Recombinant human epoetin beta in the treatment of renal anemia

Francesco Locatelli[1]
Pietro Pozzoni[1]
Lucia Del Vecchio[2]

[1]Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy; [2]Department of Hypertension and Preventive Nephrology, IRCCS Policlinico Multimedia, Sesto San Giovanni (MI), Italy

Abstract: Cardiovascular disease is the leading cause of the poor long-term survival of patients with chronic kidney disease (CKD). Anemia complicating CKD not only impairs patients' quality of life, but is also an independent risk factor for adverse cardiovascular outcomes. The availability of recombinant human erythropoietin (rHuEPO) has greatly changed the management of anemia in CKD patients. Besides improving hemoglobin levels, rHuEPO therapy has been demonstrated to significantly improve quality of life and decrease morbidity and mortality in patients with CKD. Epoetin beta, together with epoetin alfa and darbepoetin alfa, is one of the erythropoiesis-stimulating agents now available on the market. Different studies have shown that epoetin beta once-weekly administration to hemodialysis patients is as effective as three-times-weekly administration in maintaining hemoglobin levels at equivalent weekly doses. This raises the possibility of reducing the frequency of administration of rHuEPO therapy, thus increasing the alternatives available for tailoring anemia therapy to patients needs, and at the same time reducing nursing times and treatment costs. This is expected to potentially enhance patient compliance, thus helping more patients achieve their target hemoglobin levels.
Keywords: anemia, chronic kidney disease, epoetin beta, cardiovascular disease

Introduction

Chronic kidney disease (CKD) patients are affected by considerable cardiovascular morbidity and mortality. Cardiovascular complications are the main cause of death among patients on dialysis (Locatelli et al 2000; Collins et al 2005) and cardiovascular mortality rates are approximately 10–20 times greater than those observed in the general population (Foley et al 1998). The burden of cardiovascular disease is huge also during the conservative phase of CKD: the number of CKD patients progressing towards the need for renal replacement treatment is indeed much lower than the number of those dying, mainly due to cardiovascular disease itself, before reaching the point of end-stage renal disease (ESRD) (Keith et al 2004; Foley et al 2005). In this context, anemia has gained increasing attention, based on its well documented role as a specifically CKD-related cardiovascular risk factor. Anemia is a frequent complication of patients with CKD and is mainly characterized by a reduced ability of the damaged kidney to produce erythropoietin (EPO), the hormone involved in proliferation and maturation of red blood cells in the bone marrow. Hb levels can start to decrease even at an early stage of CKD (Levin 2001; Astor et al 2002). It has been found that among patients with a creatinine clearance of more than 50 mL/min (early kidney disease), 25% have already developed anemia (defined as Hb <13 mg/dL), and the prevalence of anemia increases dramatically as creatinine clearance further decreases (Levin 2001). Anemia is often more severe and occurs at an earlier stage in patients with diabetic

Correspondence: Francesco Locatelli
Department of Nephrology, A. Manzoni Hospital, Via Dell'eremo 9/11 23900 Lecco Italy
Tel +39 0341 489850
Fax +39 0341 489860
Email f.locatelli@ospedale.lecco.it

nephropathy in comparison with patients with CKD of other causes (Thomas and Rampersad 2004).

Association of renal anemia with cardiovascular morbidity and mortality

Several reports have shown an association between of anemia and the development of cardiovascular complications in patients with CKD (Harnet et al 1995; Parfrey et al 1996; Levin 2002). It is thought that these associations are mainly due to the impact of chronic anemia on cardiac function, by means of vasodilation, cardiac dilation, and increased cardiac output, finally leading to left ventricular dilation and compensatory hypertrophy (Anand et al 1993). The association between anemia and cardiovascular disease can also be explained by the reduction in oxygen delivery throughout the body, whereas it has been suggested that anemia, congestive heart failure, and CKD are all interrelated, each causing the other to worsen, resulting in a vicious cycle of disease progression (Silverberg 2003). Complications that have been most consistently associated with anemia are indeed left ventricular hypertrophy, congestive heart failure, and ischemic heart disease (Foley et al 1996; Levin 2002).

Anemia-related cardiovascular abnormalities play a significant role in mortality in patients with CKD, and a number of observational studies have described a clear relationship between anemia and mortality in CKD patients. In studies performed on large populations of prevalent hemodialysis patients in the US, both total mortality rate and cardiovascular-related mortality rate were shown to increase along with the decrease in hematocrit (Madore et al 1997; Ma et al 1999; Collins et al 2001). These registry studies were, however, much limited by considering only a few number of potentially confounding covariates. This is not the case for the DOPPS study, which took into account a large number of case-mix characteristics and found significantly lower relative risks of mortality and all-cause hospitalization for every 1 g/dL higher hemoglobin concentration, both in a European (Locatelli et al 2004) and US (Robinson et al 2005) large sample population of hemodialysis patients. More recently, a systematic review of published observational studies investigating anemia and mortality in dialysis patients confirmed a consistent trend towards increased mortality with decreasing Hb levels (Volkova and Arab 2006). Although less consistent, recent observations indicate a clear association between anemia and increased mortality also in CKD patients who are not yet on dialysis (Kovesdy et al 2006; Levin et al 2006). It should, however, be borne in mind that most observational studies have so far considered only the point values of hemoglobin or hematocrit, which may be misleading due to the fact that many patients do not have stable Hb levels over time: that is the reason why some observational studies of patients in the conservative phase of CKD have used time-averaged rather than single hemoglobin values when analyzing their impact on patients' survival (Collins et al 2001; Regidor et al 2006).

The presence of anemia during the early stages of CKD may also fasten the progression of kidney damage. Reduced oxygen delivery to the kidney caused by anemia may indeed lead to a progressive destruction of tubules, interstitial fibrosis, and increased oxidative stress, all factors which are expected to favor the progression of the disease (Rossert et al 2002). Clinical studies support the presence of a positive association between higher hemoglobin levels and a decrease in the rate of loss of renal function (Kuriyama et al 1997; Jungers et al 2001), and ongoing trials are investigating the possible benefits of correcting hemoglobin levels on the progression of CKD.

Clinical benefits of correcting renal anemia

The availability of recombinant human erythropoietin (rHuEPO) has greatly changed the management of anemia in patients with CKD, allowing hemoglobin levels to be effectively moved towards higher values. The gene encoding for EPO was cloned in 1985 (Lin et al 1985) and rHuEPO has been used in the treatment of renal anemia since 1986 (Winearls et al 1986; Eschbach et al 1987). Since then, a number of clinical trials have documented that the administration of rHuEPO maintains adequate hemoglobin levels and avoids transfusion dependency in CKD patients. Starting from the clear association observed between lower hemoglobin levels and increased mortality in CKD patients, the availability of an effective therapeutic instrument to treat renal anemia soon raised the question as to whether correcting anemia may be able to improve patient outcome. Several intervention studies have been performed to test this hypothesis. Many of these studies were also aimed at verifying, through randomized allocation of the patients to different target hemoglobin levels, whether complete rather than partial correction of renal anemia through rHuEPO administration would lead to the best results in terms of survival or surrogate endpoints (left ventricular mass, quality of life).

Patients with CKD not receiving dialysis are less likely to have already established cardiovascular disease, as the prevalence of left ventricular hypertrophy and heart disease progressively increases as renal function declines (Levin et al 1999). Therefore, it has been hypothesized that they may benefit more from anemia correction. Preliminary data from mainly small, uncontrolled studies indicated that anemia correction was able to lead to partial regression of left ventricular hypertrophy (Portoles et al 1997; Hayashi et al 2000; Frank et al 2004), although such an effect was not confirmed in more recent studies (Roger et al 2004). However, it must be pointed out that the randomized controlled trial by Roger et al (2004) suffered from the relative closeness of the achieved hemoglobin values between the two randomization groups, whereas Levin et al (2005) observed an inverse relationship between the decrease in hemoglobin levels and left ventricular mass index among the patients whose hemoglobin decreased by ≥1.0 g/dL during follow-up, regardless of the trial arm.

Besarab et al (1998) were the first who tested the effect of hemoglobin normalization, as compared with only partial anemia correction, in patients on dialysis. The study, which considered hard outcomes such as mortality and cardiac events, was actually halted after 29 months because the trends in mortality/acute myocardial infarction in the two randomization arms were such that it was unlikely that any benefit would be obtained from complete anemia correction. However, the study population consisted of hemodialysis patients aged more than 65 years with clinical evidence of congestive heart failure or ischemic heart disease, who were suggested to be affected by too many co-morbidities to benefit from anemia normalization, and it is also possible that the co-existence of reduced cardiac output and vascular grafts in the majority (almost 70%) of the study population may have increased the likelihood of adverse events secondary to complete anemia correction, including graft thrombosis. Furthermore, a secondary analysis did reveal an inverse relationship between hematocrit values and mortality rates in both groups, with the patients who actually achieved a level of 42% showing the best survival rate, although this finding might have been due to survivor selection. Other studies performed in less compromised dialysis patients did not find a significant effect of complete anemia correction on survival, but such studies were not specifically designed to test mortality (Furuland et al 2003; Parfrey et al 2005). Also surrogate endpoints, such as left ventricular mass, were not shown to be positively affected by the achievement of higher hemoglobin levels through rHuEPO administration in dialysis patients (Foley et al 2000; Parfrey et al 2005), with the exception of only quality of life, which seems to be positively influenced by complete anemia correction (Moreno et al 2000; Furuland et al 2003; Parfrey et al 2005).

Fewer data exist on the effects of complete anemia correction on clinical outcome in CKD patients not receiving dialysis. The clinical trial by Rossert et al (2006) did not find any difference in the risk of cardiovascular adverse events between patients randomized to different hemoglobin targets, but the study was primarily aimed at testing the effect of treatment on the rate of progression of CKD rather than on cardiovascular prognosis. Further important information as to this point will be provided by on-going or just ended clinical trials, such as the Cardiovascular Reduction Early Anemia Treatment Epoetin beta (CREATE) study and the Anemia CORrection in Diabetes (ACORD) trial, but the preliminary results of these studies do not seem to show any cardiovascular advantage in favor of complete anemia correction in CKD patients not yet on dialysis.

Altogether, the results of the available studies published so far indicate that partial correction of renal anemia by means of rHuEPO administration is accompanied by significant improvements in cardiac structure and function, but no further major effect on survival and left ventricular mass seems to be achieved by normalizing hemoglobin levels in patients with CKD. However, caution is warranted in interpreting these results, as in most cases they were obtained from heterogeneous studies that were not primarily designed to analyze mortality and were heavily conditioned by the relative closeness of the hemoglobin values achieved during follow-up between the groups of patients randomized to different levels of anemia correction.

Epoetin beta and renal anemia

Clinical pharmacology

Nowadays, there are three erythropoiesis-stimulating agents available on the market for the treatment of renal anemia: epoetin alfa, epoetin beta, and darbepoetin alfa. Epoetin alfa and epoetin beta are both synthesized in Chinese hamster ovary cells and share the same amino acid sequence as endogenous EPO, but differences in the manufacturing process between the two glycoproteins reflect the differences in their carbohydrate moieties (Storring et al 1998). On the contrary, darbepoetin alfa is biochemically different from endogenous EPO, due to an additional two glycosylation chains N-linked to

the protein backbone of the molecule. Differences in the carbohydrate moieties of the rHuEPOs determine differences in the pharmacokinetic and pharmacodynamic properties between these agents.

The differences in pharmacokinetic and pharmacodynamic properties of epoetin beta and epoetin alfa have been confirmed in a randomized crossover study on healthy volunteers, in which the terminal elimination half-life of intravenous epoetin beta was found to be 20% longer than that observed with intravenous epoetin alfa; the half-life for epoetin beta was also longer with the subcutaneous route, although the difference did not reach statistical significance (serum concentration after subcutaneous administration appears to be higher for epoetin beta than for epoetin alfa from 48 to 66 hours after dosing, and this reflects delayed drug absorption with epoetin beta compared with epoetin alfa; in addition, epoetin beta seems to induce a greater absolute reticulocyte response than epoetin alfa after subcutaneous administration). These differences are most probably explained by the differences in the types and relative proportions of the carbohydrate side chains on the glycoprotein molecules present in the two preparations.

Pharmacokinetic and pharmacodynamic responses to epoetin beta differ greatly according to the route of administration. Although peak serum concentration is more than 10 times greater after intravenous than subcutaneous administration, the terminal elimination half-life for epoetin beta administered via subcutaneous injection is almost three-fold that of the same dose given intravenously (Halstenson et al 1991), likely due to the delayed absorption following subcutaneous administration. Interestingly, the absolute reticulocyte response is greater when epoetin beta is administered subcutaneously rather than intravenously (Halstenson et al 1991), suggesting that the response to epoetin is not related to its peak plasma concentration but rather to its maintenance above a critical threshold concentration. The prolonged half-life following subcutaneous administration of epoetin beta suggested the possibility of increasing the interval between injections when using this route of administration, as confirmed by rHuEPO levels remaining within the target range for most of the period between injections even with once-weekly subcutaneous dosing (Besarab et al 1992). In addition, dose requirements to maintain target hemoglobin levels are significantly lower when epoetin beta is administered subcutaneously compared with intravenously (Besarab et al 1992; Kaufman et al 1998). For this reason, current treatment guidelines (Locatelli et al 2004a) recommend the subcutaneous route of administration of epoetin beta in order to minimize treatment costs.

Efficacy

Although the subcutaneous route of administration is currently recommended for epoetin beta, due to pharmacological and economic considerations, it can also be given intravenously, if necessary. The efficacy of intravenous epoetin beta has actually been established in several studies in patients with CKD, either pre-dialysis or on hemodialysis (Kaupe et al 1990; Abraham and Macres 1991; Bennett 1991; Kaizu et al 1993; Sinnassamy et al 1993; Bommer et al 1998).

Nonetheless, the sustained duration of action described in pharmacokinetic studies supports the use of subcutaneous epoetin beta, administered once weekly, at least in the maintenance phase of renal anemia treatment. In fact, although traditionally rHuEPO was administered three times weekly, studies evaluating less frequent administration regimens have demonstrated that once-weekly subcutaneous administration of epoetin beta during the maintenance phase of therapy has the same efficacy in maintaining Hb levels as the three-times-weekly regimen. In particular, two large-scale, randomized, controlled studies (Weiss et al 2000; Locatelli et al 2002) showed that stable Hb levels could be maintained with once-weekly epoetin beta treatment without an increase in dose compared with administration two or three times weekly. Weiss et al (2000) conducted an open label, randomized, controlled, parallel-group study designed to detect no difference in efficacy between once-weekly and two- or three-times-weekly subcutaneous epoetin beta treatment in 158 patients on hemodialysis. Patients with Hb levels maintained between 10 and 12.5 g/dL during an 8-week pre-treatment period with subcutaneous epoetin beta two or three times weekly were randomized either to receive once weekly subcutaneous epoetin beta treatment or to remain on their original regimen for 24 weeks. No significant differences were observed in Hb levels and in weekly epoetin beta dose between the treatment regimens. The study by Locatelli et al (2002) was designed to demonstrate therapeutic and statistical equivalence between once-weekly and three-times-weekly subcutaneous epoetin beta treatment in stable patients on hemodialysis. This was an open-label, randomized, parallel-group study conducted over a 24-week period: 173 patients on hemodialysis were randomized to treatment with once- or three-times-weekly epoetin beta. Mean hematocrit levels remained stable

throughout the study and the mean weekly epoetin beta dose was not different in the two treatment groups.

Several small-scale studies have investigated the use of once-weekly subcutaneous epoetin also in patients on peritoneal dialysis (Lui et al 1991; Saleh et al 1991; Nomato et al 1994; Frifelt et al 1996), suggesting that a maintenance dose of subcutaneous epoetin is effective when given once weekly in these patients. For example, a prospective, randomized study compared the dosage requirements of subcutaneous epoetin beta administered either once weekly or three times weekly in 39 patients on peritoneal dialysis previously stabilized on epoetin beta three times weekly (Frifelt et al 1996). At the endpoint there was no difference in hemoglobin levels between treatment regimens, and over the 3-month study period the average dose of epoetin beta was slightly lower for patients receiving once-weekly compared with three-times-weekly treatment. More recently, another study investigated whether epoetin beta administered once weekly was effective at maintaining hemoglobin levels in patients on peritoneal dialysis previously stabilized on epoetin two or three times weekly and whether once every two weeks administration was effective in patients previously stabilized on a once-weekly regimen (Grzeszczak et al 2005). In both cases, over the 6-month study period, the patients were able to maintain hemoglobin levels within the target range without a significant increase in overall weekly dose compared with their respective previous regimen.

As well as being effective in patients on dialysis, subcutaneous epoetin beta is effective in correcting renal anemia also in patients with CKD who do not require renal replacement therapy (Koch et al 1995). An open-label, multicenter study including 84 pre-dialysis patients suggested that once-weekly subcutaneous epoetin beta is as effective as more frequent administration in maintaining hemoglobin levels in CKD patients in the conservative phase (Albetazzi et al 1998).

Safety and tolerability

More than a decade of experience with epoetin beta has demonstrated its favorable safety and tolerability profile in patients with CKD. During its clinical trial program, no long-term trend or distinct pattern in adverse events was identified (F. Hoffmann-La Roche, data on file). As with other erythropoiesis-stimulating agents (ESA), the most common adverse event is hypertension. A number of pathophysiological mechanisms have been postulated to explain the rise in blood pressure values observed after ESA administration. The increase in blood viscosity secondary to anemia correction appears as the most obvious one. This is particularly true when anemia correction is achieved too rapidly or higher hemoglobin targets are reached. However, often blood pressure changes are not clearly related to achieved hemoglobin levels. Enhanced vascular reactivity and vasoconstrictor responses have been thus suggested to play a role. Given that ESA-induced hypertension seems to be dose-related, it is possible that switching patients from intravenous to subcutaneous epoetin therapy, by allowing lower doses, may reduce the incidence of adverse events, above all hypertension. This is suggested by the results of a study on hypertensive hemodialysis patients under intravenous epoetin therapy, whose pre-dialysis blood pressure levels significantly decreased after switching to subcutaneous administration, so that within 6 months nearly half of them were no longer considered hypertensive (Navarro et al 1995). A larger study of 406 patients receiving maintenance intravenous or subcutaneous epoetin treatment who were switched to subcutaneous epoetin beta showed epoetin beta to be well tolerated and effective, with adverse events occurring at a very low rate during the study (Kleophas et al 2003). Finally, different studies reported that once-weekly subcutaneous epoetin beta is as well tolerated as two- or three-times-weekly regimens (Weiss et al 2000; Locatelli et al 2002). It must also be considered that the reduced dosage requirements when epoetin is administered subcutaneously compared with intravenously may allow substantial cost savings, without compromising effectiveness or safety of therapy (Kaufman et al 1998; Besarab et al 2002; Hynes et al 2002).

Antibody-mediated pure red cell aplasia (PRCA) is a rare complication following therapy with ESA. Between 1998 and 2002, an upsurge of PRCA cases have been described, but this was mainly related to treatment with epoetin alfa (Casadevall et al 2002; Bennett et al 2004). Reports of PRCA with epoetin beta have been sporadic and limited (Locatelli et al 2004b).

Conclusions

Anemia is a frequent and early complication of CKD and is associated with adverse cardiovascular outcomes and poor patient survival. Renal anemia can be effectively managed by the administration of rHuEPO, which is able to increase hemoglobin levels and has been associated with significant improvements in the cardiovascular status of patients with CKD. Epoetin beta represents one of the three erythropoiesis-stimulating agents available on the market for the treatment of renal anemia. The increased effectiveness and the longer half-life shown by epoetin beta when administered

subcutaneously, as compared with intravenously, make the subcutaneous route of administration the one recommended by current best practice guidelines, allowing target hemoglobin levels to be maintained at a lower epoetin dose and lower frequency of administration.

The ability to administer epoetin beta once weekly is associated with several additional benefits. Reducing administration frequency from three times weekly to once weekly is likely to improve patients' acceptance of epoetin treatment, potentially encouraging self-administration and improving compliance. The once-weekly schedule contributes also to the reduction of treatment costs and nursing time required for optimal anemia management.

In conclusion, the proven efficacy and safety profile of epoetin beta, combined with the increased convenience of less frequent dosing, make epoetin beta a safe and effective treatment option that can help more patients to reach their therapeutic targets in the management of renal anemia.

References

Abraham PA, Macres MG. 1991. Blood pressure in hemodialysis patients during amelioration of anemia with erythropoietin. *J Am Soc Nephrol*, 2:927–36.

Albetazzi A, Di Liberato L, Daniele F et al. 1998. Efficacy and tolerability of recombinant human erythropoietin treatment in pre-dialysis patients:results of a multicenter study. *Int J Artif Organs*, 21:12–18.

Anand IS, Chandrashekhar Y, Ferrari R, et al. 1993. Pathogenesis of oedema in chronic severe anaemia: Studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J*, 70:357–62.

Astor BC, Muntner P, Levin A, et al. 2002. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med*, 162:1401–8.

Bennett WM. 1991. A multicenter clinical trial of epoetin beta for anemia of end-stage renal disease. *J Am Soc Nephrol*, 1:990–8.

Bennett CL, Luminari S, Nissenson AR, et al. 2004. Pure red-cell aplasia and epoetin therapy. *N Engl J Med*, 351:1403–8.

Besarab A, Bolton WK, Browne JK, et al. 1998. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoietin. *N Engl J Med*, 339:584–90.

Besarab A, Flaharty KK, Erslev AJ, et al. 1992. Clinical pharmacology and economics of recombinant human erythropoietin in end-stage renal disease: the case for subcutaneous administration. *J Am Soc Nephrol*, 2:1405–16.

Besarab A, Reyes CM, Hornberger J. 2002. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis*, 40:439–46.

Bommer J, Kugel M, Schoeppe W, et al. 1998. Dose-related effects of recombinant human erythropoietin on erythropoiesis. Results of a multicenter trial in patients with end-stage renal disease. *Contrib Nephrol*, 66:85–93.

Casadevall N, Nataf J, Viron B, et al. 2002. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. *N Engl J Med*, 346:469–75.

Collins AJ, Kasiske B, Herzog C, et al. 2005. The United States Renal Data System 2004 annual data report. *Am J Kidney Dis*, 45(Suppl 1).

Collins AJ, Li S, St Peter W, et al. 2001. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*, 12:2465–73.

Eschbach JW, Egrie JC, Downing MR, et al. 1987. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med*, 316:73–8.

Foley RN, Murray AM, Li S, et al. 2005. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol*, 16:489–95.

Foley RN, Parfrey PS, Harnett JD, et al. 1996. The impact of anaemia on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Am J Kidney Dis*, 28:53–61.

Foley RN, Parfrey PS, Morgan J, et al. 2000. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int*, 58:1325–35.

Foley RN, Parfrey PS, Sarnak MJ. 1998. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*, 32(Suppl 3):S112–19.

Frank H, Heusser K, Hoffken B, et al. 2004. Effect of erythropoietin on cardiovascular prognosis parameters in hemodialysis patients. *Kidney Int*, 66:832–40.

Frifelt JJ, Tvedegaard E, Bruun K, et al. 1996. Efficacy of recombinant human erythropoietin administered subcutaneously to CAPD patients once weekly. *Perit Dial Int*, 16:594–8.

Furuland H, Linde T, Ahlmen J, et al. 2003. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant*, 18:353–61.

Grzeszczak W, Sulowicz W, Rutkowski B, et al. 2005. The efficacy and safety of once-weekly and once-fortnightly subcutaneous epoetin beta is effective in peritoneal dialysis patients with chronic renal anaemia. *Nephrol Dial Transplant*, 20:936–44.

Halstenson CE, Macres M, Kats Sa, et al. 1991. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther*, 50:702–12.

Harnett JD, Kent GM, Foley RN, et al. 1995. Cardiac function and hematocrit level. Am J Kidney Dis, 25(Suppl 1):S3–7.

Hayashi T, Suzuki A, Shoji T, et al. 2000. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis*, 35:250–6.

Hynes DM, Stroupe KT, Greer JW, et al. 2002. Potential cost savings of erythropoietin administration in end-stage renal disease. *Am J Med*, 112:169–75.

Jungers P, Choukroun G, Oualim Z, et al. 2001. Beneficial influence of recombinant human erythropoietin therapy on the rate of progression of chronic renal failure in predialysis patients. *Nephrol Dial Transplant*, 16:307–12.

Kaizu K, Uriu K, Eto S. 1993. Effects of recombinant human erythropoietin (EPOCH) on the coagulation and fibrinolytic systems and platelet function in pre-dialysis patients with chronic renal failure. *Japan J Nephrol*, 35:989–97.

Kaufman JS, Reda DJ, Fye CL, et al. 1998. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. *N Engl J Med*, 339:578–83.

Kaupke CJ, Vaziri ND, Sampson JR, et al. 1990. Effect of erythropoietin therapy on diet and dialysis clearances in hemodialysis patients. *Int J Artif Organs*, 13:218–22.

KDOQI; National Kidney Foundation. 2006. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis*, 47(Suppl 3):S11–145.

Keith DS, Nichols GA, Gullion CM, et al. 2004. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*; 164:659–63.

Kleophas W, Kult J, Kreusser W, et al on behalf of the Collaborative Study Group. 2003. Tolerability and efficacy of multidose epoetin beta (NeoRecoPen®) for subcutaneous administration in patients with anemia due to renal failure. *Kidney Blood Press Res*, 26:192–8.

Koch KM, Koene RA, Messinger D, et al. 1995. The use of epoetin beta in anemic predialysis patients with chronic renal failure. *Clin Nephrol*, 44:201–8.

Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, et al. 2006. Association of anemia with outcomes in men with moderate and severe chronic kidney disease. *Kidney Int*, 69:560–4.

Kuriyama S, Tomonary H, Yoshida H, et al. 1997. Reversal of anemia by erythropoietin therapy retards the progression of chronic renal failure, especially in non-diabetic patients. *Nephron*, 77:176–85.

Levin A. 2001. Prevalence of cardiovascular damage in early renal disease. *Nephrol Dial Transplant*, 16(Suppl 2):7–11.

Levin A. 2002. The role of anemia in the genesis of cardiac abnormalities in patients with chronic kidney disease. *Nephrol Dial Transplant*, 17:207–10.

Levin A, Djurdjev O, Duncan J, et al. 2006. Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes. *Nephrol Dial Transplant*, 21:370–7.

Levin A, Djurdjev O, Thompson C, et al. 2005. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis*, 46:799–811.

Levin A, Thompson CR, Ethier J, et al. 1999. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*, 34:125–34.

Lin FK, Suggs S, Lin CH, et al. 1985. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A*, 82:7580–4.

Locatelli F, Aljama P, Barany P, et al; European Best Practice Guidelines Working Group. 2004. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant*, 19 (Suppl 2):ii1–47.

Locatelli F, Aljama P, Barany P, et al. 2004b. Erythropoietic proteins and antibody-mediated pure red cell aplasia: where are we now and where do we go from here? *Nephrol Dial Transplant*, 19:288–93.

Locatelli F, Baldamus CA, Villa G, et al; on behalf of the Study Group. 2002. Once weekly compared with three-times weekly subcutaneous epoetin β: results from a randomized, multicenter, therapeutic equivalence study. *Am J Kidney Dis*, 40:119–25.

Locatelli F, Marcelli D, Conte F, et al. 2000. Cardiovascular disease in chronic renal failure: the challenge continues. Registro Lombardo Dialisi e Trapianto. *Nephrol Dial Transplant*, 15(Suppl 5):69–80.

Locatelli F, Pisoni RL, Combe C, et al. 2004. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*, 19:121–32.

Lui SF, Law CB, Ting SM, et al. 1991. Once weekly versus twice weekly subcutaneous administration of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. *Clin Nephrol*, 36:246–51.

Ma J, Ebben J, Xia H, Collins A. 1999. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol*, l0:610–19.

Madore F, Lowrie EG, Brugnara C, et al. 1997. Anemia in hemodialysis patients: variables affecting this outcome predictor. *J Am Soc Nephrol*, 8:1921–9.

Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, et al. 2000. Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol*, 11:335–42.

Navarro JF, Teruel JL, Marcen R, et al. 1995. Improvement of erythropoietin-induced hypertension in hemodialysis patients changing the administration route. *Scand J Urol Nephrol*, 29:11–14.

Nomato Y, Kawaguchi Y, Kubota M, et al. 1994. A multicenter study with once a week or once every two weeks high dose subcutaneous administration of recombinant human erythropoietin in continuous ambulatory peritoneal dialysis. *Perit Dial Int*, 14:56–60.

Parfrey PS, Foley RN, Harnett JD, et al. 1996. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant*, 11:1277–85.

Parfrey PS, Foley RN, Wittreich BH, et al. 2005. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol*, 16:2180–9.

Portoles J, Torralbo A, Martin P, et al. 1997. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis*, 29:541–8.

Regidor DL, Kopple JD, Kovesdy CP, et al. 2006. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol*, 17:1181–91.

Robinson BM, Joffe MM, Berns JS, et al. 2005. Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. *Kidney Int*, 68:2323–30.

Roger SD, McMahon LP, Clarkson A, et al. 2004. Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): results of a randomized clinical trial. *J Am Soc Nephrol*, 15:148–56.

Rossert J, Levin A, Roger SD, et al. 2006. Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis*, 47:738–50.

Rossert J, McClellan WM, Roger SD et al. 2002. Epoetin treatment: what are the arguments to expect a beneficial effect on renal disease progression? *Nephrol Dial Transplant*, 17:359–62.

Saleh A, Krane NK, Caballero M, et al. 1991. Once weekly subcutaneous erythropoietin is an effective maintenance therapy in the treatment of anemia of end stage renal disease in patients on CAPD. *Adv Perit Dial*, 7:288–91.

Silverberg D. 2003. Outcomes of anemia management in renal insufficiency and cardiac disease. *Nephrol Dial Transplant*, 18(Suppl 2):ii7–ii12.

Sinnassamy P, Andre JL, Treize G, et al. 1993. Effect of treatment with human recombinant erythropoietin on the anemia of children with end-stage renal failure. French multicentre study. *Arch Fr Pediatr*, 50:201–8.

Storring PL, Tiplady RJ, Gaines Das RE, et al. 1998. Epoetin alfa and beta differ in their erythropoietin isoform compositions and biological properties. *Br J Haematol*, 100:79–89.

Thomas S, Rampersad M. 2004. Anaemia in diabetes. *Acta Diabetologica*, 41(Suppl 1):S13–17.

Volkova N, Arab L. 2006. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis*, 47:24–36.

Weiss LG, Clyne N, Divino Fihlho, et al; on behalf of the Swedish Study Group. 2000. The efficacy of once weekly compared with two or three times weekly subcutaneous epoetin β: results from a randomized controlled multicentre trial. *Nephrol Dial Transplant*, 15:2014–19.

Winearls CG, Oliver DO, Pippard MJ, et al. 1986. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet*, 2:1175–8.