

Review Article

Renal anaemia: Recent developments, innovative approaches and future directions for improved management

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SUMMARY: The morbidity, mortality and economic burden of chronic kidney disease (CKD) and associated anaemia are substantial. With the increasing numbers of patients who are likely to be affected in the future, approaches are required to improve anaemia management without increasing the burden on health-care professionals. A multidisciplinary approach to treatment, where early initiation of erythropoiesis-stimulating agents (ESA) is encouraged, may improve patient outcomes. Recent studies also suggest that the early use of iron therapy in patients with CKD not on dialysis may be associated with beneficial effects on haemoglobin levels. Another strategy to reduce the burden on health-care providers is to simplify anaemia management by extending the administration interval of ESA. Indeed, recent studies have explored the efficacy of extending the administration interval of ESA in clinical practice in CKD patients on dialysis and not on dialysis. The ability to maintain haemoglobin levels within guideline ranges at extended administration intervals may improve patient care and reduce the workload of health-care providers.

KEY WORDS: anaemia, chronic kidney disease, erythropoiesis-stimulating agent.

Chronic kidney disease (CKD) is highly prevalent, with increasing numbers of patients affected by the disease worldwide.¹ In Australia alone, 95 patients per million population start chronic dialysis each year.² The progressive nature of CKD and the increased need for renal replacement therapy is associated with a significant burden on global health-care resources.³ Furthermore, treatment costs associated with CKD are increasing. In the USA, it has been estimated that in 2010 the number of patients receiving treatment for advanced CKD will rise to over 2 million and the total cost of treatment during this decade will exceed \$US1 trillion.⁴ To manage the increasing prevalence, projections suggest that the number of new nephrologists will need to double from 1997 to 2010.⁵

Anaemia is a common complication that contributes to the burden of disease associated with CKD.^{6–11} Anaemia impacts negatively on cardiovascular disease,^{12,13} cognitive function,¹⁴ exercise capacity¹⁵ and quality of life,^{16,17} resulting in significant mortality and morbidity in patients with CKD.^{18,19}

The development of erythropoiesis-stimulating agents (ESA) represented a major advance in the treatment of renal anaemia. It is now well recognized that in patients with CKD, partial correction of anaemia is associated with

improved quality of life, reduced hospitalizations and reduced mortality.^{20–23} This review will describe current treatment of renal anaemia and discuss recent developments and their potential impact on future management.

CURRENT ANAEMIA TREATMENT

The first ESA were human recombinant erythropoietin (epoetin alfa and beta), which can be administered either intravenously or subcutaneously, and are generally given two or three times a week for anaemia correction. The frequency of administration is dictated partly by the short half-life of epoetin, 6–9 h following intravenous injection and 19–24 h following subcutaneous injection.²⁴ More recently, a hyperglycosylated analogue of epoetin, darbepoetin alfa, was introduced which contains five N-linked carbohydrate chains compared with three in epoetin. The two additional sialic acid-containing carbohydrate chains increase the elimination half-life of darbepoetin alfa threefold compared with epoetin.²⁵ As a result, darbepoetin alfa is generally administered intravenously or subcutaneously once weekly or once every 2 weeks.

Clinical practice guidelines exist to facilitate the management of anaemia, which include recommendations regarding the use of currently available ESA.^{26–28} Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) conducted in 12 countries worldwide suggest that changes in management practice as a result of these guidelines have improved anaemia control; however, many patients still have haemoglobin (Hb) levels outside guideline targets and iron status is often inadequate.²⁹ In Australia

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lia, 28% of patients on dialysis have Hb <11 g/dL and poor iron status (using percentage of transferrin saturation (TSAT) <20%) is common in a similar proportion.²

Results from a number of studies have demonstrated that maintaining Hb levels within recommended targets is associated with positive clinical outcomes.^{20,21,23,30–32} Extrapolation of data from DOPPS indicates that an estimated 23 910 patient-years could be gained over a 5-year period if US patients on haemodialysis achieved Hb \geq 11 g/dL.³¹ With the increasing numbers of patients who are likely to be affected by CKD in the coming years, approaches are required that will improve patient outcomes without increasing the burden on health-care professionals.

OPPORTUNITIES FOR IMPROVEMENTS IN ANAEMIA MANAGEMENT

The use of ESA before the initiation of dialysis is uncommon in some countries.^{10,33} In a survey of 4333 patients from 21 countries with CKD starting on dialysis, only 26.5% of patients were receiving ESA treatment before dialysis initiation and the mean Hb levels were 9.5 g/dL, although these data were collected between 1999 and 2000.³³ Recent evidence suggests that low Hb levels, before dialysis, are associated with increased mortality.³⁴ In 3028 patients with CKD not receiving dialysis with glomerular filtration rate <60 mL/min/1.73 m², Hb levels at the time of referral to a nephrologist were an independent predictor of survival (risk ratio = 0.88 for every 1 g/dL, 95% confidence interval (CI): 0.84–0.92, $P = 0.0001$) (Fig. 1).

A number of studies highlight the benefits of early initiation of ESA therapy.^{35–38} In a retrospective cohort study of 15 807 patients, use of epoetin predialysis was associated with a reduced risk of mortality compared with epoetin treatment after dialysis initiation (adjusted risk ratio = 0.87, 95% CI: 0.82–0.92).³⁸ Similar results were obtained in a study of 88 patients with CKD not receiving dialysis with Hb = 9–11.6 g/dL who were randomized to receive epoetin treatment either early (immediate treatment to achieve Hb \geq 13 g/dL) or deferred (treatment only when Hb <9 g/dL).³⁶ The relative hazard ratio of renal replacement, creatinine increasing twofold or death, was 0.42 (95% CI: 0.21–0.83, $P = 0.012$) in patients in whom epoetin was initiated early compared with deferred treatment. However, Regidor *et al.* showed that treatment of anaemia at any stage improved survival relative to those who received no treatment.²³

Normalization of Hb levels by epoetin treatment in CKD patients on dialysis has been associated with improvements in left ventricular mass index (LVMI).³⁹ However, studies investigating the effects of immediate versus delayed epoetin treatment on LVMI have not been conclusive;^{40,41} both trials were probably underpowered and there was poor separation of the treatment and non-treatment groups in terms of achieved Hb levels. Further randomized controlled trials are required to fully investigate the association between early treatment and improvements in LVMI.

Recent studies suggest that improved patient outcomes may also be achieved by adopting a multidisciplinary

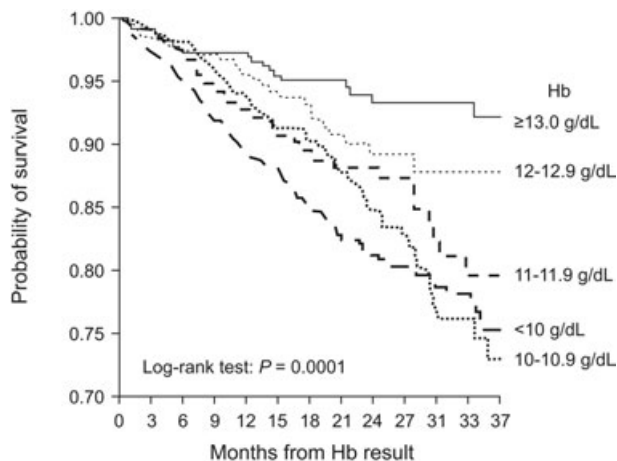


Fig. 1 Haemoglobin (Hb) levels at the time of referral, before dialysis, predict survival. Reproduced with permission from Oxford University Press.³⁴

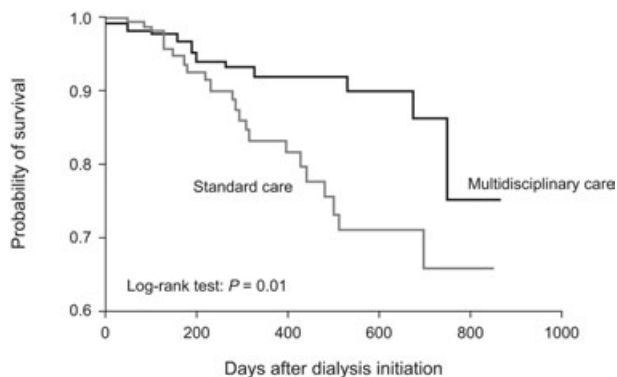


Fig. 2 Multidisciplinary care of patients on dialysis is associated with improved survival compared with standard care. Reproduced with permission from Oxford University Press.⁴³

approach, involving nephrologists, diabetologists, cardiologists, nurses, social workers, nutritionists and pharmacists, both at an early stage and in patients already receiving treatment. In 184 patients starting dialysis, multidisciplinary predialysis care, compared with conventional care, was associated with significantly fewer hospitalizations (10.8 days/patient/year vs 57.4 days/patient/year, $P < 0.05$) and fewer deaths (21% vs 42%, $P < 0.05$).⁴² Beneficial effects on patient outcomes were also observed in another study of patients starting dialysis who attended a formalized multidisciplinary clinic compared with those receiving standard nephrologist care.⁴³ Attending the standard clinic versus the multidisciplinary clinic was an independent predictor of death (hazard ratio = 2.17, 95% CI: 1.11–4.28, $P = 0.01$) (Fig. 2). Furthermore, patients attending the multidisciplinary clinic had significantly higher Hb levels (10.2 g/dL vs 9.0 g/dL, $P < 0.0001$).

The specialist nurse has a particularly important role in the multidisciplinary team. They are often in an ideal position to identify, assess and manage anaemia at an early stage

in patients with CKD. Early recognition and management of anaemia by nurses may also contribute to the prevention of comorbid conditions in renal patients.⁴⁴ Responsibilities vary between countries, but roles generally include involvement in the preparation of anaemia management protocols, monitoring of the patient's response to ESA and iron therapy, and patient education.⁴⁴

In addition to encouraging early anaemia treatment by a multidisciplinary team, further improvements in anaemia management may also be achieved by adopting innovative approaches to iron therapy and ESA administration.

IRON THERAPY

Erythropoiesis-stimulating agent therapy is most successful when adequate iron stores are present.⁴⁵ Iron assessment in patients with CKD is frequently performed using measures of serum ferritin and TSAT; ferritin levels >100 µg/L and TSAT >20% are generally recommended.^{26,27,46} Other newer methods may also provide valuable information relating to iron status (Table 1).

Oral formulations are the simplest, most convenient and least expensive method for supplementing iron; however, they may not be effective for the majority of patients on haemodialysis. Gastrointestinal side-effects are common with oral iron; typical symptoms include dyspepsia, constipation and bloating.⁵¹ Further, oral iron may not provide sufficient iron to maintain adequate stores in patients receiving ESA. Preliminary studies with heme iron polypeptide in epoetin-treated haemodialysis patients suggest that it is efficacious and has improved tolerability compared with iron salts.⁵²

Intravenous iron is frequently administered to patients on dialysis and its efficacy in increasing Hb levels and reducing ESA dose requirements has been widely demonstrated.⁵¹ For example, in patients on haemodialysis receiving epoetin, intravenous iron dextran increased Hb levels from 7.3 g/dL to 11.9 g/dL; the increase in Hb was significantly greater than in patients receiving oral iron or no iron supplementation ($P < 0.005$).⁵³ Anaphylactoid reactions can occur in patients receiving iron dextran; however, iron sucrose and ferric gluconate are associated with fewer adverse events.⁵⁴

Although the efficacy of iron supplementation has been clearly demonstrated in dialysis patients, its role in patients with CKD not on dialysis is less clear. Recently, the effects of intravenous iron sucrose were compared with oral iron over 56 days in 188 patients with CKD stages 3–5 not receiving dialysis.⁵⁵ A total of 63 patients were receiving epoetin or darbepoetin alfa treatment. A significantly greater proportion of patients receiving intravenous iron sucrose had a Hb increase of ≥ 1 g/dL compared with those receiving oral iron (44.3% vs 28.0%, $P = 0.034$).

Results from another recent study suggest that iron therapy can increase Hb levels in patients not on the dialysis in the absence of ESA treatment. The effect of intravenous iron sucrose on Hb levels was investigated in 60 patients with CKD and anaemia not receiving dialysis or epoetin treatment.⁵⁶ Intravenous iron significantly increased Hb levels (from 9.7 g/dL to 11.3 g/dL; $P < 0.05$), with a 36% increase in the number of patients achieving Hb >10 g/dL in the 12-month study. Further investigations are required to fully elucidate the role of iron supplementation in patients with CKD not on dialysis.

Table 1 Iron status: methods for assessment and targets for patients with chronic kidney disease

	Australian guidelines ⁴⁶		European guidelines ²⁶		KDOQI guidelines ^{27†}	Comment
	Target	Ideal level	Minimum target	Ideal target	Target	
Serum ferritin (µg/L)	>100	200–500	>100	200–500	>200	Provides an indirect measure of iron stores. Levels may increase markedly with inflammation, malignancy or liver disease ⁴⁷
Percentage of transferrin saturation (%)	>20	30–40	>20	30–40	>20	Assesses the availability of circulating iron. Associated with high day-to-day fluctuations and varies with nutritional status ⁴⁸
Percentage of hypochromic red cells (%)	<10	<2.5	<10	<2.5	NA	Directly reflects the proportion of cells with suboptimal Hb levels. Analysis must be performed on a fresh sample as storage may result in changes in cellular volume ⁴⁹
Reticulocyte Hb content (pg/cell)	NA	NA	>29	~35	>29	Provides a direct measure of iron status at the level of the reticulocyte. Found to be less variable than other iron monitoring assessments ⁵⁰

†Patients with CKD on dialysis. Hb, haemoglobin; KDOQI, Kidney Disease Outcomes Quality Initiative; NA, not applicable.

Another area of increasing interest relates to the role of hepcidin in iron homeostasis. Hepcidin inhibits the cellular efflux of iron and controls extracellular iron by regulating its intestinal absorption, recycling by macrophages and release from stores.⁵⁷ Elevated hepcidin levels have been found in patients on haemodialysis, which may be due to functional iron deficiency and anaemia.⁵⁸ Furthermore, the inflammation that is frequently found in patients with CKD may also contribute towards increased hepcidin levels.⁵⁸ These observations may help to explain the high iron requirements of patients with advanced CKD and the hyporesponsiveness to ESA therapy that is common under inflammatory conditions. A greater understanding of the association of hepcidin with CKD, anaemia and inflammation may help to optimize the use of both iron and ESA therapy.

ESA: THE ROLE OF EXTENDED ADMINISTRATION INTERVALS

Extending the administration interval of ESA may simplify the management of anaemia and recent clinical studies have explored the efficacy of extending the administration interval of ESA to once every 2 weeks or longer in CKD patients on dialysis^{59,60} and not on dialysis.^{61–66}

Clinical studies

A short 16-week study examined the use of epoetin alfa at extended administration intervals of up to once monthly in more than 500 patients with CKD not on dialysis who were previously stable on a once-weekly schedule.⁶⁵ Stable Hb levels (≥ 11 g/dL) were maintained in most patients; however, comparability and interpretation of the results is limited by the short duration of the study. Further long-term studies are required to confirm these results.

Another study investigated the effect of epoetin beta administered once every 2 weeks in 128 patients receiving peritoneal dialysis who were already stable on once-weekly administration.⁶⁰ Mean change in Hb levels from baseline remained within the target range (10–12 g/dL) throughout the 25-week study in patients administered once weekly or once every 2 weeks; however, an increase in mean dose was required with the once every 2 weeks schedule (2% dose increase in the once-weekly group compared with 13% in the once every 2 weeks group).

Recent studies have evaluated the efficacy and safety of extending the administration interval of darbepoetin alfa.^{59,62,64,66} In a 29-week study of 97 patients with CKD not on dialysis who had previously received darbepoetin alfa once every 2 weeks, once-monthly administration maintained Hb levels in 79% of patients.⁶⁴ In a similar study, mean Hb change from baseline was -0.42 g/dL (-0.73 , -0.10) in 40 patients with CKD not on dialysis receiving once-monthly darbepoetin alfa who had previously received administration once every 2 weeks.⁶² In these studies, the aim was to maintain Hb levels >10 g/dL⁶² or within a target range of 10–12 g/dL.⁶⁴ It is important that further studies are conducted to evaluate whether darbepoetin alfa once

monthly can maintain Hb levels to current guideline targets.

Only one study has investigated once-monthly darbepoetin alfa administration in patients with CKD on dialysis.⁵⁹ In this study, the administration interval was sequentially adapted according to patients' responses. A total of 54 patients who had previously received darbepoetin alfa every 2 weeks were switched to administration every 3 weeks for 20 weeks and then, if Hb levels were 10–13 g/dL, were switched to once-monthly administration. Hb levels within the target range were only achieved by 38 patients receiving administration every 3 weeks, and of these, 36 patients were evaluable for once-monthly administration. The Hb range was maintained in 83% of evaluable patients receiving once-monthly administration. The low-dose requirements in studies investigating once-monthly administration suggest that their design favoured selection of the most responsive patients. Large-scale, long-term comparative investigations are required to determine whether once-monthly administration of currently available ESA can maintain Hb levels in the broad spectrum of patients in the standard clinic population.

Potential impact

Extended administration intervals may reduce the amount of intervention required by health-care staff to maintain stable Hb levels by decreasing the number of monthly ESA administrations and potentially reducing the number of dose adjustments. A study conducted in nine dialysis centres in five European countries estimated that anaemia management for 50 dialysis patients receiving epoetin three times weekly required 503 h of physician/nurse time per year; this could be reduced by 350 h per year by switching to once-weekly administration.⁶⁷ The results of this study suggest that substantial staff-time savings may be made if administration intervals were extended to once monthly for patients requiring maintenance therapy. The time gained by staff may be used to improve other aspects of patient care using a multidisciplinary approach. For example, increasing achievement of other guideline targets is likely to prove highly beneficial. Extrapolated data from DOPPS suggest that, in addition to Hb control, attaining targets related to dialysis dose, phosphate control, serum albumin, interdialytic weight gain and the use of catheters for vascular access may save 70 000–144 000 life-years in the USA.³¹

Extending the administration frequency may be more convenient for the patient and may also improve long-term compliance with therapy.⁶⁸ In a survey of patients with renal disease, the number of patients missing doses of erythropoietic therapy appeared to be higher with administration 2–3 times per week compared with weekly administration. A total of 72.5% of patients reported that they would prefer fewer injections.⁶⁸

Future considerations and developments

Haemoglobin levels may fluctuate over short periods of time in many patients with CKD.^{29,69–72} The increased workload

required to manage fluctuating Hb levels and correct towards target (i.e. dose adjustments and additional monitoring) may add to the burden on already hard-pressed renal units.

The causes of Hb variability are multifactorial and not yet fully understood; however, frequent ESA dose adjustments, inadequate iron status, changes in fluid balance and the occurrence of acute illnesses that require hospitalization may all contribute towards fluctuating Hb levels.⁷² In addition, there may also be a relationship between Hb variability and the pharmacologic properties of different currently available ESA when administered at extended intervals. Further studies are required to investigate whether extended administration of currently available ESA, particularly those with shorter half-lives, might exacerbate Hb fluctuations.

A prolonged half-life of approximately 130 h has recently been reported for the innovative agent C.E.R.A. (Continuous Erythropoietin Receptor Activator) in patients with CKD.^{73,74} Results from Phase II investigations in patients with CKD on dialysis and not on dialysis suggest that C.E.R.A. can control anaemia and maintain Hb levels within guideline targets in the majority of patients when administered at extended intervals of up to once monthly.^{75,76} Phase III trials are ongoing to confirm Phase II findings.

CONCLUSION

With the increasing morbidity, mortality and economic burden of anaemia, strategies to improve and simplify management are necessary. A multidisciplinary approach to treatment, where early initiation of erythropoietic agents is encouraged, may help to reduce disease progression and improve patient outcomes, and this may have a positive impact on health-care resources. Attention to appropriate iron management is equally important and new strategies to improve iron status in patients with CKD are in development. Another approach, administering ESA at extended intervals, may simplify anaemia management. The ability to maintain Hb levels within guideline ranges at extended administration intervals may improve patient care and reduce the workload of health-care providers.

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