 21, 2011 "On the fundamentals of protecting the health of citizens." According to the law, the prescription and use for medical reasons of drugs not included in the Vital and Essential Drugs list is possible if they are replaced due to individual intolerance or for health reasons by decision of the medical commission. Vital indications are determined by the consultation for each individual patient.

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