REVIEW ARTICLE

Renal Disease and Transplantation Forum
2022, vol. 15, no. 2, 63–74
Copyright © 2022 Via Medica
ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/RDTF.2022.0010

Andrzej Chamienia[1,2], Alicja Dębska-Ślizień[1]

[1]Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdańsk
[2]Department of Medical and Pediatric Nursing, Institute of Nursing and Midwifery, Medical University of Gdańsk

Roxadustat — a new therapeutic option for treatment of anemia in patients with chronic kidney disease

ABSTRACT

Chronic kidney disease (CKD) is an increasingly common public health issue. It is estimated that it affects 8–16% of the global population. Anemia is a very common complication of chronic kidney disease, and its occurrence is associated with a reduced quality of life, increased morbidity, and mortality. The main causes of CKD anemia include erythropoietin (EPO) deficiency and iron deficiency (absolute and functional). In addition, the bone marrow response to EPO is reduced in patients with chronic inflammation, which is often present in patients with advanced stages of CKD and dialyzed patients. According to the current guidelines, the treatment of anemia in CKD involves recombinant erythropoiesis-stimulating agents (ESAs) along with iron supplementation. In some patients, intensive correction of anemia requiring high doses of ESA and intravenous iron may increase the risk of adverse events. The correction also requires injections, outpatient visits, and hospital stays, which is especially troublesome for pre-dialysis patients.
The discovery of hypoxia-inducible factors (HIFs) responsible for stimulating cells to EPO synthesis and increased activity of oxygen-dependent genes enabled the development of new drugs, so-called HIF-PHI inhibitors (hypoxia-inducible factor-prolyl hydroxylase inhibitors, prolyl hydroxylase inhibitors). Those compounds reversibly inhibit the activity of the enzyme responsible for inactivating the HIF and thus increase endogenous EPO synthesis and affect iron metabolism. This discovery opened new options for the treatment of anemia in CKD patients. Phase 2 and 3 clinical trials are conducted with several drugs: daprodustat (GSK-1278863), roxadustat (FG-4592), and wadadustat (AKB-6548). To date, only roxadustat has been approved for treatment of CKD-related anemia. Roxadustat (FG-4592) is a novel orally active, potent, and reversible inhibitor of prolyl hydroxylase (PHI), causing functional activation of target genes that encode proteins such as EPO, EPO receptor, heme biosynthesis enzymes, and proteins that enhance iron absorption and transport and thus promote formation and maturation of red blood cells (RBCs).
This study aims to summarize the available results of studies on the use of roxadustat in both pre-dialysis and dialysis patients with CKD.

Renal Disease and Transplantation Forum 2022, vol. 15, no. 2, 63–74

Key words: chronic kidney disease, anemia, erythropoiesis-stimulating agents, prolyl hydroxylase inhibitors

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health problem. It is estimated that it affects 8–16% of the global population [1]. In Poland, about 200 000 people are diagnosed with advanced-stage CKD, and about 20 000 are dialysis patients [2]. About 2 million patients depend on dialysis worldwide. Anemia is a very common complication of kidney diseases, and its occurrence is associated with a reduced quality of life, as well as increased morbidity and mortality [3, 4]. The main causes of CKD-related anemia include erythropoietin (EPO) deficiency and iron deficiency (absolute and functional). In addition, the bone marrow response to EPO is reduced in patients with chronic inflammation, particularly in patients with advanced-stage CKD and hemodialysis patients. Since the introduction of synthetic erythropoiesis-stimulating agents (ESAs; initially epoetin alpha-EPO-α, fol-

Address for correspondence:
Andrzej Chamienia,
Department of Nephrology,
Transplantology and Internal
Diseases, GUM,
ul. Smoluchowskiego 17,
80-214 Gdańsk,
email: chamien@gumed.edu.pl

lowed by EPO-β, darbepoetin, and pegylated epoetin beta) on the market in the 1980s, it has become possible to correct anemia in patients with impaired renal function. According to the current guidelines, the treatment of anemia in CKD includes recombinant ESA together with iron supplementation [3, 5, 6]. Initially, this treatment was aimed at reducing the need for blood transfusions, then studies were undertaken to see if that full correction of anemia improves the quality of life and reduces overall and cardiovascular mortality in patients with CKD. However, the results of those studies were inconclusive, and in some patients, the use of ESA in high doses increased the risk of cardiovascular events and death [7–9]. This resulted in a change in recommendations and target ranges for hemoglobin levels in both pre-dialysis and dialysis patients [5]. The analysis of adverse effects of intensive anemia correction showed that one of the important factors may be administration of intravenous iron, especially in patients with high ferritin levels and functional iron deficiency. This results from increased concentrations of factors preventing utilisation of stored iron such as hepcidin, and decreased levels of transferrin and total iron-binding capacity (TIBC). Treatment with ESA and intravenous iron requires injections, outpatient visits, and hospital stays, which have a particularly negative effect on patients in the pre-dialysis period. Thus, many patients treated according to the current standard of care do not achieve adequate anemia correction, and there is a need for additional clinical research in many areas [4, 5, 10].

A better understanding of the mechanisms regulating the body's response to hypoxia led to the identification of several transcription factors whose activity depends on tissue oxygen concentration. The most important factors include the hypoxia-induced factors (HIF) responsible for stimulating cells to synthesize EPO and increase the activity of oxygen-dependent genes [11]. Hydroxylation of appropriate proline residues in the HIFα subunit by a specific enzyme, i.e. prolyl hydroxylase (PHD), triggers its inactivation [12, 13]. The activity of PHD depends on the oxygen concentration and increases proportionally to oxygen content within tissues. Under hypoxia, HIFα does not degrade; it translocates to the nucleus where it forms a heterodimer with HIFβ and activates transcription of various genes. HIF factors facilitate oxygen supply and cellular adaptation to hypoxia by regulating a broad spectrum of responses to hypoxia responses such as angiogenesis, anaerobic glucose metabolism, mitochondrial biogenesis, and others [14]. PHD/HIF is an important mechanism that is involved in adaptation of tissues to low oxygen environments, regulates response to hypoxia, influences renal and hepatic EPO synthesis, controls iron uptake and utilization [15], and facilitates maturation and proliferation of erythroid cells in the bone marrow [16].

The discovery of HIF-PHI inhibitors (hypoxia-inducible factor-prolyl hydroxylase inhibitors) that reversibly inhibit PHD hydroxylation opened new possibilities for treatment of anemia in patients with CKD. These molecules induce a transient increase in expression of genes regulated by HIF, including the EPO gene in the kidney and liver, and cause a moderate increase in plasma EPO in patients with end-stage renal failure. Those drugs also have a beneficial effect on iron metabolism as they lower the levels of hepcidin and ferritin and increase TIBC and the level of transferrin in CKD patients [17]. It has been shown in clinical trials that drugs from this group, apart from stimulating erythropoiesis, induce additional effects such as lowering cholesterol levels [17–19]. Phase 2 and 3 trials are being conducted with several drugs, including daprodustat (GSK-1278863), roxadustat (FG-4592), and wadadustat (AKB-6548). Currently, only roxadustat has been approved for the treatment of CKD-related anemia [18, 20].

Roxadustat (FG-4592) is a new potent reversible inhibitor of prolyl hydroxylase (PHI) which is administered orally [9, 21, 22]. Roxadustat can stabilize the HIFα subunits and prevent their degradation by mimicking hypoxia, resulting in an increased HIF transcriptional activity. This, in turn, leads to functional activation of target genes encoding proteins such as EPO, EPO receptor, heme biosynthesis pathway enzymes, and proteins enhancing iron absorption and transport, which promotes formation and maturation of red blood cells (RBCs) [23].

This study aims to discuss the results of phase 2 and 3 studies on the use of roxadustat in pre-dialysis patients with CKD, as well as in dialysis patients.

RESULTS IN PRE-DIALYSIS PATIENTS

PHASE 2

The results of preclinical studies of roxadustat made it possible to conduct preliminary

phase 2 studies. Besarab et al. [24] recruited 116 patients into the study focused on the effects of various doses of the drug (1.0, 1.5, 2.0, or 0.77 mg/kg, 2 or 3 times a week) or placebo over 4 weeks of treatment and 2 weeks of observation. Additionally, pharmacokinetic parameters were assessed in some patients. There was a significantly greater increase in hemoglobin (Hb) level compared to placebo in all treatment groups, with 80% and 100% of patients in the two highest dose groups, respectively, achieving an increase of > 1 g/dL. Approximately 40% of patients received oral iron supplementation, and intravenous iron supplementation was not allowed. There was a significant increase in TIBC and a decrease in hepcidin and ferritin levels in the treatment groups compared to the placebo group. In a few patients, changes in endogenous erythropoietin levels were measured after administering the drug. Significant transient increases in erythropoietin levels were observed within the first 8 hours after administration. Overall, the treatment was well-tolerated, and the incidence of adverse events was comparable between roxadustat and placebo-receiving patients [24].

Provenzano et al. [19] conducted a study on a group of 145 patients with stage 3 and 4 CKD aimed to assess the response to different drug doses administered 2 or 3 times a week for 24 weeks. All subjects had Hb < 10.5 g/dL and had not been receiving ESA for at least 12 weeks before study enrollment. Overall, 92% of patients responded to treatment and the mean increase in Hb was 1.83 (± 0.09) g/dL. The observed increases in Hb concentration were independent of the initial C-reactive protein (CRP) level and iron metabolic status. The authors also observed a significant reduction in hepcidin levels and, additionally, total cholesterol levels, regardless of statin use. The study drug was generally well-tolerated, 57 serious adverse events were reported in 35 patients, 11 cardiovascular events were reported, and a total of 9 patients died. None of those events was classified as drug-related [19].

Szczech et al. [25] conducted another randomized double-blind placebo-controlled study including 91 patients randomly assigned to either 2 different starting doses of roxadustat or placebo, given over 8 weeks. Among the participants, 80–87% achieved an increase in Hb of more than 1 g/dL, compared to 23% in the placebo group. Patients received only oral iron supplementation. Hepcidin and cholesterol levels were significantly lower in the treatment group, and higher levels of iron, transferrin, and TIBC were also observed. The incidence of serious adverse events was low and comparable in the treated group and the placebo group [25].

PHASE 3

Chen et al. [26] conducted a phase 3 randomized double-blind study of roxadustat in China. The study was divided into two stages. Patients were initially given roxadustat or placebo 3 times a week for 8 weeks (Hb levels were tested in both groups between weeks 7 and 9), and then all volunteers received roxadustat for an additional 18 weeks. Patients weighing more than 40 kg and less than 60 kg received the dose of 70 mg, and patients weighing more than or equal to 60 kg — 110 mg. The study included 154 patients with CKD who had not started renal replacement therapy, randomly assigned to treatment with roxadustat (n = 102) or the placebo (n = 52) group. The main aim of the study was to evaluate the change in Hb levels between the 7th and 9th weeks of the study. Other goals included determination of the number of patients with an increase in Hb level by more than 1 g/dL, patients with an Hb level above 10 g/dL between the 7th and 9th week of the study, and patients with an increase in Hb concentration of at least 1 g/dL with baseline Hb > 8 g/dL and an increase in Hb of at least 2 g/dL at week 9 of the study with baseline Hb < 8 g/dL. Changes in serum total cholesterol (TCH), low-density lipoprotein cholesterol (LDL-CH), hepcidin, and serum iron levels between weeks 7 and 9 of the study were also measured. After 9 weeks of treatment, mean Hb levels increased by 1.9 ± 1.2 g/dL in the roxadustat group and by 0.4 ± 0.8 g/dL in the placebo group. An increase in Hb of more than 1 g/dL after 9 weeks of the study was observed in 84% of the roxadustat patients; mean Hb levels of at least 10 g/dL between week 7 and week 9 of the study were reported in 68% of patients receiving roxadustat and 6% of those receiving placebo. There was a reduction in hepcidin concentration by 56.14 ± 63.40 ng/mL in the roxadustat group and by 15.10 ± 48.06 ng/mL in the placebo group. Significant reductions in TCH and LDL-CH levels were also observed in the roxadustat group compared to placebo. Among the adverse events in the roxadustat arm, hyperkalemia and metabolic acidosis were more frequently observed. There were no

significant differences between the groups as to the incidence of serious adverse events. One hundred and thirty-one patients (87 on roksadustat and 44 on placebo) continued the study until week 18. Patients who continued roxadustat maintained stable Hb levels, and in the placebo group, after starting the drug, Hb levels above 11.0 g/dL were observed in 72% of patients. The reduction of TCH and LDL-CH was maintained until the end of treatment in all patients [26].

Further research was carried out in Japan and other locations. Akizawa et al. [27] in a multicenter study involving 100 patients with CKD and eGFR estimated glomerular filtration rate < 89 mL/min/1.73 m^2 evaluated the effect of roxadustat treatment at an initial dose of 50 or 70 mg for 24 weeks. The dose was adjusted from week 4 to maintain the Hb level in the range of 10–12 g/dL; the maximum dose could have been 3 mg/kg or 300 mg, whichever was reached first. Forty-four percent of patients included in the study had eGFR < 15 mL/min/1.73 m^2, and the mean Hb concentration was 9.82 ± 0.57 g/dL. The mean concentrations of ferritin, transferrin, and transferrin saturation (TSAT) were 113.79 ± 87.7, 2.04 ± 0.303, and 27.91 ± 8.2%, respectively. Ninety-seven percent of patients in the 50 mg group and 100% of patients in the 70 mg group achieved an increase in Hb level of more than 1 g/dL and level of at least 10 g/dL. The mean Hb concentration increased until week 12 and remained within the target range (10–12 g/dL) until the end of the study (mean 11.17 ± 0.62 g/dL). In terms of iron metabolism, there were no significant changes in the level of ferritin, transferrin, TIBC, and TSAT. Hepcidin levels decreased indiscriminately and were the lowest in the first 4 weeks of treatment. The drug was generally well-tolerated, with approximately 11% of patients having serious adverse reactions. The most common included pharyngitis, hyperkalemia, diarrhea, and hypertension [27].

The same authors conducted another study on 334 pre-dialysis CKD patients previously treated with ESA. Patients receiving EPO-α or darbepoetin (DA) were randomly assigned to either roxadustat (132) or DA (131); additional 71 patients previously treated with pegylated erythropoietin switched to roxadustat. The main study period was 24 weeks, and the patients treated with roxadustat were followed up until week 52. The primary endpoint was the change in Hb levels between weeks 18–24. In addition, secondary endpoints were also assessed over the period of weeks 18–24 and weeks 44–52, including the mean Hb level, percentage of patients achieving the target Hb level (10–12 g/dL), change in Hb level in each week relative to the baseline value, and other laboratory tests (parameters of iron metabolism and hepcidin level). The mean Hb level in the roxadustat group was 11.14 ± 0.07 over the period of 18–24 weeks, and the comparison of mean differences in Hb levels between patients treated with roxadustat and DA confirmed that roxadustat was non-inferior to DA. The analysis of the secondary endpoints showed no significant differences between the groups, except for a slightly lower proportion of roxadustat-treated patients who achieved the Hb target at week 24. The authors explained this by a greater proportion of patients with baseline Hb < 10 g/dL in this group. Treatment with roxadustat has also been shown to be effective for up to 52 weeks. Iron levels did not change significantly, transferrin and TIBC levels increased, and hepcidin decreased in roxadustat-treated patients. The incidence of adverse events was comparable across the groups. An interesting aspect of the study was the analysis of eye examination in relation to the potential risk of angiogenesis in patients treated with roxadustat [depending on VEGF (vascular endothelial growth factor) stimulation by HIF-PHI]. There were no significant differences between the groups in the incidence of new retinal hemorrhage; in the roxadustat group, the incidence was even slightly lower in absolute terms. It was the first study to compare the effect of treatment using a new drug with an active comparator in pre-dialysis patients [28].

The results obtained in the cited studies led to registration of roxadustat for treatment of anemia in non-dialyzed CKD patients in China and Japan. Subsequently, phase 3 studies necessary for drug registration in Europe and the United States were conducted.

In the ALPS study, Shutov et al. [29] included 594 patients with stage 3–5 CKD. They were randomly assigned to treatment with roxadustat (n = 391) or placebo (n = 203) in a 2:1 ratio for a substantial initial period of 52 weeks, then they continued treatment for up to 104 weeks. Anemia was defined as Hb < 10 g/dL; the patients could not receive ESA or intravenous iron for 12 weeks before randomization. The mean baseline Hb level was 9.1 g/dL, whereas eGFR was

16.5–17.2 mL/min/1.73 m^2. The primary endpoints were changes in Hb levels required by the European Medicines Agency (EMA) (> 11 g/dL and an increase of 1–2 g/dL depending on the baseline in the first 24 weeks of treatment) and the Food and Drug Administration (FDA) (change in Hb between weeks 28 and week 52). Additionally, arterial pressure, selected quality of life parameters, and iron balance were assessed. The analysis of the results confirmed achievement of both primary endpoints (OR 34.75, $p < 0.001$ for the EMA and + 1.692 g/dL, $p < 0.001$ for the FDA). There was also a significant reduction in LDL-CH and LDL-CH/high-density lipoprotein cholesterol (HDL-CH) ratios in roxadustat treated patients compared to placebo. There were no significant differences in blood pressure or iron metabolism parameters (hepcidin levels were not tested). The drug was generally well-tolerated and no statistically significant differences in adverse events were noted [29].

ANDES was another international, multicenter, randomized, placebo-controlled trial including 922 patients with stage 3–5 CKD [roxadustat (n = 616) and placebo (n = 306)]. The primary endpoints were change in hemoglobin level (weeks 28–52) and proportion of patients who achieved a hemoglobin response [hemoglobin 11.0 g/dL and increase of 1.0 g/dL (baseline > 8.0 g/dL), or an increase of 2.0 g/dL (baseline < 8.0 g/dL)] (week 24). Iron metabolism, including hepcidin level, as well as changes in LDL-CH level and LDL-CH/HDL-CH ratio, were also assessed. The baseline hemoglobin level (mean (SD) was 9.10 (0.75) and 9.09 (0.69) g/dL respectively, and the mean eGFRs were 21.9 (11.5) and 22.4 (11.4) mL/min/1.73 m^2 respectively for roxadustat vs. placebo. The median duration of treatment was 95.6 and 52.1 for both groups respectively, and the maximum duration of drug exposure was 4.5 years. In the final analysis, as in the ALPS study, both primary endpoints (for the FDA and EMA) were met, regardless of the baseline ferritin level. Significant reductions in LDL-CH and the LDL-to-HDL-cholesterol ratios were observed. Iron and TSAT concentrations were lower and TIBC significantly higher at the end of treatment in the active drug group. Similarly, a significant reduction in hepcidin levels was observed from week 4 of treatment, which was maintained up to week 44. Treatment with roxadustat was generally well-tolerated, the incidence of adverse events and serious adverse events did not differ between the groups, and there was no difference in the risk of death between the groups [30].

The OLYMPUS study was the largest study to date assessing the effectiveness of roxadustat compared with placebo. It was an international multicenter study that enrolled 2781 patients with stage 3–5 CKD (mean baseline Hb 9.1 ± 0.7 g/dL, eGFR 19.7 ± 11.7 mL/min/1.73 m^2), and the patients were randomly assigned to treatment with either roxadustat (n = 1393) or placebo (n = 1388). The starting dose was 70 mg three times a week, adjusted every 4 weeks until week 52, and then every 8 weeks to maintain Hb levels in the range of 11 ± 1 g/dL. The total duration of treatment was determined by the number of cardiovascular events, as the data from this study were to be included in the pooled cardiovascular safety analysis of 3 clinical trials (a total of 4 000 patients). Median drug exposure was 20 months. The primary endpoint was the mean change in Hb levels over weeks 28–52. A number of secondary endpoints were also defined, including changes in Hb levels in a group of patients with an elevated baseline CRP level, changes in LDL-CH levels, necessary rescue therapy (intravenous iron administration, ESA, or blood transfusion), mean annual change in eGFR and assessment of selected aspects of quality of life. Changes in iron metabolism parameters, including hepcidin levels, over the first 24 weeks of treatment were also studied. The analysis of the results confirmed that the primary endpoint was achieved (increase in Hb concentration by 1.75 and 0.4 g/dL in the roxadustat and placebo groups, respectively). A similar increase in Hb levels was observed in patients with initially elevated CRP; the treatment effect was independent of the baseline iron metabolism. In patients treated with the tested drug, a significantly greater reduction in LDL-C levels and a slight improvement in physical fitness tested with the SF-36 form were observed. Hepcidin levels dropped significantly by 24 weeks of treatment in the treated group. As in the previous studies, there was an increase in iron and TIBC concentrations and a decrease in ferritin; TSAT did not change significantly. There were no significant differences in the incidence of adverse events between the groups. This also applies to the rates of events classified as cardiovascular. The results of the OLYMPUS study confirmed the efficacy of anemia treatment with roxadustat in patients with advanced kidney disease [31].

Contrary to the previously cited studies, Barrat et al. [32] conducted another assessment of the efficacy of roxadustat in comparison with the active comparator (DA) on 616 patients with CKD in Europe (baseline eGFR 20.3 mL/min/1.73 m^2, and hemoglobin level 9.55 g/dL), treated for 104 weeks. The primary endpoint of the study was a hemoglobin response defined as Hb > 11.0 g/dL and an increase in Hb by > 1.0 g/dL in patients with baseline Hb > 8.0 g/dL or > 2.0 g/dL in patients with baseline Hb < 8 g/dL. Secondary endpoints included assessment of the quality of life (tested with the SF-36 form), iron metabolism, changes in eGFR, and necessary rescue therapy. The results allowed the authors to state that roxadustat was not inferior compared to DA for all predefined endpoints. As in the previous studies, a significant decrease in LDL-CH levels and a steady decrease in ferritin and TSAT levels were observed in the roxadustat group. The adverse event profile did not differ significantly between the groups [32].

The results of the described research were the basis for registration of roxadustat by the European Medicines Agency (EMA) to the treatment of anemia in non-dialysis patients patients with CKD.

RESULTS IN DIALYSIS PATIENTS

PHASE 2

Phase 2 studies were initially conducted in already dialyzed patients, similar to the pre-dialysis patients. As in the case of patients not yet undergoing dialysis, phase 2 trials were initially conducted among CKD patients already undergoing dialysis. Provenzano et al. [18] conducted a multicenter study in the United States to compare different doses of roxadustat in dialysis patients previously treated with EPO-α. In the first part of the study, 54 patients were randomly assigned to either the EPO or roxadustat groups. The latter received doses of 1.0–2.0 mg/kg for 6 weeks. Part 2 included 90 patients randomly assigned to either treatment with roxadustat (n = 67, with different starting doses) or continuation of epoetin alfa therapy (n = 23) for 19 weeks. The primary endpoint in Part 1 was the proportion of participants in whom the Hb level did not drop by 0.5 g/dL from the baseline value, while in Part 2 it was the proportion of participants whose mean Hb level averaged over the past 4 weeks was 11 g/dL. Additionally, hepcidin levels and iron metabolism parameters, as well as serum cholesterol, were measured. In the first part, changes in Hb level in the group of patients receiving roxadustat at the lowest dose (1 mg/kg) did not differ from the group treated with EPO-α; for groups of patients receiving doses > 1.5 mg/kg, the results were better among those treated with roxadustat. In the second part, 51% of roxadustat-treated patients, compared to 36% of those who continued EPO-α, had Hb levels > 11 g/dL. In the subgroup of patients with initially elevated CRP levels, the patients did not require higher doses. Hepcidin levels decreased in roxadustat-treated patients in both parts of the study; in the groups treated with EPO-α, hepcidin levels increased. The concentration of total cholesterol changed in a similar way. The safety analysis showed no significant differences between the groups [18].

In the second part of the previously discussed study from China, Szczech et al. [25] randomly assigned 87 dialyzed patients to 3 different doses of roxadustat (1.1–2.3 mg/kg 3 times a week) or continuation of EPO-α administered for 8 weeks. The results showed that in patients treated with low, medium, or high dose of roxadustat, 59.1%, 88.9% (p = 0.008), and 100% (p = 0.0003), respectively, maintained their Hb levels after 5 and 6 weeks compared with 50% of patients treated with EPO-α. In the roxadustat group, a significant reduction in cholesterol levels was noted, with an increase in serum iron, TIBC, and transferrin (without intravenous iron administration). Hepcidin levels also decreased in a statistically significant dose-dependent manner compared to the EPO-α treated group. The incidence of serious adverse events was low and comparable in the treated group and the placebo group [25].

PHASE 3

The same group conducted another study in China on patients with end-stage renal failure treated with renal replacement therapy and compared the effectiveness of roxadustat and EPO-α. Overall, 305 patients (roxadustat, n = 204 and EPO-α, n = 101) were enrolled in the study after continuing hemodialysis or peritoneal dialysis for at least 16 weeks. The initial dose of roxadustat was 100 mg for patients weighing 45–60 kg and 120 mg for patients weighing more than 60 kg. Patients receiving EPO-α were divided into subgroups depending on the starting dose (< 8 000 and > 8 000 IU/week). Oral iron

supplementation was allowed. Administration of intravenous iron or RBC transfusion were considered a rescue therapy. The study lasted for 26 weeks. Its primary purpose was to analyze changes in Hb levels at 23 and 27 weeks from the beginning of the study. Additionally, changes in serum lipids, transferrin, ferritin, and hepcidin concentrations, as well as changes in blood pressure measured before each hemodialysis session, were examined. The effect of treatment on inflammatory markers was also taken into account by monitoring the CRP level. Ultimately, 254 patients (162 in the roxadustat group and 96 in the EPO-α group) completed the study. An increase in Hb level by 0.7 ± 1.1 g/dL and 0.5 ± 1.0 g/dL was observed in the roxadustat and EPO groups, respectively; this increase was less than 1 g/dL in 92.5% in both groups. Hb levels above 10 g/dL were achieved in 87% and 88.5%, respectively. In the roxadustat group, serum hepcidin level decreased by 30.2 ± 113.3 ng/mL, and in the EPO-α group by 2.3 ± 130.7 ng/mL. Serum iron concentration was stable, while in the patients receiving roxadustat, a greater increase in serum transferrin concentration (by 0.43 ± 0.05 g/L) was achieved compared to the group receiving EPO-α. In week 27 of the study, there was a reduction in TCH levels by 22 mg/dL and LDL-CH by 18 mg/dL in patients treated with roxadustat compared to EPO-α. The higher baseline CRP levels had no effect on treatment outcomes and dosage in the roxadustat group; in the EPO-α group, however, the patients required higher doses of the drug and had a worse response to treatment. The incidence of adverse events was comparable in both groups, hyperkalemia and metabolic acidosis were more frequently reported in patients receiving roxadustat [33].

Akizawa et al. [34] conducted a phase 3 study in Japan comparing the efficacy of oral roxadustat and DA in dialysis patients. Overall, 303 patients were randomly assigned to either roxadustat (n = 151) or darbepoetin alfa (n = 152) group. Doses were adjusted to maintain a Hb level of 10–12 g/dL over 24 weeks. The primary endpoint was the change in mean hemoglobin from the baseline to the value at week 18–24. Secondary endpoints included mean hemoglobin and the proportion of patients with a hemoglobin range of 10–12 g/dL (the maintenance index) at week 18–24 and iron metabolism parameters. In terms of safety, abnormalities on eye examination were additionally taken into account. The analysis of the results showed that roxadustat helped maintain Hb levels within the 10–12 g/dL range in hemodialyzed patients and was not inferior to darbepoetin alfa. Treatment-related adverse events were consistent with previous reports. The proportion of patients with new or worsening retinal hemorrhage was comparable and was 32.4% in the roxadustat group and 36.6% in the darbepoetin-α group [34].

Two smaller clinical trials have also been conducted in Japan comparing roxadustat versus ESA in peritoneal dialysis patients. A total of 95 patients were enrolled in the study. Roxadustat was found to be equally effective in maintaining target Hb levels over the 24-week treatment period. There was no effect on the deterioration of the peritoneal membrane function. The treatment was well-tolerated, and there were no significant differences in the frequency of adverse events between the drugs. In the first of the described studies, the levels of hepcidin were also measured, which decreased significantly in the group receiving roxadustat [35, 36].

The results of the described studies allowed for registration of roxadustat for treatment of anemia in dialysis patients with CKD in China and Japan. Subsequently, phase 3 studies necessary for drug registration in Europe and the United States were conducted.

SIERRAS was a randomized, open-label, EPO-α controlled, phase 3 study evaluating the efficacy and safety of roxadustat for treatment of anemia in CKD patients dialyzed at 76 US centers. In this study, 370 patients received roxadustat (starting dose 70–200 mg 3 times a week, based on prior EPO requirement), while 371 continued EPO-α therapy. The doses of both drugs were adjusted at 4-week intervals to maintain Hb levels at around 11 g/dL. The primary endpoint was the mean change in hemoglobin from baseline to week 28–52 regardless of rescue therapy. The key secondary endpoints included the proportion of patients with mean hemoglobin > 10.0 g/dL at week 28–52 (FDA requirement) and the proportion of patients responding to treatment with Hb 10.0–12.0 g/dL between weeks 28 and 36 without a need for rescue therapy in weeks 28–36 (European Union). Other secondary endpoints included, but were not limited to, the following: (1) mean change in LDL-CH level from baseline over weeks 12–28, (2) mean change in hemoglobin level from baseline in patients with high baseline CRP, (3) mean monthly intravenous iron consumption,

(4) time since the first RBC transfusion. Additionally, changes in hepcidin level up to week 52 and iron metabolism parameters were examined. For all primary endpoints, there were no significant differences between the groups, confirming that roxadustat is not inferior to EPO-α in this patient population. Roxadustat decreased the level of LDL-CH significantly, more than EPO-α, especially in the subpopulation with an initial level > 100 mg/dL. Patients with elevated CRP levels at baseline did not require dose escalation of roxadustat; in patients treated with EPO, it was necessary to significantly increase the doses. Iron consumption was also significantly higher in patients treated with EPO-α, and the risk of necessary blood transfusions in those patients was also higher. The decrease in hepcidin level was significantly greater in the group treated with roxadustat, and similar changes applied to iron levels; other parameters of iron metabolism were not different. The analysis of adverse events did not show any differences between the groups [37].

Another study (PYRENEES) conducted mainly in Central Europe covered 836 stable dialyzed patients (roxadustat, n = 415; ESA, n = 421), randomly assigned to treatment with a new drug or continuation of ESA (EPO-α or DA), who were followed up to week 104. Primary endpoints were formulated according to the EMA and FDA requirements (as described previously). There were also many secondary endpoints; the most important included changes in LDL-CH level, quality of life assessed with the SF-36 form, changes in systolic blood pressure, frequency of hospitalization, and hepcidin level. As in the previously cited studies, the analysis of the primary endpoints led to the conclusion that roxadustat is not inferior to ESA. Patients treated with roxadustat required blood transfusions less frequently, and the total dose of intravenous iron was significantly lower in this group. A significant decrease in LDL-CH was also observed in patients treated with roxadustat compared to patients treated with ESA. There were no differences in the quality of life or changes in blood pressure. Hepcidin levels were significantly lower in the roxadustat group throughout the treatment period. No significant differences in the frequency of adverse events were observed, although a higher risk of death in the group of patients receiving EPO-α before randomization and included in the roxadustat group was noted. In the discussion, the authors explain this phenomenon by differences in the initial characteristics of the patients [38].

The largest published study on dialysis patients to date was the HIMALAYAS study, which included 1043 patients (roxadustat, n = 522; EPO-α, n = 521) in 19 countries. The most important feature distinguishing this study from those previously described was the fact that only patients starting dialysis treatment (2 weeks to 4 months from the start of dialysis) who had not been treated with ESA in the previous 12 weeks were enrolled in the study. Of the enrolled patients, 10% received peritoneal dialysis; the mean baseline Hb concentration was 8.4 ± 1.0 g/dL. The primary endpoints were redefined in line with American (FDA) and European (EMA) registration requirements. Secondary endpoints included, but were not limited to, the following: (1) mean change from baseline in LDL-CH levels at week 12–24, (2) mean change from baseline in Hb level in patients with elevated baseline CRP level, (3) mean monthly intravenous iron use over weeks 28–52, and (4) time to first transfusion during treatment. Additionally, hepcidin and iron concentrations were measured at baseline and during the follow-up period. Once again, with regard to the registration requirements defined as the primary endpoints, the study showed that both therapies were equal. The mean increase in Hb was 2.57 ± 1.27 and 2.36 ± 1.21 at weeks 28–52 for roxadustat and EPO-α, respectively; and 88.2% and 84.4% of patients responded to treatment, respectively. As in previous studies, there was a greater reduction in LDL-CH and a greater proportion of patients achieving LDL-CH < 100 mg/dL in the roxadustat group. The obtained increases in Hb levels in patients with elevated CRP were similar, but higher doses of the drug were required in the group treated with EPO; there was no need for dose escalation in the group of patients treated with roxadustat. Patients treated with roxadustat required significantly less intravenous iron supplementation. Hepcidin levels decreased in both groups, with a tendency to increase again in the EPO-α group by week 44; ferritin, iron, and TIBC levels were significantly different at the end of the treatment period. No significant differences in treatment safety were observed [39].

Two pooled analyzes were also published, assessing mainly the risk of cardiovascular events among dialysis patients treated with roxadustat and ESA. Provenzano et al. [39]

analyzed only patients starting dialysis who were selected from three clinical trials (SIERRAS, PYRENEES, and ROCKIES) to a total of 1530. The results of the analysis confirmed the equivalent effectiveness of both treatment methods in such a selected population. The authors also found a lower incidence of composite endpoints (MACE, major adverse cardiovascular events, MACE+, and CV MACE) in the roxadustat group compared to the ESA group, as well as a longer time to the first event of such a composite endpoint. The authors admit that such a constructed analysis does not answer the question about the mechanism of the observed differences; however, they suggest that differences in the form of lower iron requirements, lower EPO and LDL-CH levels achieved, as well as a better response to treatment in groups of patients with elevated CRP during roxadustat treatment, may explain the observed lower risk of cardiovascular events [40]. Barratt et al. [41] included participants from 4 clinical trials (PYRENEES, SIERRAS, HIMALAYAS, ROCKIES) in their analysis and focused on stable dialysis patients who switched from ESA to roxadustat when they entered the study. The authors concluded that the two analyzed groups (roxadustat or continuing ESA) were equivalent in terms of incidence of composite cardiovascular endpoints; the observed risk was not lower as opposed to patients starting dialysis and treatment of anemia at the same time [40].

META-ANALYSIS RESULTS IN PRE-DIALYSIS AND DIALYSIS PATIENTS

Recently, several meta-analyses have been published summarizing the current research on roxadustat (phase 2 and 3 studies) in pre-dialysis patients and those receiving renal replacement therapy [42–44]. Earlier publications of this type did not yet cover the largest phase 3 clinical trials. The authors of those publications confirmed the efficacy of roxadustat for treatment of anemia in patients with advanced CKD, both in comparison to placebo and ESA therapy, as well as the drug's safety [42, 43]. The last of the meta-analyses includes large phase 3 trials and over 10 000 patients in total. Again, the authors showed that roxadustat is an effective drug that increases and maintains Hb levels in patients with CKD (both pre-dialysis and dialyzed patients) compared to placebo and ESA (EPO-α or DA). At the same time, the beneficial effect of this drug on iron metabolism was emphasized, mainly by lowering the hepcidin level and increasing the transferrin and TIBC levels. The estimated frequency of adverse events was comparable for roxadustat and other types of therapy, however, the authors noted that the number of serious adverse events was significantly higher in patients treated with roxadustat [44].

DRUG DOSAGE

Roxadustat is available under the brand name Evrenzo at 20 mg, 50 mg, 70 mg, 100 mg, and 150 mg doses. The recommended starting dose for patients who have not been treated with ESA depends on the body weight (70 mg for patients weighing up to 70 kg and 100 mg for patients weighing more). The starting dose for patients already treated is determined depending on the currently used ESA dose (for patients receiving less than 25 μg/week DA or less than 5000 IU/week EPO-α, it is 70 mg 3 times a week). However, according to the summary of product characteristics, modification of treatment in stable dialysis patients receiving ESA should only be considered when there is a valid clinical reason. The drug should be administered orally three times a week. It is recommended to modify the dose depending on the obtained Hb levels at 4-week intervals; early dose modification or temporary discontinuation is recommended when there is an increase in Hb concentration by more than 2 g/dL or a level above 12 g/dL has been achieved. Detailed dosing suggestions can be found in the drug documentation [45].

SUMMARY

Chronic kidney disease is a significant and growing health problem in most countries. Anemia that develops in the course of the disease affects up to 90% of patients in the advanced stages of the disease. The currently available treatment methods, i.e. iron supplementation (often intravenously) and administration of erythropoiesis-stimulating drugs (ESA: EPO-α, DA, and pegylated epoetin beta), allow for an effective increase in hemoglobin concentration in most patients, but their use is associated with the risk of side effects. Response to treatment is usually weaker in patients with features of chronic inflammation, and much higher doses of ESA are necessary. The treatment is also not convenient for patients as it requires frequent visits to the

hospital or outpatient clinic; it is especially felt by pre-dialysis patients. In recent years, a new group of oral medications (HIF-PHI) has become available, which have proved effective both in patients who have not been previously treated with ESA, as well as in those who have been converted from ESA, regardless of whether they are dialyzed or not. In addition, the published studies indicate a beneficial effect on iron metabolism by increasing both the availability of the iron absorbed from the gastrointestinal tract and the iron stored in cells and bone marrow. Roxadustat is the first drug of this class that has been approved for treatment of anemia in both pre-dialysis and dialysis CKD patients in China, Japan, Chile, and now also in the European Union. Registration is underway in the United States. The availability of a new therapy is likely to change the current treatment guidelines for anemia associated with chronic kidney disease. The conclusions of the second part of the Kidney Disease: Improving Global Outcomes (KDIGO) conference focused on controversies in the optimal treatment of anemia in CKD are expected to be published (the first part of the publication deals mainly with iron metabolism and treatment with iron supplementation) [10, 46]. However, patients with CKD already have the option of choosing an alternative treatment for anemia. This is especially important for patients in the pre-dialysis period, who, thanks to the oral route of drug administration, do not require injections and need fewer hospital stays or outpatient visits. A full evaluation of long-term safety is not yet possible and requires careful observation after the drug is introduced to the market.

References

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013; 382(9888): 260–272, doi: 10.1016/S0140-6736(13)60687-X, indexed in Pubmed: 23727169.
2. Dębska-Ślizień A, Rutkowski B, Jagodziński P, et al. Aktualny stan dializoterapii w Polsce — 2020. Nefrol Dial Pol. 2021; 25: 7–20.
3. KDOQI, National Kidney Foundation. Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis. 2006; 47(5 Suppl 3): S16–S85, doi: 10.1053/j.ajkd.2006.03.011, indexed in Pubmed: 16678661.
4. Akizawa T, Okumura H, Alexandre AF, et al. Burden of anemia in chronic kidney disease patients in Japan: a literature review. Ther Apher Dial. 2018; 22(5): 444–456, doi: 10.1111/1744-9987.12712, indexed in Pubmed: 30022586.
5. Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012; 2(4): 279–335.
6. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013; 62(5): 849–859, doi: 10.1053/j.ajkd.2013.06.008, indexed in Pubmed: 23891356.
7. Solomon SD, Uno H, Lewis EF, et al. Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010; 363(12): 1146–1155, doi: 10.1056/NEJMoa1005109, indexed in Pubmed: 20843249.
8. Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. Kidney Int. 2008; 74(6): 791–798, doi: 10.1038/ki.2008.295, indexed in Pubmed: 18596733.
9. Kaplan J. Roxadustat and anemia of chronic kidney disease. N Engl J Med. 2019; 381(11): 1070–1072, doi: 10.1056/NEJMe1908978, indexed in Pubmed: 31340090.
10. Babitt JL, Eisenga MF, Haase VH, et al. Conference Participants. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2021; 99(6): 1280–1295, doi: 10.1016/j.kint.2021.03.020, indexed in Pubmed: 33839163.
11. Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 1992; 12(12): 5447–5454, doi: 10.1128/mcb.12.12.5447-5454.1992, indexed in Pubmed: 1448077.
12. Jaakkola P, Mole DR, Tian YM, et al. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001; 292(5516): 468–472, doi: 10.1126/science.1059796, indexed in Pubmed: 11292861.
13. Epstein AC, Gleadle JM, McNeill LA, et al. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. Cell. 2001; 107(1): 43–54, doi: 10.1016/s0092-8674(01)00507-4, indexed in Pubmed: 11595184.
14. Semenza GL. HIF-1 and mechanisms of hypoxia sensing. Curr Opin Cell Biol. 2001; 13(2): 167–171, doi: 10.1016/s0955-0674(00)00194-0, indexed in Pubmed: 11248550.
15. Lönnberg M, Garle M, Lönnberg L, et al. Patients with anaemia can shift from kidney to liver production of erythropoietin as shown by glycoform analysis. J Pharm Biomed Anal. 2013; 81–82: 187–192, doi: 10.1016/j.jpba.2013.04.009, indexed in Pubmed: 23666255.
16. Chin K, Yu X, Beleslin-Cokic B, et al. Production and processing of erythropoietin receptor transcripts in brain. Brain Res Mol Brain Res. 2000; 81(1-2): 29–42, doi: 10.1016/s0169-328x(00)00157-1, indexed in Pubmed: 11000476.
17. Holdstock L, Meadowcroft AM, Maier R, et al. Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anemia. J Am Soc Nephrol. 2016; 27(4): 1234–1244, doi: 10.1681/ASN.2014111139, indexed in Pubmed: 26494831.
18. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) versus epoetin alfa for anemia in patients receiving maintenance hemodialysis: a phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. Am J Kidney Dis. 2016;

67(6): 912–924, doi: 10.1053/j.ajkd.2015.12.020, indexed in Pubmed: 26846333.
19. Provenzano R, Besarab A, Sun CH, et al. Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. Clin J Am Soc Nephrol. 2016; 11(6): 982–991, doi: 10.2215/CJN.06890615, indexed in Pubmed: 27094610.
20. Szczyra D, Śnit M, Grzeszczak W. Czy nowe doustne inhibitory hydroksylazy prolilowej to przyszłość w leczeniu niedokrwistości u chorych z przewlekłą chorobą nerek? Forum Nefrologiczne. 2020; 13(1): 1–13.
21. Liu P, Wang L, DuBois BG, et al. Discovery of orally bioavailable and liver-targeted hypoxia-inducible factor prolyl hydroxylase (HIF-PHD) inhibitors for the treatment of anemia. ACS Med Chem Lett. 2018; 9(12): 1193–1198, doi: 10.1021/acsmedchemlett.8b00274, indexed in Pubmed: 30613325.
22. Dhillon S. Roxadustat: first global approval. Drugs. 2019; 79(5): 563–572, doi: 10.1007/s40265-019-01077-1, indexed in Pubmed: 30805897.
23. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD . Am J Kidney Dis. 2017; 69(6): 815–826. Erratum in: Am J Kidney Dis. 2017; 69(6): 869, doi: 10.1053/j.ajkd.2016.12.011, indexed in Pubmed: 28242135.
24. Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. Nephrol Dial Transplant. 2015; 30(10): 1665–1673, doi: 10.1093/ndt/gfv302, indexed in Pubmed: 26238121.
25. Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. Nephrol Dial Transplant. 2017; 32(8): 1373–1386, doi: 10.1093/ndt/gfx011, indexed in Pubmed: 28371815.
26. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med. 2019; 381(11): 1001–1010, doi: 10.1056/NEJMoa1813599, indexed in Pubmed: 31340089.
27. Akizawa T, Yamaguchi Y, Otsuka T, et al. A phase 3, multicenter, randomized, two-arm, open-label study of intermittent oral dosing of roxadustat for the treatment of anemia in Japanese erythropoiesis-stimulating agent-naïve chronic kidney disease patients not on dialysis. Nephron. 2020; 144(8): 372–382, doi: 10.1159/000508100, indexed in Pubmed: 32580188.
28. Akizawa T, Iwasaki M, Otsuka T, et al. Phase 3 study of roxadustat to treat anemia in non-dialysis-dependant CKD. Kidney Int Rep. 2021; 6(7): 1810–1828, doi: 10.1016/j.ekir.2021.04.003, indexed in Pubmed: 34307976.
29. Shutov E, Sułowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). Nephrol Dial Transplant. 2021; 36(9): 1629–1639, doi: 10.1093/ndt/gfab057, indexed in Pubmed: 33630072.
30. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related anemia in non-dialysis patients. Kidney Int Rep. 2021; 6(3): 624–635, doi: 10.1016/j.ekir.2020.11.034, indexed in Pubmed: 33732977.
31. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. J Am Soc Nephrol. 2021; 32(3): 737–755, doi: 10.1681/ASN.2020081150, indexed in Pubmed: 33568383.
32. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant. 2021; 36(9): 1616–1628, doi: 10.1093/ndt/gfab191, indexed in Pubmed: 34077510.
33. Chen N, Hao C, Liu BC, et al. Roxadustat treatment for anemia in patients undergoing long-term dialysis. N Engl J Med. 2019; 381(11): 1011–1022, doi: 10.1056/NEJMoa1901713, indexed in Pubmed: 31340116.
34. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. J Am Soc Nephrol. 2020; 31(7): 1628–1639, doi: 10.1681/ASN.2019060623, indexed in Pubmed: 32493693.
35. Akizawa T, Otsuka T, Reusch M, et al. Intermittent oral dosing of roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: a randomized, phase 3, multicenter, open-label study. Ther Apher Dial. 2020; 24(2): 115–125, doi: 10.1111/1744-9987.12888, indexed in Pubmed: 31222951.
36. Hirai K, Nonaka H, Ueda M, et al. Effects of roxadustat on the anemia and iron metabolism of patients undergoing peritoneal dialysis. Front Med (Lausanne). 2021; 8: 667117, doi: 10.3389/fmed.2021.667117, indexed in Pubmed: 34307403.
37. Charytan C, Manllo-Karim R, Martin ER, et al. A randomized trial of roxadustat in anemia of kidney failure: SIERRAS study. Kidney Int Rep. 2021; 6(7): 1829–1839, doi: 10.1016/j.ekir.2021.04.007, indexed in Pubmed: 34307977.
38. Csiky B, Schömig M, Esposito C, et al. Roxadustat for the maintenance treatment of anemia in patients with end-stage kidney disease on stable dialysis: a european phase 3, randomized, open-label, active-controlled study (PYRENEES). Adv Ther. 2021; 38(10): 5361–5380, doi: 10.1007/s12325-021-01904-6, indexed in Pubmed: 34537926.
39. Provenzano R, Shutov E, Eremeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant. 2021; 36(9): 1717–1730, doi: 10.1093/ndt/gfab051, indexed in Pubmed: 33629100.
40. Provenzano R, Fishbane S, Szczech L, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. Kidney Int Rep. 2021; 6(3): 613–623, doi: 10.1016/j.ekir.2020.12.018, indexed in Pubmed: 33732976.
41. Barratt J, Sulowicz W, Schömig M, et al. Efficacy and cardiovascular safety of roxadustat in dialysis-dependent chronic kidney disease: pooled analysis of four phase 3 studies. Adv Ther. 2021; 38(10): 5345–5360, doi: 10.1007/s12325-021-01903-7, indexed in Pubmed: 34523074.
42. Zheng Q, Yang H, Fu X, et al. The efficacy and safety of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis. Nephrol Dial Transplant. 2021; 36(9): 1603–1615, doi: 10.1093/ndt/gfaa110, indexed in Pubmed: 33051677.
43. Liu C, Fu Z, Jiang J, et al. Safety and efficacy of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis and trial sequential analysis. Front Med (Lausanne). 2021; 8: 724456, doi: 10.3389/fmed.2021.724456, indexed in Pubmed: 34532333.
44. Tang M, Zhu C, Yan T, et al. Safe and effective treatment for anemic patients with chronic kidney disease: an updated systematic review and meta-analysis on roxadustat. Front Phar-

macol. 2021; 12: 658079, doi: 10.3389/fphar.2021.658079, indexed in Pubmed: 34276361.
45. Charakterystyka Produktu Leczniczego (ChPL) Evrenzo. https://www.ema.europa.eu/documents/product-information/evrenzo-epar-product-information_pl.pdf (dostęp: 22.12.2021).
46. Locatelli F, Del Vecchio L. A new paradigm in treating patients with chronic kidney disease and anaemia after a journey lasting more than 35 years. Nephrol Dial Transplant. 2021; 36(9): 1559–1563, doi: 10.1093/ndt/gfab177, indexed in Pubmed: 34014305.