Anemia is a complication of chronic kidney disease. It is seen early in the course of chronic kidney disease, with the decline in hemoglobin concentration starting at levels of creatinine clearance of around 70 mL/min in men and 50 mL/min in women, and becomes more severe as renal failure progresses [1]. Anemia is predictive of morbidity and mortality from cardiovascular causes in patients with chronic kidney disease or on dialysis [2]. It leads to reduced oxygen delivery to tissues, causing organ dysfunction. It also causes hemodynamic adaptations including a high cardiac output state to maintain adequate tissue oxygenation leading to left ventricular dilatation and hypertrophy [3].

Traditionally, the target hematocrit level for therapy is 30–33%, though there is little supporting data. Prior to the mid-1980s, repeated blood transfusion was the only strategy for managing the severe anemia that complicates chronic kidney disease. Early investigations have established the erythropoietic effects of androgens, but the effect was too weak and unpredictable to be adopted as a routine therapy. The mechanism of action is not completely understood. It was initially considered to be due to an increase in erythropoietin production. However, it was subsequently observed that androgen did not elicit an increase in serum erythropoietin levels in all subjects. Other possible mechanisms include synergistic action with erythropoietin, an increase in the sensitivity of erythroid progenitors to erythropoietin, increased red blood cell survival, or a direct effect on erythropoietic precursor cells at various stages of maturity.

In the mid-1980s, recombinant human erythropoietin (rHuEPO) was developed and was proven to be effective in treating renal-related anemia. Recombinant HuEPO acts by binding to the dimerized erythropoietin receptor on the surface of erythroid progenitor cells, leading to phosphorylation of tyrosine residues on several intracellular molecules, gene activation in the cell nucleus, and stimulating proliferation and inhibiting apoptosis of the erythroid progenitor cells [4]. Due to its relatively short half-life (8.5 hours), rHuEPO is usually given once to thrice per week.

Later on, darbepoetin alfa (Aranesp™; Amgen Inc., Thousand Oaks, CA, USA) was developed [5]. It is a hyperglycosylated analog of rHuEPO that stimulates erythropoiesis by the same mechanism as the endogenous hormone. Darbepoetin has five N-linked glycosylation (carbohydrate) side chains, whereas both rHuEPO and the endogenous hormone have three [5]. This leads to darbepoetin having a three-fold terminal half-life (25.3 hours) and greater in vivo biologic activity compared to conventional rHuEPO. Less frequent dosing is needed, with expected increase in compliance and improvement in the treatment of renal anemia. A number of studies have shown the efficacy and safety of using darbepoetin in patients with chronic kidney disease or on dialysis [6,7]. It has also been shown to be efficacious when administered once every month in patients with chronic kidney disease [6]. However, the optimal dosing interval of darbepoetin in patients on dialysis remains unknown.

In this issue of the Hong Kong Journal of Nephrology, Tang et al describe a study using once monthly darbepoetin in peritoneal dialysis patients previously on rHuEPO [8]. Fourteen patients were recruited, 11 of whom completed the study. There was a mean drop in hemoglobin level from a baseline of 1.03 g/dL, which was statistically insignificant (95% CI: –2.23, 0.27). The authors concluded that darbepoetin administered once a month effectively maintained hemoglobin level in continuous ambulatory peritoneal dialysis patients. Although the sample size was small and there was an insignificant drop in hemoglobin, this study provides prove-of-principle evidence that monthly rHuEPO treatment is practically feasible.

Apart from erythropoietin, there are other novel agents being developed for correction of anemia related to kidney disease without the need for frequent injection. One of the new advances is continuous erythropoietin receptor activator (CERA) [9]. CERA was created by integration of a single 30 kDa polymer chain into the erythropoietin molecule, doubling its molecular weight and prolonging its elimination half-life to about 130 hours. CERA has a lower affinity for the erythropoietin receptor compared with epoetin in vitro. However, it interacts and leads to continuous activation of the erythropoietin receptor through its half-life. With the prolonged elimination half-life, CERA has increased erythropoietic activity in vivo [10]. Preliminary data from phase III clinical studies suggests that administration of CERA once every 3–4 weeks is safe and effective [9].
Also in the developmental stages are the erythropoietin-mimetic peptides. These synthetic peptide-based erythropoiesis-stimulating agents have amino acid sequences that are completely unrelated to that of native or recombinant erythropoietin [11]. However, they interact with and activate the erythropoietin receptor, and stimulate erythropoiesis by the same intracellular tyrosine phosphorylation signaling cascade. Hematide™ (Affymax Inc., Palo Alto, CA, USA) is one of the product candidates that is currently undergoing phase II clinical trials. As a pegylated peptide, Hematide™ has the advantage of a long circulating half-life and a long duration of erythropoietic action that allows for once monthly dosing [12]. Due to its novel amino acid sequence, it is supposed to have a lack of cross-reactivity with anti-erythropoietin antibodies. It could potentially be used as rescue therapy for patients with anti-erythropoietin-antibody-mediated pure red cell aplasia.

The first oral therapy for the treatment of anemia in chronic kidney disease is in phase II of clinical development. This oral agent is a hypoxia-inducible factor (HIF) stabilizer. HIF is a gene product that activates erythropoietin production during hypoxic conditions. The HIF stabilizer inhibits the enzyme that degrades HIF (prolyl hydroxylase) and, consequently, HIF-1 alfa is stabilized and activates erythropoietin gene production. It is a novel form of therapy to activate and regulate endogenous erythropoietin production.

There are currently some controversies surrounding the use of erythropoietin and optimal hemoglobin level in patients with renal insufficiency. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial found that correction of hemoglobin level to 13.5 g/dL, compared with 11.3 g/dL, was associated with increased risk and no incremental improvement in the quality of life [13]. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial also concluded that early complete correction of anemia does not reduce the risk of cardiovascular events [14]. Thus, it is suggested that hemoglobin level might have a J-shaped relationship with outcomes in subjects with chronic kidney disease. On the one hand, anemia is predictive of complications and death from cardiovascular causes in patients with chronic kidney disease [2]. Observational studies also indicate that correction of anemia is associated with improved outcomes [2,15]. On the other hand, normalization of hemoglobin level in prospective trials involving patients receiving hemodialysis did not lead to improvement in left ventricular indexes or decrease the risk of death [16].

In summary, the study by Tang et al [8] provides evidence that monthly injection of darbepoetin alfa is a feasible option for the treatment of anemia in peritoneal dialysis patients. Other new agents that can serve the same purpose without the need for frequent injection are in the pipeline. Let’s keep our eyes and minds open.

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REFERENCES


