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Erythropoiesis Stimulating Agents (ESA) for the treatment of Anemia in Patients with Chronic Kidney Disease (CKD)

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Abstract

Anemia is a major complication of chronic kidney disease (CKD), with erythropoietin (EPO) deficiency being the major cause. Use of erythropoiesis stimulating agents (ESA) has resulted in remarkable improvement in the quality of life of CKD patients. ESA cause conformational changes of the EPO receptor, resulting in phosphorylation or activation of signaling molecules. It causes inhibition of apoptosis and activation of erythropoiesis, leading to the formation of red blood cells. It also results in triggering various cellular processes that include progenitor stem cell development, cellular integrity, and angiogenesis. These mechanisms induce pleiotropic effects in other organ systems, viz.,

cardiovascular, central nervous and renal systems. Studies like NHCT, CHOIR, CREATE, DRIVE, and TREAT which were conducted to understand the use of ESA in patients undergoing dialysis, led to the development of new drug molecules with improved pharmacokinetic and pharmacodynamic characteristics. Darbepoetin alpha and pegylated epoetin beta were the first long-acting ESAs. In addition to these, other ESA molecules with structural modifications and mechanisms have recently been developed. Of these, few are under clinical and preclinical review. These molecules/therapies include EPO gene therapy, Hypoxia-inducible factor (HIF) stabilizers, EPO fusion proteins, GATA inhibitors and Activin receptor ligand traps.

Keywords: Anemia, Chronic Kidney Disease (CKD), Erythropoietin (EPO), Erythropoiesis stimulating agent (ESA), Hemodialysis, Pleotropic.

Introduction

In patients with chronic kidney disease (CKD), anemia is a common complication and also an important contributor for worsening of cardiovascular disease (CVD) [1-4]. Based on KDIGO guidelines (2012), anemia in CKD is defined as Hb level < 13g/dl in men and Hb< 12g/dl in women [5]. Anemia in CKD can occur due to factors such as deficiency of iron, vitamin B12, folic acid, shortened lifespan of RBCs, blood loss, inflammation, hyperparathyroidism and hypothyroidism [1, 3]. However, decreased production of erythropoietin (EPO), a hormone synthesized and secreted by the interstitial cells of kidney, which stimulates the production of red blood cells (RBCs), is a major factor causing anemia in CKD [6]. Anemia is more prevalent in people with CKD when compared to the general population [7]. Further, as the severity of CKD increases, severity of anemia also worsens. The prevalence of anemia has been shown to increase manifold from stage 1 to stage 5 of CKD [1, 4, 7, 8].

Patients with CKD associated anemia may experience weakness, fatigue, dyspnea, cognitive impairment and sleep disturbances and is associated with a higher risk of CKD progression, cardiovascular co-morbidity and mortality. Blood transfusions were the major mode of treatment for such patients prior to the discovery of ESAs [6]. Though blood transfusions may lead to improvement in symptoms of anemia immediately, repeated blood transfusions are known to cause iron overload and other associated risks such as transfusion reactions and allo-sensitization, which limit potential kidney transplantation [7]. Various types of ESAs have been launched in the pharma market for the treatment of anemia [8, 9]. This review article discusses the treatment of CKD associated anemia using various ESAs and also focuses on the emerging ESA therapies.

Discovery of EPO

EPO deficiency, as the main cause of anemia in CKD, was first hypothesized in 1950. In the late 1980s, purification and cloning methods were developed to carry out immunoassays for quantifying the levels of EPO in blood [10]. The first Human EPO was isolated from the urine of patients with a plastic anemia in 1977 [11]. Thereafter, the identification of the EPO gene and its cloning led to the development of recombinant human EPO (rHuEPO). Recombinant EPOs are man-made versions of natural EPO, also known as ESA. Discovery of ESAs was a turning point in the management of anemia. Exogenous replacement of EPO by rHuEPO, along with iron, became a standard of care for the treatment of anemia in patients with CKD. It not only improved the quality of life but also reduced the

mortality rates associated with CKD associated anemia [12].

Mechanism of Action

Conventional ESAs act through different pathways and cause conformational changes. The mechanism of action of ESAs is shown in Figure 1. The basic mechanisms through which ESAs show their action are described below.

a) Phosphorylation: EPO binds to the EPO receptor and causes phosphorylation of associated JAK2 molecules, STAT5, PI3-Kinase and IkB molecules, which results in activation of genes encoding anti-apoptotic molecules and inactivation of pro-apoptotic molecules [9].

b) Blocking of SMAD Pathway: The SMAD pathway is primarily involved in Hepcidin transcription. Activin traps bind to activin, preventing it from binding to endogenous receptors, thereby blocking the SMAD pathway. BMP6 monoclonal antibodies prevent phosphorylation of the SMAD molecule which also results in blocking of the SMAD pathway. Both these mechanisms cause inhibition of hepcidin production [13].

c) Stabilization of Hypoxia Inducible Factor (HIF): HIF is involved in regulation of EPO levels through EPO gene expression. Propyl hydroxylase inhibitors (PHIs) prevent degradation of HIF and cause stabilization of HIF molecule thereby increasing EPO production [14, 15].

d) GATA Inhibition: GATA negatively regulates hypoxia-inducible factor-1 (HIF-1), which regulates EPO gene expression**.** GATA inhibitors decrease the binding capacity of GATA molecule thereby sparing HIF and resulting in increasing production of EPO [16].

e) Pleiotropic effects of ESA: ESA also shows some pleiotropic effects by binding to the EPO receptor and triggering various cellular processes that include progenitor stem cell development, cellular integrity, and angiogenesis. This makes it a potential agent to provide organ protection by inhibiting apoptosis and amelioration of inflammation. ESA can protect organs via a hematopoiesis dependent and independent manner [17]. The pleiotropic effects of ESA are studied in central nervous system, cardiovascular system and in renal system. The nephroprotective effects of EPO are achieved by mechanisms such as reduction of oxidative stress, apoptosis, and ischemic/reperfusion injury, boosting vascular repair, or balance of the inflammatory response with subsequent reduction of glomerular and tubular fibrosis [18]. EPO can also cross the blood-brain barrier, thereby providing neuroprotection by limiting damage to the central nervous system following injury [19].

Currently Available ESAs

The first generation ESAs include recombinant human EPOs, like epoetin alfa and epoetin beta, which have been in clinical use for overthree decades.The amino acid sequence of both these molecules is identical,with a minor difference being in their glycosylation pattern. Though they are highly potent, they have a short half-life of 6 to 8 h, resulting in need for administration of two to three injections weekly [20]. Other epoetins include epoetin omega, epoetin delta, and other biosimilars.The discovery that a greater number of sialic acid residues in the recombinant human EPO molecule increases the circulating half-life, led to the development of the second generation of ESAs, which includes darbepoetin alfa. It supports a maximum of 22 sialic acid residues, compared to recombinant or endogenous EPO, which support a maximum of 14 sialic acid residues [6]. These molecular modifications resulted in greater metabolic stability and a three-fold increase in the half-life of darbepoetin alfa which has allowed for less frequent dosing, with most patients receiving injections once weekly or once every

two weeks [21]. Though the binding affinity of darbepoetin alfa for the EPO receptor is less than that for natural or recombinant EPO, the benefit of greater stability in vivo shown by darbepoetin alfa, outweighs this minor disadvantage. Integration of the EPO molecule with a large methoxy polyethyleneglycol polymer chain resulted in the synthesis of CERA (Continuous Erythropoietin Receptor Activator), a third generation ESA. It has a prolonged half life of around 130 h, enabling it to be administered once every 2 weeks and once every month [22]. USFDA approved CERA for sale in USA in November 2007. The European Agency for the Evaluation of Medicinal Products (EMEA) recommended and approved its salein July 2007. Following the approval, CERA was made available in Austria, Sweden, Germany, the UK and Norway [23]. Currently, CERA is licensed for use in the treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis. It is not approved for the treatment of anemia associated with cancer chemotherapy [23].

ESA use in Clinical Practice and Various Studies of ESA

The usage of ESA in clinical practice in patients with CKD largely depends on the baseline Hb levels. As per the recommendations of National Anemia Action Council and the World Health Organization, in adults and children aged <15 years, a diagnosis of anemia is confirmed if Hblevel is <13g/dL in men and <12g/dL in women. In children aged 0.5 to 5 years, Hb level <11g/dL, in children aged 5 to 12 years, Hb level <11.5g/dL and in children aged 12 to 15 years, Hb level of <12g/dL, is considered as anemia [24, 25]. The first line of therapy to treat CKD associated anemia, involves administration of oral or parenteral iron and the second line of treatment involves the administration of either intravenous or subcutaneous ESAs. Initial ESA dose is dependent upon Hb concentration, body weight and clinical circumstances. It is necessary to re-evaluate the ESA dose if the patient suffers an ESA-related adverse event or has an acute or progressive illness that may cause ESA hypo-responsiveness. The details of management of CKD associated anemia using ESA are shown in **Figure 2** and the dosing details are included in **Table 2.**

In early 1990s, many clinical studies were conducted to understand the usefulness of EPO in improving Hb levels and quality of life in patients undergoing hemodialysis. The first such trial using EPO was the Canadian group of EPO (CanEPO) study conducted in 118 patients in 1990. The patients were randomized into three groups; placebo, low erythropoietin group (targeting a Hb-concentration of 9.5-11.0 g/dL) and high erythropoietin group (targeting a Hb-concentration of 11.5-13.0 g/dL). Results reported that the mean Hb-levels of 7.4 g/dL, 10.2 g/dL and 11.7 g/dL respectively, were achieved at 6 months. Patients who were administered erythropoietin were appreciably less fatigued, complained of less severe physical symptoms, and had moderate improvements in exercise tolerance and depression compared to placebo group [26]. Other landmark studies of ESA molecules in the last few decades are discussed in **Table3.**

In 1998, the **United States Normal Hematocrit Cardiac Trial (NHCT)** was carried out to evaluate the benefits and risks of normalizing hematocrit levels in patients with cardiac disease on dialysis. Group 1 received increasing doses of epoetin to achieve and maintain 42% hematocrit and group 2 received doses of epoetin sufficient to maintain a 30% hematocrit. After 29 months, 183 deaths and 19 nonfatal myocardial infarctions were reported in the normal-hematocrit group

and 150 deaths and 14 nonfatal myocardial infarctions were reported in the low-hematocrit group. Additionally, the mortality rates decreased with increasing hematocrit values in both the groups. The patients in the normal-hematocrit group required intravenous iron dextran more frequently than those in the low-hematocrit group and had a decline in the adequacy of dialysis. Therefore the trial concluded that it is not recommended to raise the hematocrit to 42% in patients with congestive heart failure or ischemic heart disease undergoing dialysis [27].

In the **Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial**, it was assessed whether the use of recombinant erythropoietin (epoetin alfa) to achieve a higher hemoglobin level (13.5 g/dL) would decrease the risk of complications, compared to a lower hemoglobin level (11.3 g/dL) in patients with CKD. The outcome of this multi-centric trial in United States showed increased risk and no incremental improvement in the quality of life with a higher hemoglobin target [28].

In 2000-2004, a multi-centric, **Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)** trial was conducted in 22 countries to evaluate whether the complete correction of anemia in patients with stage 3 or 4 CKD improves cardiovascular outcomes as compared with partial correction of anemia. No significant difference was found in the combined incidence of adverse events between the two groups, but hypertensive episodes and headaches were more prevalent in Group 1 (complete correction of anemia). Though general health and physical function improved significantly, dialysis was required in more patients in Group 1 than in Group 2 [29].

A double blind, placebo controlled, **Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)** (2004-2007) involved 4038 patients with anemia, chronic kidney disease not on dialysis and type 2 diabetes. The active treatment arm comprised darbepoetin alfa given subcutaneously with the aim of achieving Hb values >13 g/dL. Administration of darbepoetin alfa did not reduce the risk of death or cardiovascular event or renal event. Further, there was an increased risk of stroke in these patients. The requirement of blood transfusions was lower in the group treated with darbepoetin [30].

It is essential for patients receiving ESA to have adequate iron stores, as there will be improvement in the hemoglobin levels only when there is a sufficient iron available for red cell production. Results from the **Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE)** study, which was conducted across 37 sites in the United States, reinforces this statement. In this study, 134 patients were randomized to receive 125 mg of ferric gluconate versus no iron. Levels of hemoglobin increased at a faster rate and to a higher level in the ferric gluconate group compared to no iron therapy [31]. Similarly, Macdougall et al (2019) assessed the safety and efficacy of a high-dose regimen of intravenous iron administered proactively, as compared with a low-dose regimen of intravenous iron administered reactively, in patients undergoing hemodialysis in the **Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial.** They found that the high-dose regimen was superior to the low-dose regimen and resulted in lower dose requirement of ESAs [32].

Newer ESAs

Several new combinations of molecules are currently undergoing preclinical and clinical trials. Synthetic Erythropoiesis Proteins (SEP) is one of them. It was manufactured using solid-phase peptide synthesis and

branched precision polymer constructs. It stimulates erythropoiesis by activating the EPO receptor and has a longer circulating half-life than EPO [33]. Another fusion protein combining EPO and granulocyte macrophage colony stimulating factor (GM-CSF) has been created, with the rationale that GM-CSF is required for early erythropoiesis [20].

Epoetin alfa has been combined with a polysialic acid (PSA) derived from Escherichia coli. This PSA-EPO fusion protein allows once monthly administration. EPO has also been combined with hybrid human crystallizable fragment (Fc) molecules, by Genexine (Seongnam, Korea), thereby increasing its stability and plasma half-life [34, 35].

EPO mimetics are another class of synthetic polypeptides. Though they act upon the EPO receptor, they show no resemblance to EPO or ESAs. Peginesatide was the first EPO mimetic developed by Affymax. It is a peptide based pegylated ESA which was licensed for use in the USA in 2012. Later, it was discontinued due to hypersensitivity reactions occurring when administered through the IV route [36, 37]. A combination of erythropoietin mimetic peptides (EMP) and immunoglobulin G (IgG) led to the production of CNTO 528 and CNTO 530 fusion proteins which are still in the pre-clinical testing phase [38]. **Table 1** enlists the various types of ESAs, their history and market approval details [12, 36, 39, 40].

Limitations of the above protein based therapies include immunogenicity (pure red cell aplasia caused by anti EPO antibodies); storage and stability; and administration conditions. They must be stored at temperatures of approximately 4°C, and must be administrated intravenously or subcutaneously [9]. To overcome these limitations, various potential strategies have been developed in the formulation techniques to improve the efficacy and delivery of ESA molecules. The various new strategies are discussed below.

a) Activin Traps

Activins belong to a large family of proteins known as transforming growth factor-β (TGF-β). It forms a complex between the ligand, type I and type II receptors. This complex eventually phosphorylates the Small Mother Against Decapentaplegic homologue (SMAD) proteins which regulate gene expression in concert with other transcription factors [41]. Sotatercept (ACE-011) is a novel recombinant fusion protein developed by Acceleron Pharma and Celgene Corporation by combining an extracellular chain of the activin receptor IIA and the Fc domain of human IgG1 [34]. The drug binds to activin, preventing it from binding to endogenous receptors and blocks the SMAD pathway. By blocking this pathway which is involved in hepcidin synthesis and iron homeostasis, sotatercept causes increase in Erythropoiesis [13].

b) Hypoxia Inducible Factor- Propyl Hydroxylase Inhibitors (HIF-PHIs)

A novel therapeutic approach to correct anemia in patients with CKD is the induction of EPO synthesis by stabilizing HIFs with PHI. HIF is a heterodimer composed of HIF-α and HIF-β subunits. HIF-β is constitutively expressed, whereas HIF-α is modulated by oxygen tension via a family of HIF-propyl hydroxylases (PHD) regulating its degradation by the proteasome. During hypoxia, HIF plays an important role in regulating the levels of EPO, glucose transporter-1, vascular endothelial growth factor (VEGF), and pyruvate dehydrogenase kinases 1 and 4. HIF stabilizers also called PHIs, are small-molecule oral agents that stabilize HIF and prevent its degradation, allowing the stimulation

of EPO gene expression in the kidneys [14, 15]. Three oral HIF-PHIs, daprodustat, roxadustat and vadadustat, are being studied in phase III of clinical trials. Among them, roxadustat is licensed for the treatment of renal anemia in China [42]. Clinical studies have proved that HIF stabilizers adequately increase Hb levels in both non-dialysis and dialysis CKD patients without causing serious adverse effects [43-45]. HIF stabilizers have additional advantages of lipid lowering, improving iron utilization, lowering blood pressure, ischemia protection and improving neovascularization. However, since it is associated with the an increased risk of growth of renal cysts and tumors, increased pulmonary arterial pressure and increased vascular calcification, its clinical use should be judicious and monitored [34].

c) EPO Gene Therapy

Gene therapy is a novel therapeutic approach for the treatment of monogenetic diseases, using non-viral or viral delivery systems. It involves delivery of therapeutic proteins in the body. Anemia in CKD is treated with rHuEPO. However, the short half-life of the currently available recombinant products, their potential to cause antibodies against rHuEPO, and their high cost is one of the triggering factors to include gene therapy in the management of anemia. EPO gene therapy is a useful technique to overcome the harmful effects of excessive dosage of EPO in blood. The ideal level of EPO to provide the most efficient erythropoiesis is approximately 40 to 200mU/mL above the baseline levels. Higher levels lead to rHuEPO wastage, and lower levels cause inefficient erythropoiesis [46]. Gene therapy helps to generate low but continuous release of EPO in blood circulation. It not only improves the efficiency of Erythropoiesis but also avoids the risk of forming antibodies against recombinant proteins [9]. The technique produces rHuEPO from human cells, which directly secretes the protein in the body without any additional formulation or manufacturing [46]. Various gene delivery systems for EPO gene therapy investigated include; injection of naked DNA [47], adenovirus transfection [48],use of artificial human chromosomes [49] and transplantation of autologous or allogeneic cells manipulated ex vivo [46].

d) GATA Inhibition

GATA inhibition is a genetic approach to increase the production of EPO thereby restoring hemoglobin concentrations in patients with CKD. The GATA family consists of six transcription factors, GATA 1 through 6. EPO gene expression is under the control of HIF-1 which is negatively regulated by GATA. Interleukin 1 (IL-1β) and tumor necrosis factor (TNF-α), increase the binding activity of GATA and inhibit EPO promoter activity. Preclinical studies for GATA inhibitor molecules K-7174 and K-11706 are underway to establish its further safety and efficacy in humans. Studies have shown that these molecules given intra-peritoneally and orally to mice respectively reversed the decrease in hemoglobin and serum EPO concentrations, reticulocyte counts, and number of erythroid colony-forming units (CFU-Es) induced by IL-1β and TNF-α [16].

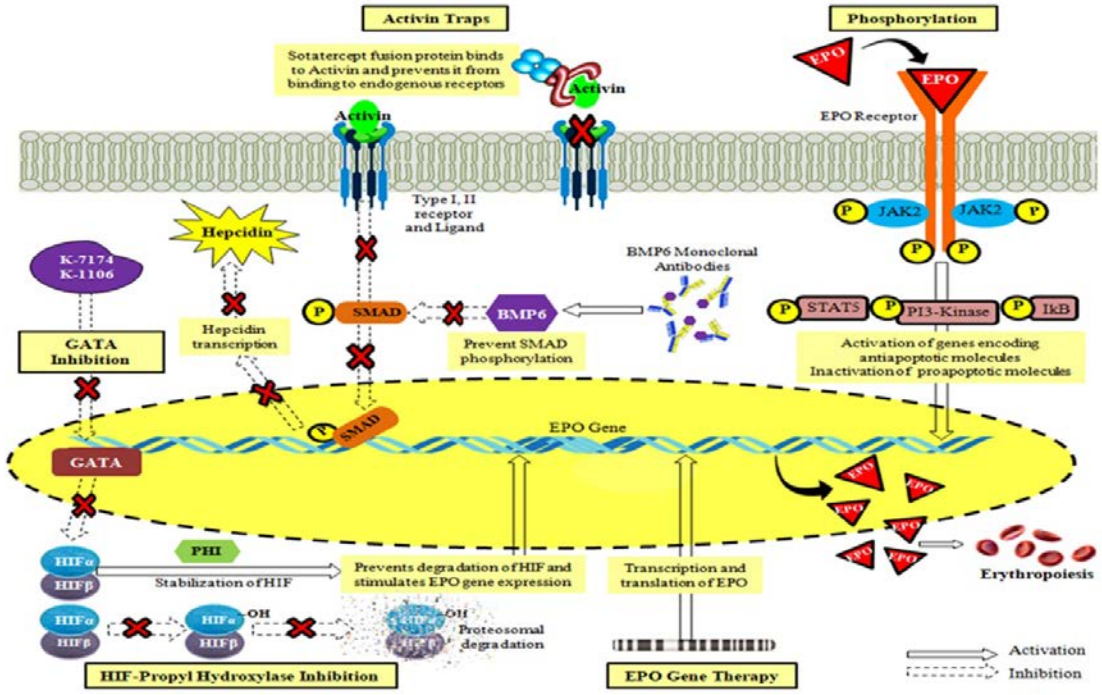

Figure 1 Mechanism of Action of ESAs

BMP=Bone Morphogenic Protein, EPO=Erythropoietin, HIF=Hypoxia Inducible Factor, JAK=Janus Kinases, PHI=Propyl Hydroxylase Inhibitors, PI=Phosphorylated Phosphatidyl Inositol, SMAD=Small Mother Against Decapentaplegic homologue, STAT=Signal Transducer and Activator of Transcription.

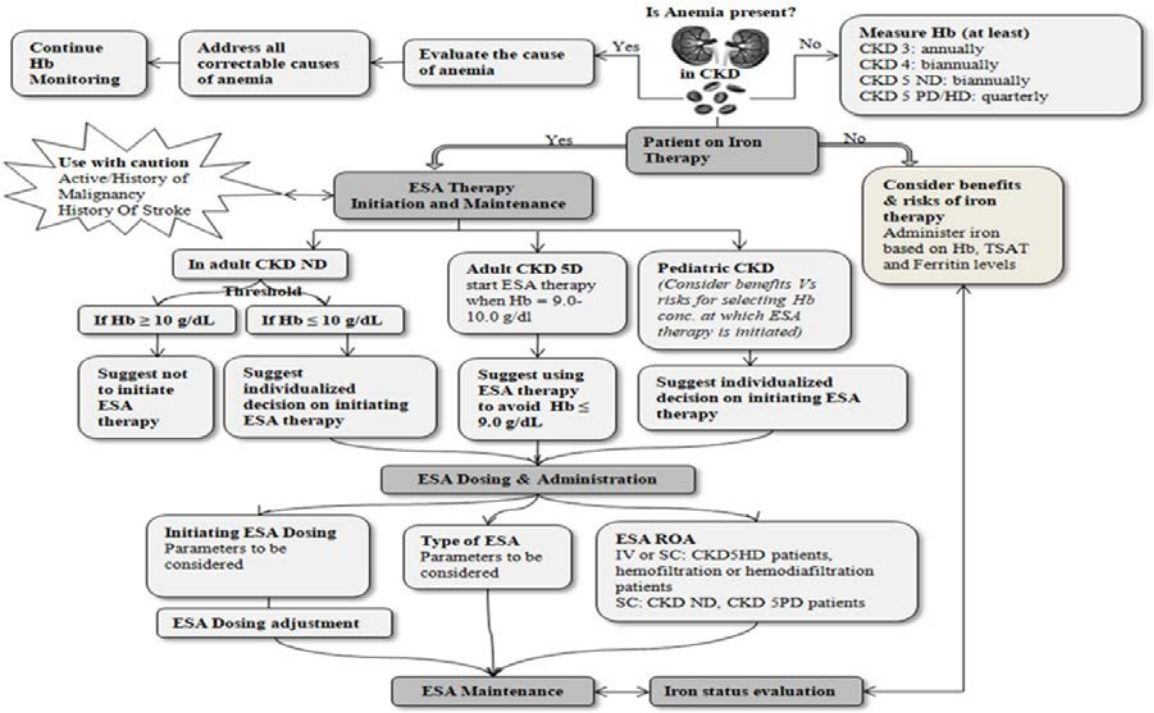

Figure 2: Management of CKD-Associated Anemia using ESA

CKD=Chronic kidney disease, ESA=Erythropoiesis stimulating agent, Hb=Hemoglobin, HD=Hemodialysis, IV=Intravenous, ND=Non-dialysis, PD=Peritoneal dialysis, ROA=Route of administration, SC=Subcutaneous, TSAT=Transferrin saturation.

Source: KDIGO recommendations: Anemia in CKD.

Table 1: Types of Erythropoietin Stimulating Agents (ESA)

	International Nonproprietary Name	Trade Name	Year of Approval	Countries Licensed in
First Generation	Epoetin alfa	Epogen®	1989	USA
		Eprex®	1988	USA, European Union, Other regions
		Procrit®	1989	USA
	Epoetin beta	Recormon®	1990	European Union
	Epoetin omega	Epomax® Hemax®	1990	South Africa, Other regions
Second Generation	Epoetin beta	NeoRecormon®	1997	European Union, Other regions
	Darbepoetin alfa	Aranesp®	2001	USA, European Union Australia, Asia
	Epoetin delta	Dynepo®	2002	Marketing stopped in 2009[g]
Third Generation	Methoxy polyethyleneglycol epoetin beta (CERA)	Mircera®	2007	USA, European Union
	Epoetin alfa(biosimilar)	Binocrit® Abseamed® Epoetin Alfa Hexal®	2007	European Union
	Epoetin zeta(biosimilar)	RetacritTM SilapoTM	2007	European Union Other regions
	Epoetin theta	Biopoin® Eporatio®	2009	European Union
EPO Proteins	SyntheticErythropoiesis Protein (SEP)	R 1516 (Gryphon Therapeutics)	-	Phase-I clinical trials in anemia in USA (unspecified route)
Fusion Proteins	Recombinant Granulocyte Macrophage Colony StimulatingFactor (GM-CSF)	PF-11 (Profarma)	-	No recent reports of development identified for research development in Cancer in Lithuania (Parenteral)

EPO Mimetics	Recombinant erythropoietin fusion protein	FC EPO	-	Discontinued - Phase-I for anemia in Switzerland (Parenteral)
	Hematide -Peptide based pegylated ESA	Peginesatide (AF 37702)	2012	USA. Discontinued now
	CNTO 528		-	No recent reports of development identified for phase-I development in anemia in USA
HIF-PHI Inhibitor	Small Molecule ESA	Roxadustat (FG-2216)	2018 and 2019	China for DD-CKD and ND-CKD
		Roxadustat - FibroGen (FG-4592)	-	Phase IIIb trial ongoing (NCT04484857, NCT04484857)
		Molidustat (BAY-85-3934)	-	Phase III development ongoing in Japan (NCT03350321, NCT03350347)

CKD=Chronic Kidney Disease, DD=Dialysis dependent, EPO=Erythropoietin, ESA=Erythropoiesis Stimulating Agent, ND=Non-dialysis.

Table 2: Dosing Details of Erythropoietin Stimulating Agents (ESA)

Name	Dosage forms and strengths available	Starting Dose	Dose Adjustment	Maintenance Dose
Epoetin alfa Ref (50)	Epogen: Single dose vial - 2,000;3,000; 4,000 and 10,000 Units/mL. Multi dose vial - 20,000 Units/2 mL (10,000 Units/mL) and 20,000 Units/mL.	Adults: 50-100 Units/kg 3 times weekly IV or SC. Children: 50 Units/kg 3 times weekly IV or SC.	CKD-DD: If the Hb level approaches or exceeds 11 g/dL, reduce or interrupt the dose. CKD-ND: If the Hb level exceeds 10 g/dL, reduce or interrupt the dose and use the lowest dose sufficient to reduce the need for RBC transfusion. Children:If the Hb level approaches or exceeds 12 g/dL, reduce or interrupt the dose.	To maintain the Hb between 10 to 12 g/dL, a dose of 75 -100 Units/kg 3 times weekly.
Epoetin	Recormon:	SC: 3 x 20	SC: Dosage may be increased	To maintain Hb between 10-12

beta Ref (51)	Lyophilisate powder and solvent for injection: 50,000 IU = 415 micrograms epoetin beta / vial + 10 ml solvent. Pre-filled syringes: 500, 2000, 3000, 4000, 5000, 6000, 10,000, 20,000, 30,000 IU.	IU/kg body weight per week. IV: 3 x 40 IU/kg per week	every 4 weeks by 3 x 20 IU/kg per week if the increase of Hb is not adequate (< 0.25 g/dl per week). IV:Dosage may be raised after 4 weeks to 80 IU/kg three times per week and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.	g/dl, the dosage is initially reduced to half of the previously administered dose. Subsequent dose is adjusted at intervals of 2-4 weeks. SC: Weekly dose can be given as one injection per week or in divided doses 3-7 times per week. If patient is stable on a once weekly dose, dose may be switched to once every two weeks.
Darbepoetin alfa Ref (52)	Aranesp: Single-dose vials: 25, 40, 60, 100, 200, 300, and 500 mcg/1 mL, and 150 mcg/0.75 mL. Single-dose prefilled syringes: 25 mcg/0.42mL, 40 mcg/0.4mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, and 500 mcg/1 mL	CKD-DD: 0.45 mcg/kg IV or SC weekly or 0.75 mcg/kg IV or SC every 2 weeks. CKD-ND: 0.45 mcg/kg IV or SC at 4 week interval.	CKD-DD:IfHb level approaches or exceeds 11 g/dL, reduce or interrupt the dose. CKD-ND:If Hb level exceeds 10 g/dL, reduce or interrupt the dose and use the lowest dose sufficient to reduce the need for RBC transfusions.	Lowest dose that will maintain a Hb level sufficient to reduce the need for RBC transfusions should be used.
Methoxy polyethylene glycol epoetin	MIRCERA: Single dose syringes: 30, 50, 75, 100, 120, 150,	CKD-DD and CKD-ND: 0.6 mcg/kg body weight	CKD-DD: If Hb level approaches or exceeds 11 g/dL, reduce or interrupt the dose. CKD-ND: If Hb level exceeds	Lowest dose that will maintain aHb level sufficient to reduce the need for RBC transfusions should be used.

beta (CERA) Ref: (53)	200, or 250 mcg in 0.3 mL and 360 mcg in 0.6 mL.	administered as a single IV or SC injection once every two weeks.	10 g/dL, reduce or interrupt the dose and use the lowest dose sufficient to reduce the need for RBC transfusions.	A once monthly dose that is twice that of everytwo week dose may be given and subsequently titrated as necessary.

CKD=Chronic Kidney Disease, DD=Dialysis dependent, Hb=Hemoglobin, IV=Intravenous, ND=Non-dialysis, RBC=Red Blood Corpuscles, SC=Subcutaneous.

Table 3: Landmark Studies of Erythropoietin Stimulating Agents (ESA)

Study Name, Author and Year	Objective	Study Type	Study Design (Patients Size, `\Groups andInterventio n)	Study Parameters	Study Outcomes
Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) study Daniel W. Coyne (2007) (31).	To assess the efficacy of IV ferric gluconate in anemic hemodialysis patients with high ferritin and low transferrin saturation	Randomized open-label, controlled, multicenter trial in 37 sites across United States	Patient size N=134 N1=66 (No Iron) N2=68 (1 g of ferric gluconate administered in 8 consecutive 125-mg doses) Intervention: IV Iron + Epoetin	Primary end point: CFB hemoglobin. Secondary end point: percentage of patients who achieved an increase in Hb ≥ 2 g/dl, Adverse events.	At 6 week, Hb increased significantly more (p=0.028), quickly (p=0.035)and more patients responded after IV iron (p=0.041)compared to control group.IV iron resulted in a greater increase in TSAT than in control subjects (p< 0.001). Higher epoetin dosage resulted in a greater CFB in Hb by 0.5 g/dl (p=0.022).

Correction of Anemia with Epoetin Alfa in CKD (CHOIR) Ajay K. Singh (2006) (28)	To assess if achieving higher Hb levels has beneficial effects on the rate of cardiovascular events and death in CKD patients.	Randomized open-label trial	Patient size N=1432 N1= 715 (Received epoetin alfa to achieve Hb level=13.5 g/dl. N2=717 (Received epoetin alfa to achieve Hb level=11.3 g/dl.	Primary end point: composite of death, MI, hospitalization for congestive heart failure (without renal replacement therapy), and stroke.	Around 125 events occurred in high Hb group compared to 97 events in the low Hb group (p=0.03). There were 65 deaths (29.3%), 101 hospitalizations for congestive heart failure (45.5%), 25 MIs (11.3%), and 23 strokes (10.4%), congestive heart failure and MIs combined (3.2%). Improvements inQOL were similar in both the groups.
Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial Tilman B. Drüeke (2006)(29)	To assess whether complete correction of anemia in patients with stage 3 or 4 CKD improves cardiovascular outcomes compared to partial correction of anemia	Randomized, open-label study with a parallel-group design	Patient size N=603 N1=301(epoetin beta given to normalize Hb values (Hb=13-15 g/dl) N2=302 (epoetin beta given to partially correct anemia (Hb=10.5-11.5 g/dl) and it is given only when Hb	Primary end point: Time to a first cardiovascular event, including sudden death, MI, acute heart failure, stroke, transient ischemic attack, angina pectoris resulting in hospitalization for 24 hours or more or prolongation of hospitalization, complication of peripheral vascular disease, or cardiac arrhythmia resulting in hospitalization for 24 hours or more. Secondary end points: Left ventricular mass index, QOL scores, progression of CKD,	Complete correction of anemia did not affect the likelihood of a first cardiovascular event (p=0.20). Left ventricular mass index remained stable in both groups. More number of patients in group 1 required dialysis than in group 2 (127 vs. 111, p=0.03). General health and physical function improved significantly (p=0.003 and p<0.001,

			levels fall below 10.5 g/dl.	death from any cause, death from cardiovascular causes, and hospitalization.	respectively, in group 1 vs group 2). No difference was found in the incidence of adverse events.
The United States Normal Hematocrit Cardiac Trial (NHCT) Anatole Besarab (1998)(27)	To examine benefits and risks of normal hematocrit in patients with cardiac disease undergoing hemodialysis and receiving epoetin, compared to low hematocrit values	Randomized prospective, open-label trial	Patient size N=1233 N=618 (Received increasing doses of epoetin to maintain a hematocrit of 42%) N=615 (Received doses of epoetin sufficient to maintain a hematocrit of 30%) Intervention: Epoeitin	Primary end point: Time to death or a first nonfatal MI	Around 183 deaths and 19 first nonfatal MIs were reported in the normal hematocrit group and 150 deaths and 14 nonfatal MIs were reported in the low hematocrit group. The mortality rates decreased with increasing hematocrit values in both groups. The normal hematocrit group had a decline in the adequacy of dialysis and received IV iron dextran more often than those in the low hematocrit group.
Time to reconsider evidence for anemia treatment (TREAT) Marc. A Pfeffer et al. 2009,	To determine whether increasing the Hb levels would lower the rates of death,	Randomized, double-blind, placebo-controlled trial, multicenter conducted at 623 sites in 24 countries	Patient Size N= 4038 N1=2012 administration of darbepoetinalfa to achieve aHb level of 13g/dl. N2=2026	Primary end points: Composite outcomes of death or a cardiovascular event (nonfatal MI, congestive heart failure, stroke, or hospitalization for myocardial ischemia) and of death or end-stage renal disease.	Death or a cardiovascular event occurred in 632 patients assigned to darbepoetinalfa and 602 patients assigned to placebo (p=0.41). Death or end-stage renal disease occurred in 652 patients

(30)	cardiovascular events, and end-stage renal disease.		patients in placebo: Hb level of ≥9.0g/dl Intervention ESA used: darbepoetinalfa		assigned to darbepoetinalfa and 618 patients assigned to placebo (p=0.29). Fatal or nonfatal stroke occurred in 101 patients assigned to darbepoetinalfa and 53 patients assigned to placebo (p<0.001).
PRIMAVERA Fliser, 2017(54)	To assess whether early initiation of ESA treatment could delay the progression of renal function loss	Randomized single blind, 24- month trial	N=400 N1= 115 (CERA), N2= 120 (placebo) Intervention: Low dose CERA (monthly dose 30–75 μg)	Primary endpoint: Annual change in eGFR from baseline to month 24. Secondary endpoints: Changes in UACR, serum cystatin C and serum creatinine from baseline.	Mean eGFR was 40.7 mL/ min/1.73 m^2 vs 39.8 mL/min/1.73 m^2 at baseline for CERA and placebo, respectively, and 39.0 g/dL vs 39.7 g/dL at the final visit (p>0.05). Adverse events occurred in 22.0% and 16.2% of patients in CERA or placebo group respectively, and adverse events led to study drug discontinuation in 11.0% and 8.5% of patients.

BP=Blood Pressure,CFB=Change from baseline, CKD=Chronic Kidney Disease, CERA=Continuous Erythropoiesis Receptor Activator, eGFR=estimated Glomerular Filtration Rate, ESA=Erythropoesis Stimulating Agents, Hb=Hemoglobin, IV=Intravenous, MI=Myocardial Infarction, QOL=Quality of life, RR=Relative Risk, RRT=Renal Replacement Therapy, TSAT=Transferrin Saturation, UACR=Urinary Albumin to Creatinine Ratio.

Conclusion

Management of CKD associated anemia has greatly advanced in the last few decades due to the discovery of ESAs. Various studies have shown that the use of ESAs significantly improve anemia of CKD. Recombinant ESAs such as epoetin, darbepoetin alfa and CERA are the currently available ESAs. In recent years, newer molecules are on the horizons which have better molecular stability, solubility, in vivo activity, serum half-life and immunogenicity. Undoubtedly, ESAs have changed the treatment options and reduced the necessity of blood transfusions to a great extent in patients with CKD associated anemia. Besides improving the Hb levels, ESA molecules have also been shown to retard the progression of CKD, reduce cardiovascular events and induce pleiotropic effects in other organs.

References

1. Sathyan S, George S, Vijayan P. Prevalence of anemia and cardiovascular diseases in chronic kidney disease patients: A single tertiary care centre study. International Journal of Advances in Medicine. 2017;4(1):247-51.
2. Alani H, Tamimi A, Tamimi N. Cardiovascular co-morbidity in chronic kidney disease: Current knowledge and future research needs. World journal of nephrology. 2014;3(4):156.
3. Kaze FF, Kengne A, Mambap AT, Halle M-P, Mbanya D, Ashuntantang G. Anemia in patients on chronic hemodialysis in Cameroon: prevalence, characteristics and management in low resources setting. African health sciences. 2015;15(1):253-60.
4. Sofue T, Nakagawa N, Kanda E, Nagasu H, Matsushita K, Nangaku M ,et al. Prevalence of anemia in patients with chronic kidney disease in Japan: A nationwide, cross-sectional cohort study using data from the Japan Chronic Kidney Disease Database (J-CKD-DB). PloS one. 2020;15(7):e0236132.
5. Drüeke TB, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide) line (s). Kidney international. 2012;82(9):952-60.
6. Kiss Z, Elliott S, Jedynasty K, Tesar V, Szegedi J. Discovery and basic pharmacology of erythropoiesis-stimulating agents (ESAs), including the hyperglycosylated ESA, darbepoetin alfa: an update of the rationale and clinical impact. European journal of clinical pharmacology. 2010;66(4):331-40.
7. Spinowitz B, Pecoits-Filho R, Winkelmayer WC, Pergola PE, Rochette S, Thompson-Leduc P ,et al. Economic and quality of life burden of anemia on patients with CKD on dialysis: a systematic review. Journal of Medical Economics. 2019;22(6):593-604.
8. Rodelo Ceballos J, Páez-Canro C, Urrútia G, Yomayusa González N, Ariza García A, Loza Munárriz C ,et al. Early versus delayed erythropoietin for the anaemia of end-stage kidney disease. 2015;
9. Elliott S, Pham E, Macdougall IC. Erythropoietins: a common mechanism of action. Experimental hematology. 2008;36(12):1573-84.
10. Babitt JL, Lin HY. Mechanisms of anemia in CKD. Journal of the American Society of Nephrology. 2012;23(10):1631-4.
11. Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. Journal of Biological Chemistry. 1977;252(15):5558-64.

12. Kalantar-Zadeh K. History of erythropoiesis-stimulating agents, the development of biosimilars, and the future of anemia treatment in nephrology. American journal of nephrology. 2017;45(3):235-47.
13. Del Vecchio L, Locatelli F. New treatment approaches in chronic kidney disease-associated anaemia. Expert opinion on biological therapy. 2014;14(5):687-96.
14. Sanghani NS, Haase VH. HIF-prolyl hydroxylase inhibitors in renal anemia: current clinical experience. Advances in chronic kidney disease. 2019;26(4):253.
15. Hasegawa S, Tanaka T, Nangaku M. Hypoxia-inducible factor stabilizers for treating anemia of chronic kidney disease. Current opinion in nephrology and hypertension. 2018;27(5):331-8.
16. Nakano Y, Imagawa S, Matsumoto K, Stockmann C, Obara N, Suzuki N ,et al. Oral administration of K-11706 inhibits GATA binding activity, enhances hypoxia-inducible factor 1 binding activity, and restores indicators in an in vivo mouse model of anemia of chronic disease. Blood. 2004;104(13):4300-7.
17. Nangaku M, Fliser D. Erythropoiesis-stimulating agents: past and future. Elsevier; 2007.
18. Bartnicki P, Kowalczyk M, Rysz J. The influence of the pleiotropic action of erythropoietin and its derivatives on nephroprotection. Medical science monitor: international medical journal of experimental and clinical research. 2013;19(599.
19. Brines ML, Ghezzi P, Keenan S, Agnello D, De Lanerolle NC, Cerami C ,et al. Erythropoietin crosses the blood–brain barrier to protect against experimental brain injury. Proceedings of the National Academy of Sciences. 2000;97(19):10526-31.
20. Macdougall IC. Novel erythropoiesis-stimulating agents: a new era in anemia management. Clinical Journal of the American Society of Nephrology. 2008;3(1):200-7.
21. Elliott S, Lorenzini T, Asher S, Aoki K, Brankow D, Buck L ,et al. Enhancement of therapeutic protein in vivo activities through glycoengineering. Nature biotechnology. 2003;21(4):414-21.
22. Macdougall IC, Robson R, Opatrna S, Liogier X, Pannier A, Jordan P ,et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (CERA) in patients with chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2006;1(6):1211-5.
23. Topf JM. CERA: third-generation erythropoiesis-stimulating agent. Expert opinion on pharmacotherapy. 2008;9(5):839-49.

24. CDSCO. Centers for Disease Control and Prevention. (2012) National Health and Nutrition Examination Survey Analytic and Reporting Guidelines. http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/analytical_guidelines.htm. Last accessed on 03-11-2020. 2012;
25. Anaemia ID, Assessment P. Control: A Guide for Programme Managers. World Health Organisation: Geneva, Switzerland. 2001;
26. Group CES. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ: British Medical Journal. 1990;573-8.
27. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM ,et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. New England Journal of Medicine. 1998;339(9):584-90.
28. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M ,et al. Correction of anemia with epoetin alfa in chronic kidney disease. New England Journal of Medicine. 2006;355(20):2085-98.
29. Drüeke TB, Locatelli F, Clyne N, Eckardt K-U, Macdougall IC, Tsakiris D ,et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. New England Journal of Medicine. 2006;355(20):2071-84.
30. Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, De Zeeuw D, Eckardt K-U ,et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. New England Journal of Medicine. 2009;361(21):2019-32.
31. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV ,et al. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. Journal of the American Society of Nephrology. 2007;18(3):975-84.
32. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA ,et al. Intravenous iron in patients undergoing maintenance hemodialysis. New England Journal of Medicine. 2019;380(5):447-58.
33. Chen S-Y, Cressman S, Mao F, Shao H, Low DW, Beilan HS ,et al. Synthetic erythropoietic proteins: tuning biological performance by site-specific polymer attachment. Chemistry & biology. 2005;12(3):371-83.
34. Biggar P, Kim G-H. Treatment of renal anemia: Erythropoiesis stimulating agents and beyond.

Kidney Research and Clinical Practice. 2017;36(3):209.

35. NCT02044653. Study to evaluate the efficacy and safety of GX-E2 in the anemic patient diagnosed with chronic kidney disease (CKD) 2014. Available at: https://clinicaltrials.gov/ct2/show/NCT02044653.
36. (EMA) EMA. Withdrawal Assessment report for Omontys (INN name: Peginesatide) by Europeon Medicine Agency, EMA/419554/2013. Committee for Medicinal Products for Human Use (CHMP). 2013;
37. Bennett CL, Jacob S, Hymes J, Usvyat LA, Maddux FW. Anaphylaxis and hypotension after administration of peginesatide. The New England journal of medicine. 2014;370(21):2055.
38. Scully MS, Ort TA, James IE, Bugelski PJ, Makropoulos DA, Deutsch HA ,et al. A novel EPO receptor agonist improves glucose tolerance via glucose uptake in skeletal muscle in a mouse model of diabetes. Experimental Diabetes Research. 2011;2011.
39. Jelkmann W. Erythropoiesis stimulating agents and techniques: a challenge for doping analysts. Current medicinal chemistry. 2009;16(10):1236-47.
40. Li Z-L, Tu Y, Liu B-C. Treatment of Renal Anemia with Roxadustat: Advantages and Achievement. Kidney Diseases. 2020;6(2):65-73.
41. Breda L, Rivella S. Modulators of erythropoiesis: emerging therapies for hemoglobinopathies and disorders of red cell production. Hematology/Oncology Clinics. 2014;28(2):375-86
42. Zhong H LW, Lin S, Zhou T. Current and Emerging Drugs in the Treatment of Anemia in Patients with Chronic Kidney Disease . Available from: www.cspsCanada.org. J Pharm Pharm Sci. 2020;23(
43. Besarab A, Provenzano R, Hertel J, Zabaneh R, Klaus SJ, Lee T ,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. Nephrology Dialysis Transplantation. 2015;30(10):1665-73.
44. Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. Kidney international. 2016;90(5):1115-22.
45. Akizawa T, Tsubakihara Y, Nangaku M, Endo Y, Nakajima H, Kohno T ,et al. Effects of daprodustat, a novel hypoxia-inducible factor prolyl hydroxylase inhibitor on anemia management in Japanese hemodialysis subjects. American Journal of Nephrology. 2017;45(2):127-35.

46. Lippin Y, Dranitzki-Elhalel M, Brill-Almon E, Mei-Zahav C, Mizrachi S, Liberman Y ,et al. Human erythropoietin gene therapy for patients with chronic renal failure. Blood. 2005;106(7):2280-6.
47. Fattori E, Cappelletti M, Zampaglione I, Mennuni C, Calvaruso F, Arcuri M ,et al. Gene electro-transfer of an improved erythropoietin plasmid in mice and non-human primates. The Journal of Gene Medicine: A cross-disciplinary journal for research on the science of gene transfer and its clinical applications. 2005;7(2):228-36.
48. Rivera VM, Gao G-p, Grant RL, Schnell MA, Zoltick PW, Rozamus LW ,et al. Long-term pharmacologically regulated expression of erythropoietin in primates following AAV-mediated gene transfer. Blood. 2005;105(4):1424-30.
49. Kakeda M HM, Nagata K, Kuroiwa Y, Kakitani M, Katoh M, Oshimura M, et al. Human artificial chromosome (HAC) vector provides long-term therapeutic transgene expression in normal human primary fibroblasts. Gene Therapy. 2005;12(852-6.
50. Epogen. Product Information leafle (Amgen). Available on URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125164s078lbl.pdf. Last accessed on 2 Feb 2021. 2018.
51. Recorman (Epoeitin Beta). Product Information Leaflet by Roche . Available on URL: https://www1.ndmctsgh.edu.tw/pharm/pic/medinsert/005REC03E.pdf. Last accessed on 02 Feb 2021. 2012.
52. Aranesp (darbepoetin alfa) . Product information leaflet by Amgen. Available on URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdf . Last accessed on 02 Feb 2021. 2011.
53. MIRCERA (methoxy polyethylene glycol-epoetin beta) injection Product information leaflet by Vifor Pharma. Avaialble on URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125164s078lbl.pdf. Last accessed on 02 Feb 2021. 2018.
54. Fliser D ,et al. Early low-dose erythropoiesis-stimulating agent therapy and progression of moderate chronic kidney disease: a randomized, placebo-controlled trial. Nephrology Dialysis Transplantation. 2017;32(2):279-87.