CHAPTER

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Management of Anemia in Chronic Kidney Disease: Revisited

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INTRODUCTION

Chronic Kidney Disease (CKD) leads to a wide range of systemic derangements. Anemia is a common complication among CKD patients.[1] Anemia begins to manifest when GFR falls below 60ml/min/1.73 m^2 (Stage III).[2] In our previous review published in 1999,[3] we did an effort to explain the basic pathophysiology and elaborate various treatment modalities for treatment of anemia. Management of anemia in these patients has undergone a significant evolution resulting in wide variety of treatment protocols. Hence, this chapter is under taken to compare various modalities available for the management of anemia such as EPO, Iron therapy (oral versus injectable) and briefly elaborate the newer therapies with their rationale.

EPIDEMIOLOGY

The prevalence of CKD in India is escalating and is being presumed that CKD represents a major public health problem in India, at least in urban cities. However, in view of an overburdened health setup and absence of national registries, the true magnitude of CKD has largely been controversial.[4] There is a progressive increase in the incidence and severity of anemia with declining renal function. Anemia is twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increases with each stage of CKD, from 8.4% in stage 1, followed by 14.6% in stage 2, 26.4% in stages 3-4 and 53.4% in stage 5. In India, it has been recently estimated that incidence of CKD is 785 per million population,[5] with prevalence of 78% in Delhi and 16% in Chennai. A cross-sectional registry involving 52,273 CKD patients showed that about 85% patients reported to the nephrologist at Stage-3 and beyond.

Table 1: Mechanisms of anemia in CKD

Mechanism	Outcome
Renal Impairment	Decreased erythropoietin production
Uremia	Bone marrow suppression Decreased RBC life span
Nutritional deficiency	Deficiency of Vitamin B_{12}, folate or Iron
Secondary Hyperparathyroidism	Fibrosis of bone marrow Failure of erythropoiesis
Chronic Inflammation Increased inflammatory cytokines Increased hepcidin	Abnormal iron homeostasis and erythroid progenitor proliferation
Aluminium Toxicity	
Hypothyroidism	Reduced GFR Increased peripheral vascular resistance

PATHOPHYSIOLOGY

Anemia in CKD is typically normocytic, normochromic and hypo-proliferative. When a patient develops CKD, anemia occurs as a result of any one or the combinations of multiple factors (Table 1).

ROLE OF ERYTHROPOIETIN (EPO)

EPO is produced by cells of Proximal Convoluted Tubule (PCT). The role of erythropoietin is to control red blood cell production by regulating the differentiation and proliferation of erythroid progenitor cells in the bone marrow. In CKD patients, EPO levels are normal to low with inappropriate erythropoiesis resulting in decreased hemoglobin levels, as found in non-renal anemias. Studies elucidating the regulation of EPO expression led to the identification of the hypoxia inducible factor-hypoxia responsive element system (Figure 1).

ROLE OF IRON DEFICIENCY

1. Absolute iron deficiency: It is often present in patients initiating hemo-dialysis and replenishing iron stores is crucial in the management of their anemia. It develops in CKD patients due to multiple factors including decrease in intestinal absorption of iron, occult gastrointestinal bleeding

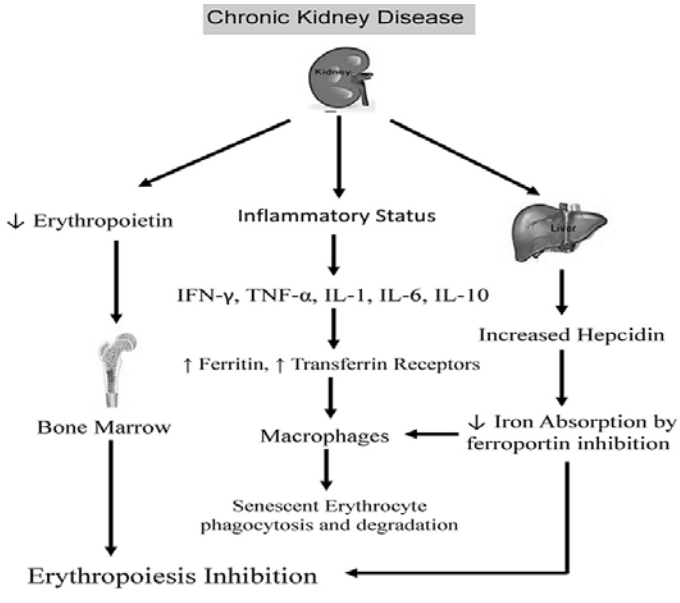

Fig. 1: Pathophysiology of anemia in CKD

due to platelet malfunction, increased incidence of arterio-venous malformation and blood loss from repetitive laboratory testing. Furthermore, the initiation of ESA treatment requires large amounts of stored iron[6] (Figure 1).

2. Functional iron deficiency (ineffective erythropoiesis): It is characterized by the presence of adequate iron stores but a slow iron mobilization rate into the site of erythropoiesis when ESA is started. In other terms, iron transporters fail to keep up with the increased rate of erythropoiesis[6] (Figure 1).
3. Iron deficiency in CKD patients on dialysis: In addition to the usual causes of iron deficiency, patients on hemo-dialysis experience routine iron loss due to the dialysis treatment, frequent blood draws for laboratory testing, surgical procedures, accidental blood loss (vascular access) and gastrointestinal blood loss. As a consequence, patients on hemo-dialysis lose approximately 1000 mg of iron per year.[7]

ROLE OF INFLAMMATION AND HEPCIDIN

It is well known that CKD is a low-grade chronic inflammatory state due to imbalance of pro-oxidants and antioxidants.[8] Hepcidin is a small peptide produced primarily by hepatocytes. It has antimicrobial properties and regulates iron absorption and metabolism. Hepcidin expression is up regulated by variety of stimuli including inflammation and iron overload. The decreased renal clearance of hepcidin due to failing kidneys further increases its serum level. This increase in hepcidin levels contributes to EPO resistance and iron restriction. Elevated serum hepcidin levels contribute to the dis-regulation of iron homeostasis in CKD patients (Figure 1).

TREATMENT OF ANEMIA IN CKD

Anemia in CKD is a multifactorial disorder. Management of these patients involves dietary improvement, prevention and treatment of blood loss and pharmacological measures in form of iron supplements, ESA etc.

1. Dietary management: Dietary lack of iron with impaired iron absorption and utilization is important nutritional factor which contribute to high prevalence of anemia in CKD patients. Rich sources of heme iron in the diet include lean meat, red meat and sea food, whereas sources of non-heme iron are nuts, beans, vegetables and fortified grain products. Milk and milk products, tannins and caffeine inhibit iron absorption and should be avoided with iron rich sources of food. Vitamin C can improve iron absorption and can be administered concomitantly with iron rich foods.
2. Chronic blood loss: Elderly population with CKD is at a higher risk of gastritis and peptic ulcers leading to chronic gastrointestinal blood loss and malena. Long term use of NSAIDs can aggravate GI bleed and deteriorate renal function. Hence, presence of malena warrants Upper GI endoscopy and further intervention as necessitated.

   Anemia in itself is an independent clinical identity. Its occurrence in CKD patient need not always imply their correlation. Hence, other causes of anemia like Vitamin B_{12}, folic acid deficiency, worm infestations, chronic infection, malignancy or hemolytic diseases should be addressed.
3. Erythropoiesis Stimulating Agents (ESA): Anemia management was revolutionized in the late 1980s with the introduction of recombinant human erythropoietin. EPO and ESAs greatly benefited patients by improving their debilitating

Table 2: Recommended dose of ESA

ESA	Dosage recommendation	Route	Remarks	Side Effects
First Generation				
Epoetin-alfa or epoetin-beta	50-100 IU/kg thrice a week.	(SC) or IV	• EPO alfa-serum albumin • EPO beta- polysorbate 20, along with urea, calcium chloride and five amino acids	More common: Blurred vision, Body aches, breathlessness, Dizziness, Fever. Less common: Bladder pain, Difficult, burning, or painful urination.
Second Generation				
Darbepoetin-alfa	0.45 mcg/kg once weekly	(SC) or IV	• 2 amino acid substitutions • greater metabolic stability • increases the elimination half-life	Increases the risk of cardiovascular problems.
	0.75 mcg/kg once every 2 weeks	SC		
Third Generation				
CERA	0.6 mg/kg once every 2 weeks	SC - CKD ND IV - CKD 5D	• additional large polymer chain. • half-life is approximately 130 hours.	Hypertension, Diarrhea, Headache and Upper Respiratory Tract Infection.
	1.2 mg/kg once every 4 weeks	SC - CKD ND		

symptoms and freeing them from dependence on blood transfusions with their associated complications (secondary iron overload, infections and sensitization impeding transplantation). After diagnosing anemia in a patient with CKD all correctable causes should be treated before considering ESA therapy. Above all, this recommendation is based on the observation that iron supplementation given to CKD patients with proven iron deficiency or impaired iron availability generally leads to an increase in Hemoglobin.[9] Commonly used ESA agents are Epoetin-alfa, Epoetin-beta, Derbepoetin-alfa and CERA as shown in Table 2.

Although relative EPO deficiency may contribute to the anemia of CKD, it is not the sole cause. Indeed, anemia of CKD is resistant to ESAs in approximately 10-20% of patients.[10] It seems likely that supra-physiologic doses of ESAs, especially at very high doses or in patients resistant to treatment, have off-target effects in other tissues. These findings have renewed interest in understanding the molecular mechanisms of anemia in CKD, with the hope of developing new therapies that more closely target the underlying pathophysiology of low hemoglobin.

RESISTANCE OF EPO

'EPO resistance' has been introduced to define the patients who fail to attain the target despite a higher than usual dose of ESA or who continuously need this higher dose in order to maintain it. Although there is no consensus about the definition for EPO resistance, the evaluation of resistance is recommended if there is an increase ≥25% in erythropoietin dose or <1 mg/dL gain in hemoglobin levels after 2–4 weeks of treatment.

Causes of inadequate response to EPO includes Hemolysis, Aluminium toxicity, Osteitis fibrosis (Secondary Hyperparathyroidism), Hemoglobinpathies (Thalessemia, sickle cell anemia), Multiple myeloma, Use of ACE-1/ARB agents, Low effectiveness of molecule. In the absence of detectable abnormalities of any one of the conditions - marrow examination is indicated including hematologist reference.

4. Iron Supplementation: Iron deficiency is a commonly encountered reversible cause of CKD related anemia and ESA hypo-responsiveness. Correction of iron deficiency with therapeutic supplementation can reduce the severity of anemia in CKD patients. It is important to diagnose iron deficiency and its cause, because its treatment can readily correct the associated anemia (Table 3). Iron administration is appropriate in patients who are likely to have a clinically meaningful erythropoietic response, when bone marrow iron stores are depleted.

Oral Iron Supplementation

Oral iron is the simplest and most physiological means of administering iron. It is also by far the cheapest therapy in terms of drug acquisition costs. Unfortunately, in CKD settings, it is often ineffective. This was recognized by nephrologists nearly 20 years ago, even prior to the discovery of hepcidin. It is, however, now very apparent that up regulation of hepcidin resulting from inflammation is the explanation for this clinical finding at a molecular level.[11] Thus, although many patients may religiously take elemental iron per day via iron tablets or syrup, often negligible or no iron is absorbed. The bioavailability of oral iron sources has been a major concern for the treatment of anemia. Iron is absorbed in the intestine in a highly regulated metabolic cycle.

Table 3: Current Guidelines for Anemia treatment

Guidelines	Hemoglobin Level	ESA Recommendation	Iron Recommendation
KDIGO (2012)	Hb<13 g/dL (men >15 yr); Hb<12 g/dL (women >15 yr)	Initiate ESA therapy in those with Hb<10 g/dL (rule out all other correctable causes of anemia)	1-3 months trial of oral iron or iv iron, if TSAT <30% and ferritin<500 mg/L or ESA therapy is to be avoided or decreased (if already on ESA therapy).
KDOQI (2015)	Hb<13.5 g/dL (men); Hb<12.0 g/dL (women)	Initial ESA dose and further adjustments are determined by the patient's baseline Hb level, target Hb level, rate of increase in Hb level and clinical response.	Oral or iv iron administered to maintain ferritin>100 mg/L and TSAT>20% during ESA treatment.
NICE (2015)	Hb<11.0 g/dL or symptomatic patient(tiredness, shortness of breath, and palpitations)	ESA therapy should not be initiated in the presence of absolute iron deficiency without also managing the iron deficiency; ESAs not recommended in the presence of co-morbidities or a prognosis that is likely to negate the benefits of correcting the anemia	Oral or iv iron to maintain hypochromic RBC, reticulocyte or TSAT and ferritin targets.
ERBP (2004)	Hb<13.5 g/dL (men ≤70 yr); Hb<13.2 g/dL (men >70 yr); Hb<12.0 g/dL (women)	In low-risk patients or those in whom a clear benefit in quality of life can be foreseen, ESA therapy can be considered at Hb<12.0 g/dL; in high-risk patients, ESA therapy should be initiated at Hb values between 9.0- 10.0 g/dL.	Oral or iv iron if TSAT<20% and ferritin<100 mg/L or if Hb increases without ESA therapy, TSAT<25%, and ferritin<200 mg/L; in patients on ESA therapy in whom increase in Hb or decrease in ESA dose is desired.

Dosage regimen

Oral iron therapy is usually best carried out in 3-4 divided doses per day, with a total of 150-200 mg of elemental iron for adults or 6 mg iron/kg body weight in children. It has also been suggested that attempts be made to individualize treatment and get patients more involved in determining the most tolerable daily iron dose, its formulation and its schedule[12] (Table 4).

Oral iron therapy should not be considered for patients on hemo-dialysis receiving ESA.

Intravenous Iron supplementation

The treatment of choice for repleting iron stores in hemo-dialysis patients is intravenous (IV) iron therapy. Although research shows IV iron is more efficacious for restoring iron status compared to oral iron supplements, it should be used judiciously due to risk of adverse events.[13] Three intravenous iron products are commercially available: Iron dextrose, Iron sucrose and Ferric carboxy-maltose (Table 5). Intravenous iron therapy is now the standard modality of iron supplementation in hemodialysis patients, but its role in pre-dialysis chronic renal failure patients is less well established. We carried out a study in 2002 to evaluate the efficacy of IV iron dextran administered as total dose infusion in pre-dialysis patients. It showed that IV iron dextran is an effective method to replenish iron stores in pre-dialysis patients.[14]

However, in some cases, the adverse effects of iron are unrecognized because of the non-specific nature of the reactions and the overlap between iron-related adverse effects and dialysis-related adverse effects, such as dizziness, dyspnea, cramps, pruritus, nausea, constipation, diarrhea and hypotension (Table 6).

At present times, it is clear that intravenous iron is generally superior over oral iron. The only exception to this is that some patients with early CKD may derive some benefits from oral iron albeit with more side effects. The greater efficacy of intravenous is almost certainly a result of limiting action of hepcidin on absorption of iron from the gut in CKD patients.

Various randomized studies on ND-CKD patients have shown a significantly greater erythropoietic response in the intravenous iron treatment groups as compared to oral iron.[15-16] Whereas, in ESA-treated hemodialysis and peritoneal dialysis patients with anemia several randomized trials have shown greater efficacy and safety of intravenous iron preparation.[17-18] A question of particular interest is whether iron supplementation alone can produce an adequate increase in hemoglobin without ESA therapy, a situation that would be desirable both in terms of cost and the avoidance of ESA-related side effects.

Schematic representation of treatment of anemia in CKD is illustrated in figure 2.

5. Vitamin B12 and Folic Acid Supplements: Vitamin B12 and Folate deficiency has been implicated as a contributory factor in renal anemia and hypo-responsiveness to EPO treatment. Deficiency of Vitamin B12 and folic acid causes megaloblastic anemia with neural symptoms. Although folate loss through dialysis is greater than by urinary excretion, these losses are easily balanced by a normal mixed diet containing 60 g protein/day. Thus, unless patients show significant folate depletion, additional supplementation of folic acid does not appear to have a beneficial effect on erythropoiesis. High-dose folate therapy (5-15 mg/day) has been shown to reduce plasma homocysteine levels by 25-30% and appears to be

Table 4: Commonly used oral iron supplements

S. No.	Compound	Dose	Iron Content
1	Ferrous sulphate	200 mg	20-32% iron
2	Ferrous gluconate	300 mg	12 % elemental iron
3	Ferrous fumarate	200 mg	33% iron
4	Colloidal ferric hydroxide	200 mg	50% iron

Table 5: Characteristics of intravenous iron supplements

Characteristics	Ideal	Iron Sucrose	Dextran	Ferric carboxy-maltose
pH	Neutral	High	Neutral	Neutral
Osmolality	Isotonic	High	Isotonic	Isotonic
Antigenicity	Low	Low	High (risk of anaphylactic reactions)	Low
Time required for administration	Short	Long (3.5 Hrs for 7 mg Fe/kg BW)	Long (6 Hrs for 20 mg Fe/kg BW)	Short
Maximum Dose (mg Iron)	High	500 mg/week	20 mg Fe/kg BW	1000 mg/week
Half Life	4-24 Hrs	6 Hrs	3-4 days	16 Hrs
Administration		As a 2-minute bolus or as a short infusion in doses up to 300 mg, When higher doses are administered, even with infusions lasting 2 hours, hypotension, nausea.	As an IV bolus or TDI, infusions of 1g over 1hour. May require weekly or more frequent visits, in short infusions.	As an infusion of 500-1500 mg in 15 minutes; however, only doses up to 1000 mg are currently approved. No test dose is required.

Table 6: Characteristics of Oral versus Intravenous Iron Therapy

Characteristic	Oral Iron	Intravenous Iron
Intestinal absorption	• Impaired by concomitant food (depending on formulation) • Impaired by concomitant medication (eg, phosphate binders, gastrointestinal medications that reduce acidity) • Iron uptake and export of iron from enterocytes via ferroportin inhibited by elevated hepcidin levels	• Parenteral administration
Iron bioavailability	• May be inadequate during ESA therapy (accelerated erythropoiesis)	• Generally high
Safety	• Gastrointestinal adverse events affect a high proportion eg, constipation, dyspepsia, bloating, nausea, diarrhea, heartburn • Most frequent with ferrous sulfate	• Good safety profile. • Risk of (rare) anaphylaxis with dextran-containing formulations • Risk of (rare) hypersensitivity reactions
Oxidative stress	• Can saturate the iron transport system if the iron is rapidly released (eg, ferrous sulfate), resulting in oxidative stress	• only observed with less stable preparations which can release some more "weaklybound" iron (eg, sodium ferric gluconate, iron sucrose similars) than stable (robust) iron complexes (eg, ferric carboxymaltose, originator iron sucrose)
Compliance	• Pill burden: usually 3 tablets per day • Affected by gastrointestinal intolerance	• Administered by health care professional
Convenience	• Administered at home	• Requires clinic visits
Cost	• Inexpensive	• More expensive per dose but fewer doses required

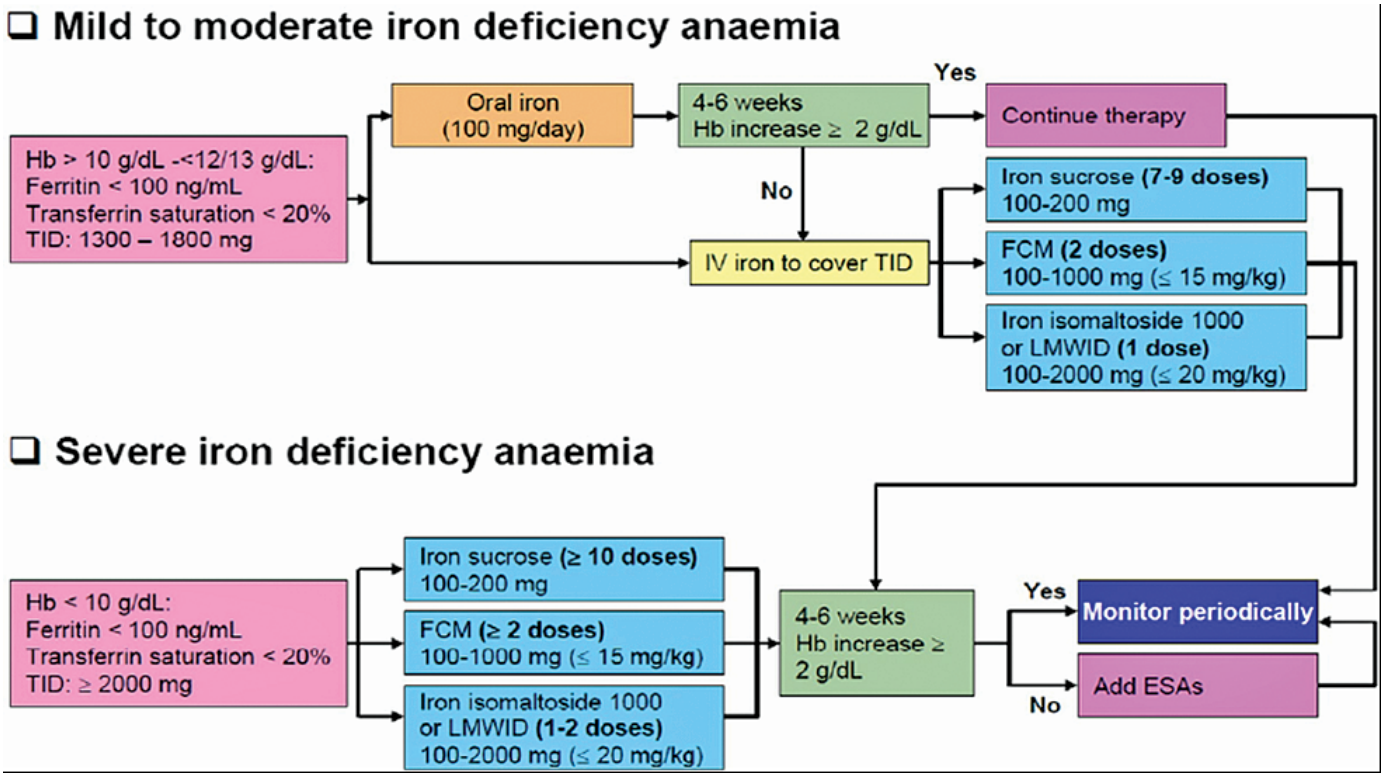

Fig. 2: Treatment and follow-up algorithm in iron deficiency anemia (Abbreviations: TID- Total infusion dose; FCM- ferric carboxymaltose; LMWID- low molecular weight iron dextra,; ESA- erythropoiesis stimulating agent)

well tolerated provided the patient has adequate vitamin B_{12} stores.[19]

6. L-carnitine: L-carnitine is derived from dietary products, mainly red meat and milk. L-carnitine has been shown to improve anemia in uremic patients by stabilizing erythrocyte membrane function or erythropoiesis. This could be a contributing factor of anemia requiring higher dose of EPO. Thus, it has been used therapeutically in dialysis patients with and without concomitant EPO. Most studies have involved hemodialysis patients with IV carnitine administration.[19]

7. Androgens: There is no literature available in ND-CKD patients. Before EPO was available, androgens were used regularly in the treatment of anemia in dialysis patients. Their use for anemia in dialysis patients has declined markedly since EPO was approved. Various studies were carried out which shows that patients receiving androgen in addition to EPO had a significantly greater increase in HCT values with treatment. These data show that androgen therapy significantly augments the action of exogenous EPO such that lower doses of EPO may be sufficient for an adequate hematopoietic response.[20]

8. Ascorbic acid: Ascorbic acid has been studied in the metabolism of iron and anemia management. It was found that ascorbic acid deprivation increased the total non-haem iron concentration in the spleen and reduced it in the liver, and in both organs ferritin was diminished and haemosiderin increased. Repleting the ascorbic acid restored the normal distribution of iron between the two storage compounds. In spleen, the total storage iron concentration returned to control levels within 24 hours. Another important property of ascorbic acid is its ability to increase the availability of storage iron to chelators. Development of resistance to EPO with "functional iron deficiency", can be overcome by giving Vitamin C instead of iron, thus avoiding hemosiderosis.[21]

9. Pentoxifylline (PTX): Pentoxifylline (PTX) is a methyl xanthine derivative, which is approved for use in peripheral vascular disease and may also have anti-inflammatory effects. Benbernou and coworkers[22] studied pentoxifyline and examined its regulatory effect on T-helper cell-derived cytokines in human whole blood and peripheral blood mononuclear cells stimulated with phyto-hemagglutinin and phorbolmyristate acetate. The results showed that PTX at the appropriate concentrations could induce selective suppression of interleukin (IL) -2 and interferon (INF) -gamma, whereas at high concentrations this drug could act as a suppressive agent of both TH1- and TH2-derived cytokines.

10. Statins: Statins (HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. As mentioned above, cytokines play a role in inhibition of erythropoiesis. Statins have been evaluated as an adjuvant to EPO with the thought that they have anti-oxidant and anti-inflammatory properties.

    The data suggest that statin therapy may benefit patients with ESA hypo-responsiveness. This benefit in ESA hypo-responsiveness is associated with the effects of statins on inflammation.These preliminary studies may justify future studies to use statins as an EPO dose reducing adjuvant in patients with inflammation-mediated EPO resistant anemia of CKD.[23]

11. Red cell transfusion: Before the mid-1980s, there were no effective therapies for the treatment of anemia in patients with CKD. Anemic patients were managed primarily by regular blood transfusions performed every 2 to 3 weeks. Red cell transfusion has a limited role in patients with CKD. These are severely anemic patients with hemoglobin less than 5g/dl and hypo-responsive to EPO therapy with chronic blood loss. The benefits of red cell transfusions may outweigh the risks in patients in whom ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance). Repeated transfusions or use of ESA are treatment options for anemia in CKD patients. Risks associated with blood transfusion include transfusion errors, volume overload, hyperkalemia, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), hypothermia, coagulopathy, immunologically-mediated transfusion reactions, including transfusion-related acute lung injury (TRALI) and iron overload, all of which are uncommon.

NEWER THERAPIES

- Soluble ferric pyrophosphate (SFP): It is used for treatment of iron deficiency in hemodialysis patients. SFP delivers iron via dialysate slowly during dialysis treatment and replaces 5-7 mg of iron lost during each treatment to maintain iron balance. SFP enters the blood and immediately binds to apo-transferrin, then goes directly to the bone marrow. Recent studies show that SFP delivers iron and maintains hemoglobin concentration without increasing serum ferritin and reduces ESA usage by 35%. There have also been no reported cases of anaphylaxis.[24]
- Hypoxia-inducible factor prolyl hydroxylase inhibitor (Roxadustat): A novel class of drug is under investigation that selectively inhibits hypoxia inducible factor prolyl hydroxylases (HIFPH) and stabilizes HIF. HIF is a key regulatory protein which stimulates endogenous erythropoietin (EPO) production, increases transferrin production and decreases hepcidin. Increasing HIF activity through inhibition of HIF-PH may provide an alternative treatment for anemia and may protect against damage related to ischemia-reperfusion.[25]
- Erythropoietin mimetic peptides: These are in the

development stages for the treatment of anemia in CKD. One agent in this class, hematide, is in the phase 2 of clinical development. In-vitro studies have shown that hematide binds the erythropoietin receptor, triggers intracellular signaling, and causes cell proliferation and differentiation. In vivo, studies have shown that hematide is well tolerated and stimulates erythropoiesis in multiple species to produce a sustained increase in hemoglobin level.[26]

CONCLUSION

Anemia occurs early in CKD and can begin in some people who have a GFR as high as 60 ml/min/1.73 m2. Though, only a few patients of CKD with anemia receive iron or ESA therapy before their kidney function declines enough to require dialysis. Both currently approved ESAs – Epoetin alfa and derbepoetin alfa can effectively treat the anemia in CKD. Although, controversies regarding target iron levels and in the absence of reliable markers of iron deficiency, but importance of correcting iron deficiency in patients with CKD remains indisputable. Oral iron therapies offer safe and effective options to treat iron deficiency anemia in patients with CKD in a physiologic way. In contrast to iv iron therapies, oral iron treatments require few resources for administration and are not associated with potential serious adverse events. However, traditional oral iron treatments are not optimal because of increased gastrointestinal side effects, lack of patient adherence, and very often, lack of efficacy in patients with stage 5 CKD. Overall, treatments currently under development for iron deficiency anemia may represent an improvement in therapeutic options to treat iron deficiency anemia.

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