# EMERGING THERAPIES OF ANEMIA OF CHRONIC KIDNEY DISEASE

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**Summary**

***Anaemia appears in CKD in all stages. Erythropoietin deficiency and both absolute and relative deficiency of iron are the major causes of this type of anaemia.Erythropoietin deficiency occurs due to decreased renal mass and iron deficiency occurs due to either absolute lack of available iron or increased demand of iron by bone marrow when stimulated by erythropoietin. Correction of anaemia in CKD demands either replacement of erythropoietin and or more iron intake. Currently available Erythropoietins are parenteral preparations. They have though negligible but some adverse effects like pure red cell aplasia. Scientist were in search of erythropoietin or erythropoietin like substances which can be given orally and without side effect like pure red cell aplasia.This is the basis of discovery of two newer erythropoietin stimulating agents .These are erythropoietin mimetic peptide (peginesatide) given parenterally and hypoxia inducible factor stabilizer given orally. This review will focus on these two emergent therapies of anaemia in chronic kidney disease which are still going through phase II or phase III trial.***

**Key words**

Erythropoietin; erythropoietin mimetic peptide; hypoxia inducible factor

## Introduction

Anemia is common at varying degrees of chronic kidney disease (CKD) especially at stages 4 and 5. About 60-80% of CKD stage 4 and 5 have some degree of anemia [1] . According to USRDS (United States Renal Data Syatem) about 50% of patients undergoing dialysis have haemoglobin level below 10g/dl. Causes of anemia in CKD are frequently multifactorial out of which iron deficiency and relative deficiency of erythropoietin (EPO) constitutes the major bulk.

Red Blood Cell (RBC) production starts with EPO stimulation of precursors of RBC which ultimately differentiate into proerythrocytes. Proerythrocytes and its next stage, erythroblasts consume iron and ultimately matures into matured RBC (Fig 1)[2]. the whole process from progenitor cell to mature RBC takes an average time of 1-3 weeks.

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Erythropoietin binds to a receptor on this progenitor cell and prevents their apoptosis through inhibiting Fas Ag.(Fig 1).90% of circulating EPO is secreted from peritubular fibroblasts within the renal cortex[2].

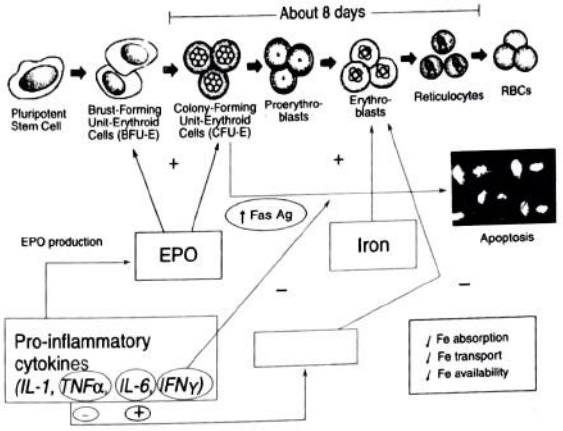


**Fig 1:** Erythropoietin in CKD. Ag,antigen;EPO, erythropoietin; Fe, iron;IFN, interferon, IL,interleukin; RBCs,red blood cells;TNF, tumour necrosis factor

The stimulation to EPO release is decreased oxygen delivery due to anemia or hypoxaemia. EPO gene expression is regulated by binding of hypoxia inducible factor (HIF), a transcription factor, to the hypoxia response element (HRE) at the loci of the EPO gene on chromosome 7q 22 (Fig 2)[3,4].

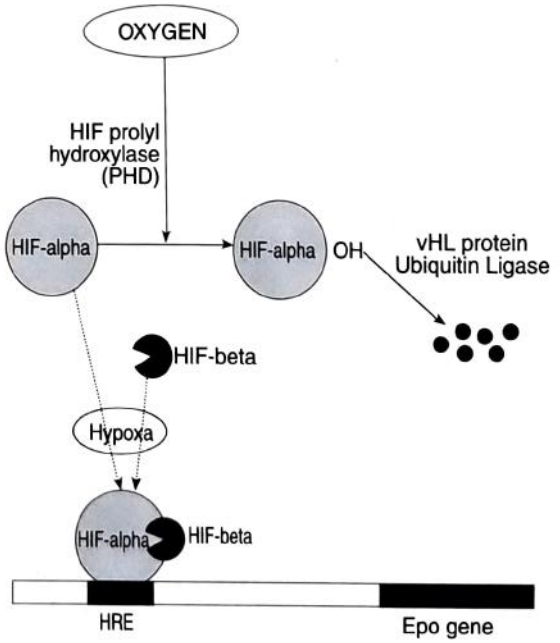


**Fig 2 :** Oxygen sensing and regulation of the erythropoietin gene. HIF, hypoxia inducible factor; HRE, Hypoxia response element;vHL, von hippal landau. Von hippal landau protein ubiquitin ligasedegrades HIF-alpha-OH into proteomes

Degradation of HIF is inhibited in the presence of decreased $O_2$ delivery due to anemia. But in case of anemia in Chronic kidney disease EPO production is not increased due to loss of functional renal mass. Anemia of CKD is a bit different from other anemia of chronic disease. In most of the cases of anemia of chronic disease hepcidin play an important role by preventing iron (Fe) absorption, Fe transport & Fe availability to bone marrow (Fig1). In patient with CKD when inflammation and infection are present hepcidin is probably the basis of anemia. But without inflammation or infection the cause of anemia in CKD is erythropoietin deficiency. The current management of anemia in CKD is replacement by recombinant human EPO which are called enythropoiesis stimulating agents (ESAs). Currently available ESAs are short acting ESAs like epoetins α, and and long acting epoetins, Derbopoetin α . All these epoetins may cause pure red cell aplasia by erythropoietin antibody [5]. In CKD who are anephric (End stage renal disease, ESRD) liver mediated erythropoietin synthesis continues. So if we would get erythropoietin stimulating agents which either do not cause Pure Red Cell Aplasia (PRCA) or we would get HIF stabilizers which will continue erythropoietin production independent of presence or absence of $O_2$ availability & or if oral ESAs are available it will obviously increase patient's compliance. It will open a new dimension in the management of anemia of CKD.

Recently newer ESAs are in the development process, they are erythropoietin mimetic peptide, peginesatide & HIF stabilizer, FG – 4592 .Peginesatide is long acting with a half life of about 60-70 hours, can be given Intravenous (IV) or subcutaneous & does not produce PRCA[6]. HIF stabilizers are oral inhibitors of prolyl hydroxylases which lead to stabilization of HIF, so increase endogenous erythropoietin production in ESRD patients, and also downregulates hepcidin synthesis[7]. This review is aimed at to focus on these newer ESAs.

**Review criteria**

A literature search was performed in PubMed using the search words "ESAs, biosimilar ESAs, HIF stabilizer, hepcidin, erythropoiesis, erythropoietin mimetic." Internet resources accessed were National Kidney Federation Dialysis Outcomes Quality Initiative (NKF-KDOQI) & http: // www.esmpo werthepatient.com/red-blood-cells.htm. and http:// bit.ly/Peginesatide

**Erythropoiesis**

EPO is the main regulator of erythropoiesis. 90% of erythropoietin is made in the kidneys and 10% in the liver. Erythropoietin synthesis is increased in response to lack of oxygen. It is a 165-amino-acid glycoprotein. Its function is one of anti- apoptosis, it inhibits program cell death of BFU- E(Burst Forming Unit – Erythroid cells)[8].

For erythropoiesis to continue iron is required. Insufficient availability of iron is the most common cause of inadequate response of EPO therapy. Iron availability to bone marrow depends upon hepcidin, a peptide produced by the liver. Hepcidin interferes with RBC production by decreasing iron availability (Fig 3) [9]. Chronic inflammation produces cytokines which in one hand decreases EPO production and at other hand increases hepcidin production (Fig 1).

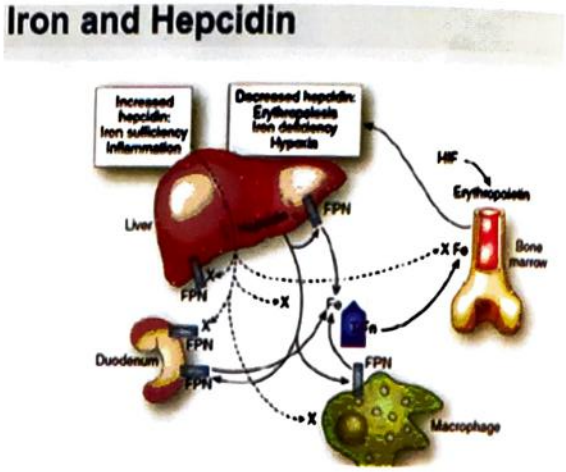


**Fig 3 :** Role of Hepcidin. FPN, Ferro portin; TrFn, transferrin; Fe, iron; HIF, hypoxia inducible factor ; x, inhibits

EPO binds to a receptor on BFU-E and CFLU-E cells, makes conformational change of the receptor. The receptor is phosphorylated and activated along with JAK2 kinases for which intracellular enzyme cascade activation occurs leading to upregulation of anti-apoptic proteins, the final result of which is erythropoiesis (Fig 4)[10].

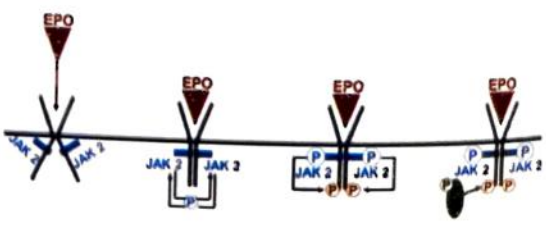


**Fig 4 :** Mechanism of EPO at receptor level. JAK2, janus family tyrosine protein kinase 2

For satisfactory erythropoiesis EPO needs constant and adequate supply of iron. Source of iron is either absorbed iron in the gastrointestinal tract or old RBC phagocytosed within macrophages. From each of the above sources iron is released by a specific cell membrane transporter called ferroportin which carries this iron into the circulation to be transported to bone marrow by transferrin. In all cases of chronic disease like CKD inflammation occurs which produces cytokines like IL-6 and IL-1 [11]. These cytokines increase the production of hepcidin which binds ferroportin and degrade it. So iron can't be available to transferrin (Fig 3).

Newer ESAs target either HIF or hepcidin. Another aim of EPO therapy is to discover erythropoietin mimetic peptide with longer half life and which will not produce anti EPO antibody so that PRCA can't occur. In 1993 EPO-α (half-life 8.5hours) was approved and at that time there was challenge to find long acting EPO which leads to discovery of Derbopoetin-α (half-life 25.3hours) in 2001. In 2007 another long acting EPO with half-life about 130hours called C.E.R.A (continuous erythropoietin activator) was approved. The newer challange is not aimed at not to supplant short acting EPO with long acting EPO, rather to discover ESA with better effectivity, patient's friendly (oral form), safe and with newer mode of pharmacological action[12].

**Novel ESAs**

Newer ESS in development include

1) Generic or biosimilar ESAs (eg. epoetin-γ) : same as other short acting EPOs.

2) Erythropoietin–mimetic peptide (Peginesatide)[13]

3) Oral agents like prolyl hydroxylase inhibitor or HIF stabilizer (FG-4592)

**Peginesatide**

It is a synthetic peptide-based ESA with molecular structure unrelated to erythropoietin with half-life of 60-70 hours and can be introduced in both IV and subcutaneous routes[6].

It binds to EPO receptor and activates it just as like as EPO. It is given once monthly. The side effect profile (stroke, hypertension, dialysis access thrombosis, heart failure, deep venous thrombosis, heart failure and increased risk of cancer associated death) is comparable to that of other ESAs[14,15].

The main advantage is that it does not produce erythropoietin antibody –mediated pure red cell aplasia[16] .This drug just completed phase III and was approved by FDA advisory board to be used in Dialysis CKD patients. This trial enrolled 2500 patients and were evaluated both in dialysis and non-dialysis patients. It was found that in case of epoetin hypo responsive patients instead of 4 fold increasing epoetin dose peginesatide requires 2 fold increment of the dose (dose sparing effect) Usual dose of peginesatide is about 5-6 mg./month in American population and only 3.5mg/month in European population [17]. So peginesatide may be one of the choices in case of EPO hypo responsive patients who requires high dose of EPO.

HIF stabilizers[18] : These prolyl hydroxylase inhibitors stabilize HIF-α subunit and help in heterodimerization with the subunit thus forming active transcription factor HIF (Fig 2). HIF is key regulator of erythropoietin gene transcription and so erythropoietin synthesis proceeds uninterruptedly. In hypoxia prolyl hydroxylases are inhibited themselves allowing HIF to be stabilized.

Interestingly even in ESRD patients where EPO is perhaps produced only in liver, if HIF stabilizer is used it can continue the sustained production of EPO. These stabilizers also down regulates hepcidin synthesis leading to improved iron availability to bone marrow and thereby reducing the need of supplemental iron to support erythropoiesis. The agent in trial is named FG-4592 and it is a phase 2b drug [19,20].It is on oral agent compared with a parenteral administered agent. It can be given in nondialysis CKD patients and CKD patients on peritoneal dialysis. It decreases mean hepcidin by 36% and thus improves anaemia without inducing inflammation. These drugs really improve compliant by cutting extra visits for parenteral EPO in nondialysis and CKD patients.

**Conclusion**

Anaemia therapy in CKD patients need to be individualized both with respect to haemoglobin target range as well as regarding safe medication. Besides benefit of ESA treatment for the individual patient should be judged considering route of administration and dosing frequency. Yet peginesatide and HIF stabilizers opened an exciting and promising chapter in management of anaemia in CKD more effectively hitting through different mechanisms of action [21]. This is really a paradigm shift in how we should currently treat anaemia of CKD.

**Disclosure**

All the authors declared no competing interestes.

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