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The effectiveness of a new drug used in anemia (roxadustat) in comparison with erythropoiesis stimulating agents in chronic kidney disease

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Abstract

In chronic kidney disease (CKD), particularly at stage 5 (G5) and stage 5 on dialysis (G5D), anemia is a common condition. Erythropoietin-stimulating agents (ESAs) have been the only treatment for many years. New drugs, Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs), have emerged as alternatives. This review aimed to summarize the effectiveness of HIF-PHDIs to intravenous ESAs as comparators in the treatment of anemia. One of the HIF-PHIs is roxadustat, which increases hemoglobin (Hb) levels by regulating iron metabolism, including reducing plasma hepcidin and ferritin levels and increasing total iron binding capacity. The efficacy of roxadustat is relevantly higher than ESAs, which can result in a better reduction in anemia. This drug is administered orally rather than by injections as ESAs treatment and is well-tolerated. Roxadustat can be considered an alternative to ESAs treatment, as it is more effective in raising hemoglobin levels than ESAs. *(Farm Współ 2024; 17: 154-158) doi: 10.53139/FW.20241719*

Keywords: anemia, chronic kidney disease, dialysis patients, roxadustat

Introduction

Chronic Kidney Disease (CKD) over the last 20 years has gained a position as one of the biggest problems for public health. Its prevalence worldwide is 8-16%, but it is supposed to rise in countries with a growing population of older people [1]. Along with the advance of CKD goes the deterioration of the kidney's endocrine function, which straightforwardly leads to the lack of sufficient erythropoietin synthesis by the interstitial cells of the kidneys. This results in developing anemia among almost 90% of the dialyzed patients suffering from CKD [2]. It is prevalent in advanced CKD stages, affecting more than 50% of patients in stages 4 and 5, and is also observed earlier in individuals with diabetes mellitus (DM). Anemia in CKD is typically characterized by normocytic, normochromic, and hypoproliferative features [3]. Human erythropoietin stood as the first historical anemia treatment since the Food and Drug Administration (FDA) approval in 1989. Throughout the last few years, patients suffering from such conditions have had the possibility of treatment with erythropoiesis stimulating agents (ESAs), which have become a worldwide standard [4]. Currently, the following types of ESAs are available: erythropoietin (EPO), epoetin alfa, beta and zeta, darbepoetin alfa, and methoxy polyethylene glycol epoetin beta. The drugs listed here are responsible for increasing impaired red blood cell maturation in the bone marrow, making their effects desirable for anemia-suffering patients. Despite its popularity and usefulness, recent studies report an increased risk of cardiovascular adverse effects and developing tumors. Additionally, hemodialysis patients can acquire resistance to such drugs after long-term use [5]. Following these facts, we should consider different treatment possibilities in renal anemia. This review aimed to summarize the effectiveness of HIF-PHDIs to intravenous ESAs as comparators in the treatment of anemia.

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HIF-PHDI

HIF-PHDIs (Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors) are a class of drugs (administered orally) that stabilize hypoxia-inducible factors (HIFs) in the body. HIFs are critical transcription factors in the response to low oxygen levels (hypoxia) in cells. They regulate erythropoiesis (red blood cell production) and iron homeostasis, among other functions. In normoxic conditions, HIFs are degraded by prolyl hydroxylases (PHDs), but under hypoxic conditions, HIFs stabilize and translocate to the cell nucleus, activating target genes related to erythropoiesis. One of the primary effects of HIF-PHDIs is that they increase the production of erythropoietin by the kidney. EPO is a hormone that stimulates the bone marrow to produce more red blood cells, thus improving the oxygen-carrying capacity of the blood. By enhancing EPO production, HIF-PHDIs can effectively treat anemia in patients with CKD. Moreover, HIF-PHDIs also influence iron metabolism. They upregulate the expression of genes involved in iron absorption from the alimentary tract. Additionally, they indirectly suppress hepcidin production, a hormone that reduces iron availability for erythropoiesis. This overall effect leads to improved iron utilization for red blood cell production. HIF-PHDIs (roxadustat, vadadustat, daprodustat) show promise as potential treatments for anemia in CKD patients, with their ability to stabilize HIFs and improve erythropoiesis. They offer a more physiologic approach to treating renal anemia, potentially increasing endogenous EPO levels close to the physiological range, as opposed to high levels achieved with current available erythropoiesis-stimulating agents (ESAs). All HIF-PHDIs are orally active drugs that can stand as a benefit for non-dialysis dependent CKD patients and kidney transplant recipients. Roxadustat represented an increase in Hb levels bigger or equal to 2 g/dL within seven weeks of treatment, with the dose ranging between 4.0-4.3 mg/kg weekly (administered three times per week). The reported adverse effects were hypertension, headache, back pain, fatigue, increases in liver enzymes, and decreases in transferrin saturated with iron [6,7].

Roxadustat

Roxadustat (also known as FG-4592 or ASP-1517) is used in the treatment of anemia associated with CKD and end-stage renal disease (ESRD) [6,7]. The drug has been extensively studied in both dialysis-dependent (DD)-CKD patients and non-dialysis-dependent (NDD)-CKD patients, demonstrating significant effects on erythropoiesis in both groups. Roxadustat's effective increase in hemoglobin (Hb) levels has been associated with the regulation of iron metabolism, including reductions in plasma hepcidin and ferritin levels and an increase in total iron binding capacity, which has been demonstrated in many clinical trials and meta-analyses [8-17]. The concentration of hepcidin is elevated in patients with end-stage renal disease and inflammatory conditions. It may be lowered by HIF stabilization, which is the effect of roxadustat and may lead to improved iron absorption in the intestines and the synthesis of iron transport proteins [17]. Roxadustat remains effective even without the iron repletion requirement that is necessary while using ESAs [18]. If iron level is still lowered, HIF remains stabilized, which maintains increased intestinal iron absorption until its restoration. In that field, ESA therapy is also inferior to roxadustat, because, in opposition to this new drug, it cannot coordinate endogenous erythropoietin production, iron availability, and lowering the level of hepcidin. Roxadustat can increase Hb levels within a few weeks, and the response rates vary depending on the dose and frequency of administration.

Anemia is a condition affecting the quality of life straightforwardly – patients experience fatigue, dyspnea, and reduced exercise tolerance; however, the effects can be much worse and include a higher risk of coronary artery disease and left ventricular hypertrophy [4]. This drug is administered orally and can take place at the patient's home, which is beneficial and does not require frequent visits to medical institutions. Patients using roxadustat are also free from frequent injections necessary during ESAs treatment. During the COVID-19 pandemic, researchers from China [19] demonstrated that, unlike ESAs, which require intravenous or subcutaneous injection and pose challenges due to cold chain storage, roxadustat offers the advantage of convenient storage, making patients more willing to use this type of drug. In addition, the use of HIF-PHIs, such as roxadustat, increases erythrocyte production without raising EPO levels [20], which may protect patients from such adverse effects as exacerbation of hypertension or working as a cell growth factor that can result in the development of tumors [5]. In addition to the previously described mechanism of action of roxadustat, which affects the production of erythrocytes, several studies indicate

its ability to lower low-density lipoprotein (LDL) and total cholesterol levels [8-10,21,22]. Roxadustat also improves LDL/high density lipoprotein (HDL) ratio which was proved previously by other studies [23]. The study of Hasegawa showed that during diabetic nephropathy, roxadustat can increase glycolysis and reduce fatty acid metabolism, leading to inhibition of diabetic nephropathy progression [24].

In many studies, roxadustat is more effective (0,7 ± 1.1 g/dL in the roxadustat group in comparison to 0.5 ± 1.0 in the ESA group) in increasing hemoglobin levels than ESA [8,9,12-17,22,25-29]. Numerous studies prove that roxadustat does not pose a higher risk of severe adverse effects such as hypertension, fatigue, diarrhea, headache, or back pain than ESA [12,22,25-29]. Studies have demonstrated that roxadustat is well-tolerated, with most adverse events being typical of the patient population with CKD or ESRD. Commonly reported side effects include diarrhea, headache, back pain, fatigue, hypertension, and mild liver enzyme alterations [6,7,30]. However, it should be noted that the meta-analysis by Zheng et al. shows that there is a higher risk of macular edema and proliferative retinopathy than with ESA [11]. There is also one systematic review showing a higher risk of cellulitis in patients with CKD (dialysis-dependent) using roxadustat than ESA [31]. Table I presents the studies characterizing the effectiveness of roxadustat. Table II presents indications and dosage of Roxadustat.

Conclusion

Roxadustat demonstrates an increase in hemoglobin levels compared to ESAs in CKD. Roxadustat can be considered an alternative to ESAs treatment, as it is more effective in raising hemoglobin levels than ESAs.

Table I. Studies characterizing the effectiveness of roxadustat [8,9,25,32-36]

Study ID	n/n* (study group)	n/n* (comparator – ESA)	Duration of the study [week]	Hemoglobin before study (study group) [g/dL]	Hemoglobin after study (study group) [g/dL]	Hemoglobin before study (comparator – ESA)[g/dL]	Hemoglobin after study (comparator – ESA) [g/dL]
	ROXADUSTAT						
Barratt J et al. 2021 (stable) [32]	1594/881	1594/1072	28-36	10.320	10.970	10.370	10.730
Barratt J et al. 2021 (incident) [32]	760/503	766/524	28-36	8.770	11.140	8.820	10.940
Csiky B et al. 2021 [33]	415/249	421/309	52-104	10.747	11.145	10.775	10.960
Fishbane S et al. 2022 [25]	1068/982	1065/990	28-52	10.200	10.970	10.300	10.980
Chen H et al. 2019 [9]	204/162	100/94	26	10.400	11.100	10.500	11.000
Hou YP et al. 2022 [8]	67/61	43/38	24	9.000	11.500	9.000	11.200
Akizawa T et al. 2020 [34]	151/119	152/131	24	11.020	11.000	11.020	10.950
Moussa O et al. 2022 [35]	53/36	53/30	26	7.950	10.150	8.390	9.490
Charytan C et al. 2021 [36]	370/125	371/177	52	10.300	10.690	10.310	10.220

Table II. Indications and dosage of Roxadustat [37]

Drug	Indications	Dosage
Roxadustat	Anemia in patients with chronic kidney disease, especially in those undergoing dialysis	70 mg 3 times per week (weight <100kg) 100 mg 3 times per week (weight >100kg) Dosage depends on patient's body weight, gender and Hb level Treatment duration: as recommended by the doctor, based on patient's condition

Conflict of interest
None

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