



# Recombinant human epoetin beta in the treatment of renal anemia

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Anemia has obtained increasing relevance and attention in patients with chronic kidney disease as an independent cardiovascular risk factor, since a number of studies have clearly described a relationship between anemia and mortality in this population. This may be a consequence of the impact of anemia on cardiac function leading to the development of left ventricular hypertrophy. The availability of recombinant human erythropoietin has deeply changed the management of anemia in chronic kidney disease patients, representing the most important improvement in the management of this condition after the discovery of dialysis. Epoetin beta is one of the erythropoiesis-stimulating agents now available on the market. Different studies have shown that this drug, when administered once-weekly to hemodialysis patients, is as effective as three-times weekly administration; the less frequent administration schedule reduces nursing times and treatment costs. This is expected to potentially enhance patient compliance, helping more patients to achieve their target hemoglobin levels.

Cardiovascular disease (CVD) is the leading cause of death and hospitalization in patients with end-stage renal disease [1,2] with mortality rates that are approximately 10–20 times greater than those observed in the general population [3]. CVD frequency progressively increases during the course of chronic kidney disease (CKD), suggesting that processes contributing to its pathogenesis are already present at earlier stages of chronic nephropathies. This is also supported by the epidemiological observation that the percentage of patients dying because of CVD during the conservative phase of CKD is much higher than that of those reaching end-stage renal disease [4,5]. In this context, anemia has gained increasing attention: this is a frequent complication of CKD patients caused 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. Anemia not only significantly impairs patients' quality of life, but has also been implicated in the genesis and worsening of CVD.

## The link between anemia, cardiovascular morbidity & mortality

Several evidences indicate an association between anemia and the development of CVD [6–8]. Certainly, anemia reflects different comorbidities possibly negatively influencing patient outcome. Besides this, chronic anemia modifies cardiac function, by means of vasodilatation, cardiac

dilation and increased cardiac output, finally leading to left ventricular dilation and compensatory hypertrophy [9]. It has also been suggested that anemia, congestive heart failure and CKD are all inter-related, each causing the other to worsen, resulting in a vicious cycle of disease progression [10].

A number of studies have clearly described a relationship between anemia and mortality in CKD patients. In studies performed on large populations of prevalent hemodialysis patients in the USA, both total mortality rate and cardiovascular-related mortality rate were shown to increase, along with the decrease in hematocrit [11,12]. The same findings were confirmed in incident dialysis patients [13]. However, these registry studies were much limited by considering only a few number of potentially confounding covariates. In addition to data obtained from large registries (i.e., the US Renal Data System), the Dialysis Outcomes and Practice Patterns (DOPPS) study is another useful source of information. This is an international, prospective, observational study involving adult hemodialysis patients randomly selected from 308 representative dialysis facilities. Compared with the former observational studies, it has the advantage of adjusting for a large number of patient case-mix characteristics. Using DOPPS Phase I data, it was found that the relative risks for mortality and all-cause hospitalization were 5 and 6% lower, respectively, for every 1 g/dl

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greater Hb concentration (RR: 0.95 and 0.94, respectively;  $p \leq 0.003$  each) [14]. Similar findings were obtained from the analysis of 11,422 prevalent hemodialysis patients coming from five European countries (Euro-DOPPS) between 1998 and 2000 [2]. 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 [15]. Although less consistent, recent observations indicate a clear association between anemia and increased mortality also in CKD patients who are not yet on dialysis [16,17]. It should, however, be kept 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 have used time-averaged rather than single hemoglobin values when analyzing their impact on patients' survival [17,18].

#### Clinical benefits of correcting renal anemia

The gene encoding for EPO was cloned in 1985 [19] and recombinant human erythropoietin (rHuEPO) has been used in the treatment of renal anemia since 1986 [20,21]. The availability of rHuEPO has deeply changed the management of anemia in patients with CKD, allowing Hb levels to be effectively moved towards higher values and avoiding transfusion dependency. This, together with ameliorations in dialysis technology, has certainly contributed to significant improvements in patient well-being and quality of life. Starting from the clear association between lower hemoglobin levels and increased mortality in CKD patients, the availability of an effective therapy to treat renal anemia soon raised the question as to whether correcting anemia may be able to also improve patient outcome. Several intervention studies have been performed to test this hypothesis. Many of them were also aimed at verifying, through randomized allocation of the patients to different target Hb 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 end points (for instance, left ventricular mass). Preliminary data from mainly small, uncontrolled studies indicated that anemia correction was able to

lead to partial regression of left ventricular hypertrophy (LVH) [22–24], although such an effect was not confirmed in more recent studies [25–28]. In particular, the Anemia Correction in Diabetes (ACORD) Study investigated the effect of anemia correction on cardiac structure, function and outcomes in 172 patients with diabetes, mild to moderate anemia and stage 1 to 3 CKD [27]. These patients were randomized to either a Hb target of 13–15 g/dl or 10.5–11.5 g/dl to be obtained with epoetin beta treatment when needed. The primary end point was the change in left ventricular mass index (LVMI). Despite a nonsignificant trend of a decrease in LVMI in the high Hb group compared with the lower Hb group, at univariate analysis no significant differences were observed in median LVMI at month 15 between study groups (high Hb group, 112.3 g/m<sup>2</sup>; low Hb group, 116.5 g/m<sup>2</sup>). However, normalization of the Hb level prevented an additional increase in LVH and improved quality of life. Another open-label randomized comparative-group study demonstrated that early intervention to maintain Hb levels at  $11.0 \pm 1.0$  g/dl in CKD patients with subcutaneous epoetin alpha had no significant impact on left ventricular mass [28].

Other clinical trials dealt with the identification of the optimal Hb target to obtain better survival. In particular, their design started from the concept that complete anemia correction would give the best results in terms of decreased morbidity and mortality and improvement in quality of life. Besarab *et al.* were the first who tested the effect of Hb normalization compared with only partial anemia correction on mortality in patients on dialysis [29]. The study was actually halted after 29 months of follow-up 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 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 comorbidities to benefit from anemia normalization. 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. The interpretation of these findings is

complicated by the results of secondary analysis showing 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. Other studies performed in less compromised dialysis patients did not find a significant effect of complete anemia correction on survival, but these studies were not specifically designed to test mortality [30,31]. In addition, surrogate end points, such as left ventricular mass, were not shown to be positively affected by the achievement of higher Hb levels through rHuEPO administration in dialysis patients [32,33], with the only exception of quality of life, which seems to be positively influenced by complete anemia correction [33–35]. Starting from the concept that LVH and heart disease secondary to anemia usually develop in the earlier stages of CKD and that CKD stage 5 patients are more likely to have already established CVD, the possibility was raised that less complicated patients might benefit more from anemia correction. However, trials testing the effect of complete anemia correction on mortality in CKD patients that are not receiving dialysis have also given unsatisfactory results. Rossert *et al.* did not find any difference in the risk of cardiovascular adverse events between patients randomized to different Hb targets [36], but the study was primarily aimed at testing the effect of treatment on the rate of progression of CKD rather than on cardiovascular prognosis. More recently, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta study [33] tested the effect of complete anemia correction on a composite primary end point including sudden death, fatal or nonfatal myocardial infarction, acute heart failure, angina pectoris or cardiac arrhythmias resulting in hospitalization, fatal or nonfatal stroke, transient cerebral ischemic attack and peripheral vascular disease. This was a randomized, multicenter, open-label, parallel group trial enrolling 603 patients with moderate CKD (estimated glomerular filtration rate [GFR] of 15–35 ml/min) and mild-to-moderate anemia (Hb 11.0–12.5 g/dl), who were randomized to receive either immediate treatment with epoetin beta to obtain a Hb level of 13–15 g/dl or delayed treatment only when Hb levels had declined below 10.5 g/dl to attain a Hb target of 10.5–11.5 g/dl. As planned, the study finished 2 years after the final patient had been randomized. After a mean follow-up of

approximately 3 years, 105 patients had had a first cardiovascular event: 58 patients (19.2%) in the group randomized to complete anemia correction and 47 (15.6%) in the group randomized to a lower Hb target. The overall cardiovascular event rate was half that expected, possibly because of patient selection, trial effect and improved medical care. According to intention-to-treat analysis, the risk of reaching the composite primary end point was not different between the two groups; the frequency of death and hospitalization, together with changes in left ventricular morphology, were also similar between the two groups. Complete anemia correction was found effective only on quality of life. Negative findings were obtained also by another open-label trial, the Correction of Hemoglobin and Outcomes in Renal Insufficiency study [37], enrolling 1432 CKD patients not on dialysis. In this study, the randomization to a higher Hb target showed increased risk of observing the primary composite end point (death, myocardial infarction, hospitalization for congestive heart failure and stroke). Despite differences in study population and results of secondary analyses, these two large, prospective, randomized trials are consistent with the lack of significant effect of complete anemia correction in reducing mortality and CVD in CKD patients. To further complicate this, very recently a meta-analysis, which also took into account these two trials, has been published [35]. The analysis of nine randomized clinical trials enrolling 5143 patients led to the striking conclusion that patients in the higher Hb target group had a significantly higher risk of all-cause mortality and arterio-venous access thrombosis than those in the lower Hb target group. When considering these results, it should be taken into account that this meta-analysis was dominated by a single study and this limited its methodological value.

Taken together, 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 is achieved by normalizing Hb levels in CKD patients. However, this should not be used as an excuse for not using maximum strength in achieving the Hb targets recommended by international guidelines [38,39].

**Epoetin beta & renal anemia**  
**Pharmacology & pharmacodynamics**

At present, there are four erythropoiesis-stimulating agents available on the market for the treatment of renal anemia: epoetin alpha, epoetin beta, epoetin delta and darbepoetin alpha (Table 1). Epoetin alpha 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 into differences in their carbohydrate moieties [40]. Epoetin delta shares the same amino acid sequence as endogenous EPO, but is synthesized in human cells [41]. Darbepoetin alpha is biochemically different from endogenous EPO, due to two additional N-linked glycosylation chains 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, with darbepoetin alpha having the longest half-life.

A randomized cross-over study on healthy volunteers has highlighted a number of differences in pharmacokinetic and pharmacodynamic properties between epoetin beta and epoetin alpha [42]. In particular, it has been found that the terminal elimination half-life of intravenous epoetin beta is 20% longer than that of intravenous epoetin alpha. The half-life for epoetin beta is also longer with the subcutaneous route, although the difference is not statistically significant. These differences are probably due to differences in the types and relative proportions of the carbohydrate side chains on the glycoprotein molecules present in the two preparations.

Apart from comparison with other erythropoiesis-stimulating agents (ESAs), it has been observed that pharmacokinetics and pharmacodynamics of epoetin beta differ according to the route of administration. Despite the peak serum concentration, which is more than ten times greater following intravenous as compared with subcutaneous administration, the terminal elimination half-life of subcutaneous epoetin beta is almost threefold that of the same dose given intra-

venously [43]. This goes together with a greater response in absolute reticulocyte count by the subcutaneous route, suggesting that the response to epoetin is not related to its peak plasma concentration, but rather to its maintenance above a critical threshold concentration in the serum [43]. This prolonged half-life following subcutaneous administration of epoetin beta has opened the possibility of delaying the injection schedule 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. In addition, dose requirements to maintain target Hb levels are significantly lower when epoetin beta is administered subcutaneously compared with intravenously [43,44]. For this reason, current treatment guidelines [38,39] recommend the subcutaneous route of administration of epoetin beta in order to minimize treatment costs.

**Clinical use**

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. 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. Weiss *et al.* 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 [45]. After 24 weeks of follow-up, no significant differences were observed in Hb levels and in weekly epoetin beta dose between the two groups randomized either to receive once-weekly subcutaneous epoetin beta treatment or to remain on their original regimen (subcutaneous epoetin beta two- or three-times weekly). Differ-

**Table 1. Mean half-life of erythropoiesis-stimulating agents according to administration route.**

Erythropoiesis-stimulating agent	Intravenous (h)	Subcutaneous (h)
Epoetin alpha	6.8	19.4
Epoetin beta	8.8	24.2
Epoetin delta	9.9	33.1
Darbepoetin alpha	25.3	48.8

ing from that by Weiss and colleagues [45], the study by Locatelli *et al.* [46] 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 on 173 patients undergoing hemodialysis. In agreement with the finding by Weiss *et al.* [45], 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 [47–50], suggesting that a maintenance dose of subcutaneous epoetin beta is effective when given once-weekly also in this setting. Subcutaneous epoetin beta also corrects renal anemia in patients with CKD who do not require renal replacement therapy, as demonstrated by two different studies [51,52].

#### **Safety & tolerability**

More than 15 years of experience with epoetin beta has demonstrated its favorable safety and tolerability profile in patients with CKD. As with other ESAs, the most common adverse event is hypertension (Box 1). The pathophysiological mechanisms underlying this phenomenon are still not completely understood. The increase in blood viscosity secondary to anemia correction appears to be the most obvious one. Indeed, a recent meta-analysis comparing different Hb targets in the CKD population found that patients randomized to higher Hb targets had a significant higher risk of poorly controlled blood pressure than in the lower target Hb group when using the fixed effects model (i.e., a type of statistical analysis) [35]. This seems to be particularly true when anemia correction is achieved too rapidly. However, often blood pressure changes are not clearly related to Hb levels. Enhanced vascular reactivity and vasoconstrictor responses have been suggested to play a role. Given that ESA-induced hypertension seems to be dose-related, it is also possible that switching patients from intravenous to subcutaneous epoetin therapy, by allowing lower doses, may reduce the incidence of adverse events, above all hypertension. The results of a study on hypertensive hemodialysis patients under intravenous epoetin therapy are in line with this hypothesis: their predialysis blood pressure significantly decreased after

#### **Box 1. Most common side effects of therapy with epoetin beta.**

- Hypertension
- Seizure
- Thrombotic complications
- Vascular access thrombosis
- Headache
- Injection site pain

switching to subcutaneous administration, so that within 6 months nearly half of them were no longer considered hypertensive [53].

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 alpha [54,55]. Starting from 2003, the number of reported cases dramatically dropped. This may have been caused by the shift in administration route, reinforcement of product cold chain, or elimination of uncoated rubber syringe stoppers. Reports of PRCA with epoetin beta have been sporadic and limited [56].

#### **Future perspective**

Its proven efficacy and safety profile makes epoetin beta a safe and effective treatment option in the management of renal anemia. This is a frequent and early complication of CKD, which is clearly associated with adverse cardiovascular outcomes and poor patient survival. Despite this, the results of randomized, controlled trials aimed at testing the effect of anemia correction with ESA on hard and surrogate end points have been somewhat disappointing. In particular, data from these trials have not proven a major effect of complete anemia correction on LV mass and mortality. In the future we certainly need to understand why the hypothesis generated by observational studies, that Hb normalization improves outcome in CKD patients, has failed to be proven by randomized clinical trials. One likely explanation may be that both observational and clinical studies have mainly focused on Hb values and put ESA in second place, despite single Hb values often reflecting a wide range of ESA doses used to obtain them. By definition, observational studies consider the relationship between achieved Hb levels and outcome. On the contrary, in clinical trials the intention-to-treat analysis groups together patients who either achieve or do not achieve the target. This is flawless from the statistical point of view. However, the CKD population

is not homogeneous. In the particular setting of anemia, those who do not obtain anemia correction despite high ESA doses are probably a distinct subset of patients at much higher risk of negative outcome than the overall population. Their enrolment in clinical trials testing complete anemia correction may have reduced potential benefits of the experimental intervention, perhaps because of the co-existence of inflammation and malnutrition. Further studies aimed at better investigation of the complex mechanisms underlying ESA responsiveness will probably help not only in clarifying the inconsistency between observational and clinical studies, but maybe also

in identifying those patients who are more likely to benefit of higher Hb targets. This would also allow the rationalization of ESA expenditure and thus reduce the cost of treatment.

#### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.*

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### Executive summary

- Cardiovascular disease is the leading cause of death and hospitalization in patients with end-stage renal disease.
- Anemia is a frequent complication of chronic kidney disease.

#### **The link between anemia, cardiovascular morbidity & mortality**

- A clear association between hemoglobin levels, morbidity and mortality has been described in chronic kidney disease.
- Anemia may reflect different comorbidities influencing patient outcome.
- Anemia may negatively influence cardiac function by means of vasodilation, increased cardiac output and compensatory hypertrophy.
- Most recent observational studies considered not only point hemoglobin values, but used time-averaged values when analyzing their impact on patients' survival, since hemoglobin values are not stable over time in the majority of patients.

#### **Clinical benefits of correcting renal anemia**

- The availability of recombinant human erythropoietin has allowed hemoglobin levels to be effectively moved towards higher values avoiding transfusion dependency.
- Several intervention studies have been performed to test the hypothesis of whether complete anemia correction in comparison with partial correction may improve patient outcome.
- Preliminary data from small, uncontrolled studies indicated that anemia correction leads to partial regression of left ventricular hypertrophy.
- This effect has not been confirmed in more recent studies.
- Complete anemia correction has no major effect on patient survival and might be even harmful.
- Only quality of life seems to be positively influenced by complete anemia correction.

#### **Epoetin beta & renal anemia**

##### Pharmacology and pharmacodynamics

- Epoetin beta is synthesized in Chinese hamster ovary cells and share the same amino acid sequence as endogenous erythropoietin.
- Its intravenous half life is 20% longer than that of intravenous epoetin alpha and shorter than that of darbepoetin alpha.
- The terminal elimination half-life of subcutaneous epoetin beta is almost threefold that of the same dose given intravenously.

##### Clinical use

- The prolonged half-life following subcutaneous administration has opened the possibility of delaying the injection schedule when using this route of administration.
- 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 hemoglobin levels as the three-times weekly regimen.

##### Safety & tolerability

- Epoetin beta has a favorable safety and tolerability profile in chronic kidney disease patients.
- The most common adverse event is hypertension, mainly due to increased blood viscosity secondary to anemia correction

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