Ironing Out the Details: New Anemia Treatments for Patients with Chronic Kidney Disease

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Introduction

There are 25 million people afflicted with kidney disease in United States. Anemia is a common complication of declining kidney function, and the severity of anemia highly correlates with the deterioration of glomerular filtration rate.[1] Prior to the advent and approval of erythropoietin stimulating agents (ESAs) in 1989, blood transfusions were the only option available for the treatment of anemia, but came at the cost of volume and iron overload, transfusion related reactions, and exposure to HLA antigens from numerous donors, which prevented some patients from becoming transplant candidates. Anemia is associated with decreased quality of life, impairment in cardiac function, and mortality.[2] Treatment of anemia in patients with chronic kidney disease is associated with a reduction in packed red blood cell (pRBC) transfusions and improved quality of life; however, no studies have validated a true mortality benefit by correcting anemia in patients with chronic kidney disease (CKD). Currently, the Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines strongly encourage the use of ESAs instead of pRBCs for the treatment of anemia associated with CKD. [1,3]

As healthcare costs continue to be a driving force for decision-making, practitioners must weigh many options in a variety of treatments. In the setting of anemia secondary to CKD, recombinant human ESAs have widely held the market since the first approval in 1989. In 2005 Medicare spent approximately $2 billion on epoetin alfa alone, which was used in approximately 95% of all dialysis patients. By 2007 the cost to Medicare nearly doubled to $3.9 billion. A year later, in 2008, epoetin alfa was Medicare's largest single pharmaceutical expenditure, and remains in the top 50 today. [4,5] Over this time period hundreds of trials have been published studying outcomes with these agents, identifying efficacy, treatment targets, adverse effects, and appropriateness of use. It has not been until recently that new treatment options have surfaced. These options include long-acting erythropoietin agents, erythropoietin receptor agonists, and the novel hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI). In this article, we will review current therapy recommendations, and discuss exciting alternatives on the horizon (Table 1). These new therapies are a very exciting topic in nephrology and have the potential to change the way anemia of CKD is treated in the near future.

Table 1. Overview of treatments for chronic kidney disease associated anemia

Drug	Mechanism of Action	Route of Administration	General Dosing
Epoetin alfa (Epogen®/Procrit®)	Recombinant Erythropoeitin	SubQ/IV	50-100 units/kg thrice weekly
Darbepoetin alfa (Aranesp®)	Recombinant Erythropoeitin	SubQ/IV	0.45 mcg/kg weekly 0.75 mcg/kg every two weeks
Methoxy polyethylene glycol-epoetin beta (Mircera®)	Continuous Erythropoietin Receptor Activator	SubQ/IV	0.6 mcg/kg every two weeks
Peginesatide (Omontys®)	Erythropoietin Receptor Agonists	SubQ/IV	0.04-0.08 mg/kg monthly
FG-4592 (Roxadustat)	HIF-Prolyl Hydroxylase Inhibitors	Oral	1.0-2.5 mg/kg thrice weekly
AKB-6548 (Vadadustat)	HIF-Prolyl Hydroxylase Inhibitors	Oral	Variable dosing once daily
GSK1278863	HIF-Prolyl Hydroxylase Inhibitors	Oral	Variable dosing once daily

Erythropoiesis Stimulating Agents: Epogen©, Procit©, Aranesp©

ESAs have a primary mechanism of action by stimulating red blood cell progenitors. Typical doses of ESAs are supraphysiologic to the natural, endogenous production of erythropoietin. The class of ESAs has significant data supporting their efficacy in increasing hemoglobin (Hgb) and reducing the need for pRBC transfusions. To promote the production of red blood cells through this mechanism, patients must have appropriate iron availability. For this reason, many patients require oral or intravenous iron therapy prior to or concomitantly with ESA therapy as iron deficiency is the most common cause of ESA resistance. Inflammatory processes including uremia, aluminum toxicity, infection and occult malignancy may cause a prolonged exposure to supraphysiologic doses of erythropoietin that may lead to sensitization and a decline in responsiveness to therapy.

Treatment thresholds and endpoints of therapy are highly studied topics in treating anemic patients with CKD. KDIGO guidelines recommend the utilization of ESAs in patients with a Hgb <10 g/dL and not to exceed 11.5 g/dL.[1] This finding comes from multiple, large, randomized controlled trials including NHT and CHOIR, which were terminated early.[2,6] The CHOIR study compared patients receiving epoetin alfa to achieve a maintenance Hgb target of 13.5 g/dL as compared to 11.3 g/dL. Higher rates or mortality, myocardial infarction, stroke or hospitalization for congestive heart failure were identified in the arm treated to a higher Hgb target (18% vs. 14%; HR 1.34; p=0.03). The difference in the composite endpoint was highly attributable to a non-significant trend toward increased risk of death in the higher Hgb goal group (7.3% vs. 5.0%; p=0.07). Following these results, the FDA issued a statement and required a boxed warning for all ESAs warning prescribers of these serious risks, particularly associated with higher Hgb targets. A cardiovascular benefit was not evident and required nearly two times the average dose of epoetin alfa to maintain these goal levels. [8] Numerous studies have further validated the increased risk of mortality, cardiovascular and cerebrovascular events, vascular access thrombosis, thromboembolic events, and hypertension with the treatment of all ESAs. Furthermore, these agents should be avoided in patients with active malignancy if possible as numerous studies allude to poorer outcomes, including disease progression or relapse, thromboembolic events, and higher rates of mortality.[9]

Recombinant Human Erythropoietin

The utilization of epoetin alfa does not naturally mimic the endogenous release of erythropoietin. Traditionally, epoetin alfa is administered thrice weekly, resulting in short, intermittent bursts of plasma erythropoietin, leading to fluctuations in Hgb. This phenomenon of Hgb cycling may have an adverse effect as it can cause dysregulation of homeostasis and suboptimal patient outcomes. In a prospective study assessing long-term effects of Hgb cycling was conducted, suggesting an increased risk of cerebrovascular and cardiovascular disease, infection, and hospitalization in patients with high-amplitude fluctuations in Hgb compared to patients who maintained a target-range Hgb level.[10-12] This finding further suggests improved outcomes with the use of long-acting erythropoietin agents, such as glycosylated recombinant human erythropoietin, and continuous erythropoietin receptor activators (CERA). Safety and efficacy studies have been performed comparing epoetin alfa administered thrice weekly versus once weekly or even every other week. These studies showed extended interval dosing of epoetin alfa to be equally efficacious at achieving goal Hgb targets but require significantly higher doses.[13] However, a metaregression analysis performed by Koulouridis et al. demonstrated higher ESA doses might be associated with all-cause mortality and cardiovascular complications independent of hemoglobin concentration.[14] Current guidelines recommend the use of ESAs as a class stating, “There is no evidence that any given ESA brand is superior to another in terms of patient outcomes.” This statement does not provide preference for one ESA over another, however this recommendation was made prior to the utilization and approval of methoxy polyethylene glycol-epoetin beta, a CERA.[1]

Glycosylated Recombinant Human Erythropoietin

Aranesp© (darbepoetin alfa) is a glycosylated human erythropoietin agent which has a similar mechanism as epoetin alfa with a longer half-life. It was approved by the FDA in 2001 for indications of anemia associated with CKD, as well as due to chemotherapy in patients with cancer**.** Darbepoetin alfa has a half-life up to approximately 140 hours in CKD patients, which allows for dosing as infrequently as weekly or twice weekly.[15]

Erythropoietin Receptor Agonists: Omontys©

An alternative to recombinant human-erythropoesis stimulating agents, peginesatide, was created by identifying peptides that interact with the erythropoietin receptor. This research led to the production of a peptide analog that mimicked the actions of ESAs as an erythropoietin receptor agonist, without the risk of causing pure red cell aplasia (PRCA), a rare hematologic disorder associated with transfusion-dependent anemia. The peptide was then pegylated to increase the half-life of this therapeutic agent to permit once monthly dosing. Four paramount randomized, controlled trials were published in New England Journal of Medicine (PEARL-1 & 2, and EMERALD-1 & 2), which validated this agent as being non-inferior to darbepoetin alfa in patients with chronic kidney disease, no matter dependence of dialysis.[16,17]

The FDA approved Affymax's Omontys© (peginesatide) as a subcutaneous and intravenous injection in 2012 for the treatment of anemia in adult patients on dialysis.[18] Common side effects associated with this treatment included diarrhea, vomiting, hypertension, and arthralgias. In 2013, pooled data from the PEARL-1 & 2 studies determined there was an increase in a composite safety endpoint which included all-cause mortality, stroke, myocardial infarction, congestive heart failure, unstable angina, and cardiac arrhythmia in patients receiving peginesatide as compared to darbepoetin alfa (HR 1.32; 95% CI 0.97 to 1.81).[19] This finding was not seen in the EMERALD studies, which was conducted in dialysis dependent patients. The drug was approved under a Risk Evaluation and Mitigation Strategy (REMS) due to a risk of potentially fatal cardiovascular and/or thromboembolic adverse events, and increased risk of these events in non-dialysis patients. Following its approval, an increased incidence of severe hypersensitivity reactions was noted in post-marketing analysis with an incidence of 0.2%. Three documented deaths were attributed to these anaphylactic reactions. No identifiable risk factors could be attributed to this reaction, and the drug was subsequently recalled and withdrawn from market.[20]

Continuous Erythropoietin Receptor Agonists: Mircera©

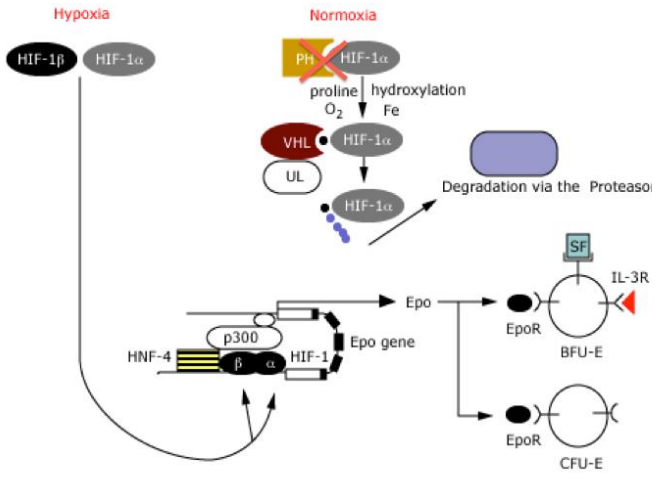
Methoxy polyethylene glycol-epoetin beta (MG-EPO), the only continuous erythropoietin receptor activator currently on the market, has a unique pharmacokinetic profile as compared to other ESAs. MG-EPO maintains a significantly long half-life of approximately one week, and a time to peak of approximately 72 hours which permits dosing up to once monthly. Mircera® was approved by the FDA in 2015, and currently holds a single indication for anemia associated with CKD.[21] A systematic review performed by Alsalimy and Awaisu evaluated articles comparing MG-EPO to darbepoetin alfa for efficacy and tolerability in non-dialysis CKD patients. Four trials met criteria consisting of 1,155 patients. Patients treated with MG-EPO had a lower incidence of Hgb above the target concentration of 12-13 g/dL (25.8% vs. 47%; $p<0.0001$), and thus fewer dose adjustments. Furthermore, patients receiving darbepoetin alfa required more RBC transfusions but achieved a Hgb response quicker (29 days vs 43 days). Although this was a systematic review and did not determine heterogeneity of the included studies, it alludes to some potential benefits of using MG-EPO.[22]

Based on high quality trials, epoetin alfa, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta have been found to be equally efficacious in reducing pRBC requirements, and improving quality of life in patients with chronic kidney disease. Of note, the most significant difference in outcomes with MG-EPO is its side effect profile. MG-EPO is associated with higher rates of treatment emergent hypertension and hypertension exacerbation, as well as higher mortality in cancer patients compared to other ESAs.[23,24]

HIF-Prolyl Hydroxylase Inhibitors

FG-4592, or roxadustat, is a new novel agent being studied for the treatment of chronic kidney disease-associated anemia. The mechanism of action is quite unique and functions on the hypoxia-induced factor (HIF) pathway (Figure 1). HIFs are transcription factors that enhance the upregulation of erythropoietin in the setting of low oxygen conditions. During hypoxia, HIF-α accumulates and dimerizes with HIF-1β, which then translocates into the cell and acts as a transcription factor for the EPO gene. HIF-1β is constitutively produced, and the dimerized product of HIF1α and HIF-2α with HIFβ can also encode proteins that increase iron absorption and mobilization, as well as promote neovascular development through vascular endothelial growth factor and angiopoietins. This neovascular activity has been associated with decreased cardiac damage from myocardial ischemia, which may have some added benefit in the setting of anemia in chronic kidney disease.25 However, under normoxic conditions degradation of HIF-α occurs by a prolyl hydroxylase, PHD2. The hydroxylated HIF-α is recognized by the von Hippel-Lindau protein, which mediates polyubiquitination and ultimately results in rapid proteosomal degradation. Agents such as roxadustat are 2-oxoglutarate analogues, which stabilize HIF-α by inhibiting HIF prolyl hydroxylase.

Figure 1. Hypoxia Inducible Factor Pathway



Red "X" indicates location of pathway roxadustat inhibits
BFU-E = erythoid blast-forming units; CFU-E = erythroid colony-forming units; Epo = erythropoietin; EpoR = erythropoietin receptor; PH = prolyl hydroxylase; UL = ubiquitin ligase complex; VHL = von Hippel-Lindau protein

The mechanistic benefit of stabilizing HIF-α is bimodal in that it can correct anemia by increasing production of erythropoietin and improve iron utilization.[26,27] A phase I trial administered a single dose of a HIF-PHI (FG-2216) to nephric and anephric hemodialysis patients, as well as healthy volunteers. Plasma concentrations of erythropoietin increased 30.8, 14.5, and 12.7 times above baseline, respectively. Increased endogenous plasma erythropoietin concentrations generally peaked within 10-12 hours after administration.[28] Furthermore, this agent can be administered orally three times weekly, which can improve compliance in the outpatient setting.

Hepcidin is a key regulator of iron metabolism and availability produced primarily by the liver. This hormone increases with inflammation and limits iron availability. It is thought that this mechanism began evolutionarily to reduce free iron during times of infection and other inflammatory processes. Hepcidin inhibits iron transport by binding to the iron export channel, ferroportin, which is located on the basolateral surface of gut enterocytes and the plasma membranes of reticuloendothelial cells. Furthermore, hepcidin also inhibits mobilization of iron from macrophages, as well as hepatocytes as part of the hepatic portal system. In vivo studies have identified many direct and indirect mechanisms in which the HIF pathway leads to downregulation of hepcidin and upregulation of erythropoietin and ferroportin, which promotes the mobilization of iron to support erythrocyte production.[29,30]

The capacity of oral roxadustat to improve iron efficiency in the treatment of anemia was validated in a Phase II study of 53 patients with a Hgb <10 g/dL, ferritin 50-300 ng/mL, transferrin saturation of 10-30%, and no intravenous iron therapy within 4 weeks prior to randomization. Intervention arms included dialysis patients receiving roxadustat with or without oral or intravenous iron products. The findings showed a dose-dependent elevation of Hgb ≥2 g/dL by week 7, regardless of iron supplementation or dialysis modality. However, the greatest Hgb changes were seen in patients receiving exogenous iron supplementation. The mean change in Hgb from baseline was 3.1 g/dL, but the largest increase was seen with intravenous iron therapy. Secondary findings showed a decrease

in hepcidin levels by 4 weeks, with largest reductions seen in patients on hemodialysis who were not receiving iron supplementation (80% of patients saw at least a decrease of 50% or greater, compared to 41% in those receiving intravenous iron). By completion of the study with 12 weeks of therapy, hepcidin rebounded beyond baseline in patients receiving intravenous iron. This finding is likely attributed to the competing feedback loop for iron regulation secondary to higher circulating iron levels. There was a greater response in Hgb in the last four weeks of therapy in patients receiving iron products compared to those who did not receive iron supplementation. This suggests initial treatment with iron supplementation to achieve an elevation in Hgb is not necessary, but may be required to maintain Hgb improvement.[31]

Common adverse events associated with roxadustat therapy included diarrhea (9.1%), headache (6.8%), back pain (4.5%), fatigue (4.5%) and hyperkalemia (4.5%) in a Phase II, multicenter, randomized, placebo-controlled trial in non-dialysis subjects with CKD. In the Phase II study conducted in dialysis patients, elevation in blood pressure, transient elevation in liver function tests, and abnormal electrocardiograms were identified.[31,32]

Currently, eight roxadustat Phase III studies are registered with the U.S. National Institutes of Health, and enrolling participants (Table 2).

Table 2. Current Phase III Trials for HIF-PHIs

Clinical Trial	Patient Population	Interventions	Primary Outcome
NCT02174731	DD-CKD	ROX vs. EPO	Time to occurrence of MACE
NCT02278341	DD-CKD	ROX vs. EPO vs. DPO	Hgb response with/without rescue therapy
NCT02273726	DD-CKD	ROX vs. EPO	Hgb response with/without rescue therapy
NCT02052310	DD-CKD	ROX vs. EPO	Hgb from baseline to average levels
NCT02174627	ND-CKD	ROX vs. placebo	Time to occurrence of MACE
NCT01887600	ND-CKD	ROX vs. placebo	Response to treatment & maintenance of Hgb
NCT02050190	ND-CKD	ROX vs. placebo	Response to treatment & maintenance of Hgb
NCT02021318	ND-CKD	ROX vs. DPO	Hgb response without rescue therapy
NCT02648347	ND-CKD	VAD vs. DPO	Hgb change from baseline and MACE
NCT02680574	ND-CKD	VAD vs. DPO	Hgb change from baseline and MACE

NCT = National Clinical Trial; DD-CKD = dialysis-dependent chronic kidney disease; ND-CKD = non-dialysis chronic kidney disease; ROX = roxadustat; EPO = epoetin alfa; DPO = darbepoetin alfa; VAD = vadadustat; MACE = major adverse cardiovascular events; Hgb = hemoglobin

These studies are comparing roxadustat to epoetin alfa, darbepoetin alfa, and placebo in patients with chronic kidney disease with or without the requirement of dialysis. Primary outcome measures include long-term efficacy of maintaining Hgb, as well as safety outcomes including time to all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke up to 104 weeks following initiation of therapy. Furthermore, secondary outcomes include supplemental iron requirements, improvement in quality of life, and lipid lowering capacity. Other HIF-PHIs are also in the pipeline, including GSK1278863 and AKB-6548 (vadadustat). These agents have completed Phase II trials, as well, with promising results. Vadadustat, too, is currently enrolling patients for Phase III trials in dialysis and non-dialysis dependent patients with CKD.

Conclusion

Although current guidelines do not show preference for one ESA as compared to another, epoetin alfa has generally remained the mainstay of therapy for CKD associated anemia. Long-acting ESAs such as darbepoetin alfa and MG-EPO are attractive alternatives due to convenience of infrequent dosing, and theoretical potential for improved long-term outcomes. Unfortunately, however, this class of drugs requires repletion and maintenance with exogenous iron. Furthermore, ESAs show diminished efficacy over time.

Previous alternatives to ESAs, such as erythropoietin receptor agonists, showed significant promise. Peginesatide was found to be non-inferior to ESA therapy, but carried increased risk of poor cardiovascular outcomes in Phase III trials. It was not until post-marketing analysis revealed a high rate of hypersensitivity reactions that it was pulled from the market.

The novel HIF-PHI agents have shown promising results in current Phase II trials. The mechanism of action of these agents closely mimics physiologic regulation of erythrocyte production. Not only are these agents capable of increasing Hgb, but they reduce hepcidin, and thus promote mobilization of endogenous iron. These agents are the first to offer an oral option for the treatment of anemia in CKD. The results of the Phase III trials are highly awaited,

as these agents are exciting and refreshing alternatives to ESAs which have remained commonplace since their approval over two decades ago. Some of these trials are expected to be completed by 2017, in which FDA approval will hopefully soon follow. These new agents may revolutionize the treatment of anemia and have the potential to impact the wellbeing of the 25 million people affected with CKD in this country. These new drug classes have the world of nephrology on the edge of its seat waiting with anticipation.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2: 1–138.
2. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9):584-90.
3. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis. 2007;50(3):471-530.
4. Swaminathan S, Mor V, Mehrotra R, Trivedi A. Medicare's payment strategy for end-stage renal disease now embraces bundled payment and pay-for-performance to cut costs. Health Aff (Millwood). 2012;31(9):2051-8.
5. Medicare Drug Spending Dashboard. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Dashboard/Medicare-Drug-Spending/Drug_Spending_Dashboard.html. Accessed April 2016.
6. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085-98.
7. Fishbane S, Besarab A. Mechanism of increased mortality risk with erythropoietin treatment to higher hemoglobin targets. Clin J Am Soc Nephrol. 2007;2:1274-1282.
8. FDA Alert: Information for Healthcare Professionals: Erythropoiesis Stimulating Agents (ESA) [Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)]. November 2007.
9. FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Procrit, Epogen and Aranesp. February 2010.
10. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int. 2005;68(3):1337-43.
11. Kuragano T, Matsumura O, Matsuda A, et al. Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients. Kidney Int. 2014;86(4):845-54.
12. Yang W, Israni RK, Brunelli SM, Joffe MM, Fishbane S, Feldman HI. Hemoglobin variability and mortality in ESRD. J Am Soc Nephrol. 2007;18(12):3164-70.
13. Pergola PE, Gartenberg G, Fu M, Wolfson M, Rao S, Bowers P. A randomized controlled study of weekly and biweekly dosing of epoetin alfa in CKD Patients with anemia. Clin J Am Soc Nephrol. 2009;4(11):1731-40.
14. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. Am J Kidney Dis. 2013;61(1):44-56.
15. Aranesp® [package insert]. Thousand Oaks, CA: Amgen Inc.; Jul 2015.
16. Macdougall IC, Provenzano R, Sharma A, et al. Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis. N Engl J Med. 2013;368(4):320-32.
17. Fishbane S, Schiller B, Locatelli F, et al. Peginesatide in patients with anemia undergoing hemodialysis. N Engl J Med. 2013;368(4):307-19.
18. FDA Press Release. FDA approves Omontys to treat anemia in adult patients on dialysis. 2012.
19. Fishbane S, Besarab A, Schiller B, et al. Primary safety and efficacy results from four Phase 3 randomized, active-controlled, open-label studies of Hematide™/Peginesatide among CKD dialysis and non-dialysis patients. In: Proceedings of the American Society of Nephrology Renal Week; November 16–21, 2010; Denver, CO. Abstract LB-FC4.

20. Affymax and Takeda Announce Termination of Omontys® (peginesatide) Product Collaboration and License Agreement. Takeda will withdraw the Omontys U.S. New Drug Application (NDA)
21. Mircera® [package insert]. San Francisco, CA: Hoffman-La Roche Inc.; Oct 2014.
22. Alsalimy N, Awaisu A. Methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa for anemia in non-dialysis-dependent CKD: a systematic review. Int J Clin Pharm. 2014;36(6):1115-25.
23. Carrera F, Lok CE, de Francisco A, et al. Maintenance treatment of renal anaemia in haemodialysis patients with methoxy polyethylene glycol-epoetin beta versus darbepoetin alfa administered monthly: a randomized comparative trial. Nephrol Dial Transplant. 2010;25(12):4009-17.
24. Levin NW, Fishbane S, Cañedo FV, et al. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). Lancet. 2007;370(9596):1415-21.
25. Koury MJ. Can Prolyl Hydroxylase Inhibition Treat EPO-Deficient Anemia of Renal Failure With Fewer Vascular Complications Than EPO Itself?. 2015;12(2).
26. Semenza GL. Oxygen sensing, homeostasis, and disease. N Engl J Med. 2011;365:537-547.
27. Ratcliffe PJ. Oxygen sensing and hypoxiasignalling pathways in animals: the implications of physiology for cancer. J Physiol. 2013;591:2027-2042.
28. Bernhardt WM, Wiesener MS, Scigalla P, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. J Am Soc Nephrol. 2010;21(12):2151-6.
29. Liu Q, Davidoff O, Niss K, Haase VH. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. J Clin Invest. 2012;122(12):4635-44.
30. Peyssonnaux C, Zinkernagel AS, Schuepbach RA, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). J Clin Invest. 2007;117(7):1926-32.
31. Besarab A, Chernyavskaya E, Motylev I, et al. Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients. J Am Soc Nephrol. 2016;27(4):1225-33
32. 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):1665-73.