Anaemia management prior to dialysis: cardiovascular and cost-benefit observations

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Abstract
Anaemia correction with recombinant human erythropoietin (rh-EPO, epoetin) in end-stage renal disease (ESRD) patients has been associated with improved survival and quality of life, as well as lower overall treatment costs. Few studies, however, have evaluated the benefits of epoetin treatment given to chronic kidney disease (CKD) patients during the pre-dialysis period. A retrospective study of 89,193 incident haemodialysis patients in the Medicare system (age ≥ 67 years) assessed consistency of epoetin treatment before the start of dialysis and the outcome of patients once they reached ESRD. Patients were grouped according to consistency of epoetin treatment based on the available months of treatment in the 2-year period before starting dialysis. Only 15.6% of patients in the study received any epoetin before the initiation of dialysis. Patients who received no or infrequent epoetin (i.e. received epoetin in < 50% of possible months) had a significantly higher relative risk of cardiac disease and death than patients treated with epoetin more frequently. Patients who received no or infrequent epoetin also had significantly higher rates of hospitalization and overall treatment costs at the time of initial dialysis. These findings suggest that early epoetin treatment warrants further investigation in prospective, randomized studies. In summary, it is evident that the care of CKD patients can be improved. Evidence suggests that timely initiation of epoetin treatment to correct renal anaemia appears to be associated with improved survival of ESRD patients in the first year after start of dialysis and reduced costs of treatment.

Keywords: anaemia; chronic kidney disease; cost-benefit; epoetin; haematocrit

Introduction
The prevalence of end-stage renal disease (ESRD) is a problem of increasing magnitude. The most recent report of the United States Renal Data System (USRDS) has estimated that there were 378,862 prevalent patients in the year 2000 [1]. A projection for 2010 has forecast that 651,330 patients will receive treatment for ESRD, and that 172,667 new cases will present during that year (Figure 1) [2].

The increasing prevalence of ESRD creates an increasing burden on healthcare resources, as ESRD patients have a high prevalence of co-morbidity and consume significantly more resources than non-ESRD patients. At the start of dialysis, many patients have concomitant diabetes and the prevalence of cardiovascular disease (CVD) in patients with ESRD is also high [1,3]. Indeed, cardiovascular complications are the predominant cause of death among ESRD patients [1,4], and death rates from CVD are 10–30 times higher in dialysis patients than in the general population [5].

In addition, it has been estimated that 5.6 million elderly adults in the USA have early renal insufficiency, which may, in some patients, eventually progress to ESRD [6–8]. CVD risk factors tend to develop early in the course of chronic kidney disease (CKD), which further complicates treatment and subsequent survival [9–11]. Therefore, how patients are managed during the CKD phase may have important implications both on long-term outcomes for the patient and on the overall cost of treatment. For example, one study showed that the incidence of CVD is nearly twice as high in patients referred to a nephrologist < 6 months before starting dialysis than in patients who received effective nephrological care for > 3 years before dialysis [12]. Also, a recent observational study of over 66,000 haemodialysis patients showed that higher haematocrit (Hct) values (≥ 33%) in the first 6 months of dialysis were associated with lower rates of hospitalization and mortality in comparison with patients with lower Hct [13]. As anaemia usually develops well before dialysis is required [14],
early management of anaemia therefore has the potential to improve patient outcomes.

The current review focuses on the use of epoetin for the treatment of renal anaemia before dialysis. The effects of epoetin on correction of anaemia and the incidence of co-morbidities, as well as on the rate of hospitalization, long-term survival of patients and overall cost of treatment are considered.

Studies evaluating epoetin treatment in CKD patients

There are few published studies of the benefits of epoetin given to patients before dialysis. However, the studies that have examined anaemia correction with epoetin in CKD patients have demonstrated regression of left ventricular hypertrophy [15,16], delayed progression of kidney disease [17,18] and improved survival [19]. Although promising, these studies were observational in nature; the demonstrated association should be tested more directly in a prospective, randomized clinical trial.

A recent retrospective analysis investigated whether the usage level of epoetin before the start of dialysis affected the outcome of CKD patients [20]. Incident haemodialysis patient records (1995–1997) from the US Medicare System were assessed; all patients (n=89 193), aged 67 years or older, with at least one Medicare part A (hospital services) or part B (physician services) claim during the 2-year period before initiation of dialysis and for 6 months after were included in the study.

Patients were grouped according to epoetin exposure in the 2-year pre-dialysis period: group 0 (n=75 316) did not receive epoetin during this period; group I (n=5276) had received epoetin for <25% of possible months; group II (n=2422) had received epoetin for 25–50% of possible months; group III (n=2081) had received epoetin for 50–75% of possible months; and group IV (n=4098) were the most consistently treated patients, receiving epoetin for >75% of the possible months.

Only 15.6% of patients in the study received any epoetin during the 2-year pre-dialysis phase and only 4.6% of patients were in the group that received epoetin therapy most consistently. The data are consistent with the results of other observational studies conducted in the USA, which also reported a low rate of epoetin use before dialysis [19,21].

Association between epoetin treatment and Hct level in the pre-ESRD period

In patients receiving epoetin treatment most consistently, the mean Hct increased steadily over the first 4 months of treatment and then reached a plateau. This Hct response was similar to that observed in dialysis patients, with plateau values maintained by regular epoetin administration, and confirmed that epoetin therapy was delivered on a routine basis to patients in the consistent epoetin group [1].

Mean Hct at the time of initiation of dialysis was lowest in the groups receiving the least or no epoetin (~28% for all groups), and highest in the groups receiving 50–75% and >75% of possible epoetin treatments (29.2% for both groups) [20]. As this study was carried out before US guidelines for epoetin therapy had been published [22], Hct was generally lower than that now considered to be optimal (i.e. 33–36%).

Association between epoetin treatment, cardiac disease and mortality

Patients who received infrequent epoetin (in <50% of possible treatment months) or no epoetin therapy during the 2-year pre-dialysis period had a higher likelihood of having cardiac disease than those receiving epoetin more frequently (Figure 2; P<0.04) [23]. Also, the relative risk of death was lower in all groups who received epoetin in this period than in patients who did not receive epoetin (Figure 3). All-cause crude death rates in the ESRD period were assessed at 90 days, 6 months and 1 year after initiation of dialysis and the risk of death was assessed.
using a Cox regression model, adjusted for incidence year, race, gender, age, diabetic status and epoetin usage group [20]. There was a rank-ordered relationship between mortality at 90 days, 6 months and 1 year after starting dialysis based on the level of epoetin exposure. Patients receiving epoetin therapy for > 75% of possible months had a significantly lower relative risk of death over the 1-year post-ESRD period than patients receiving no epoetin ($P < 0.0001$); a similar trend was seen for all other comparisons between epoetin groups [20].

Patients who received epoetin for 50–75% of the 2-year pre-dialysis period and the group that received epoetin most consistently had similar lower associated relative risks of mortality after initiating dialysis. It would appear, therefore, that treatment with epoetin for at least half of this 2-year period is associated with improved outcomes compared with less frequent epoetin dosing. It is unclear from these result, however, whether the improved outcome achieved in patients who received consistent epoetin treatment results from a higher Hct, or whether patients receiving more consistent epoetin treatment also receive better overall medical care.

Fink et al. [19] have also assessed the mortality rate after initiation of dialysis in patients who received epoetin before dialysis. They also found that the mortality rate was lower in patients who received epoetin during this time, although in this study patients were not grouped according to the consistency of epoetin treatment.

**Association between epoetin, hospitalization rates and cost of treatment**

The retrospective analysis of US Medicare haemodialysis patients also evaluated the effect of epoetin treatment in the pre-dialysis period on the rate of hospitalization and overall treatment costs [24,25].
Patients were subdivided into three groups (rather than the five described previously): group 0 included patients who received no epoetin therapy during the CKD period; group I included patients who received inconsistent epoetin therapy for less than half of the possible time; and group II included patients who received more consistent therapy, with epoetin given for greater than half of the 2-year pre-dialysis period.

During the first ESRD service month, patients in the consistent epoetin dosing group spent fewer days in hospital than patients in the inconsistent and no epoetin groups (6.5, 8 and 11 days, respectively). After the first ESRD service month, there was little difference between groups in the rate of hospitalization, probably because the majority of patients (~95%) received epoetin during the post-ESRD period.

Treatment costs were also evaluated in this 2-year period (months −24 to −1) and for 6 months after initiation of renal replacement therapy [25]. Figure 4 shows the total allowable Medicare expenditure per member per month over the course of the study. During months −24 to −6, patients in the consistent epoetin dosing group had slightly higher total expenditures per member per month than patients receiving inconsistent or no epoetin dosing (explained by the costs of epoetin and iron therapy). At ~3–4 months before the start of dialysis, total costs of treatment began to increase in all groups; however, the magnitude of the increase was greatest in patients who had not received epoetin. By the time of the first ESRD service month, the total treatment costs in patients who had not received epoetin in the pre-ESRD period were almost US$2700 more per member per month than in those who received consistent epoetin therapy (Figure 4). The increased cost of treatment in patients who did not receive epoetin can be largely explained by the increased rate of hospitalization observed in this group. Although these results need to be verified in prospective, randomized trials, consistent use of epoetin treatment during the pre-ESRD period appears to be associated with cost savings.

No other studies have evaluated the cost of treatment post-ESRD based on the consistency of epoetin use before dialysis; however, a study of 66,761 incident haemodialysis patients has assessed the allowable cost of treatment in patients grouped according to Hct determined early in the ESRD period [13]. During the 1-year follow-up, total allowable Medicare expenditures per member per month decreased as Hct increased, and patients with Hct in the range of 36 to <39% had significantly lower associated costs in total and epoetin expenditure compared with patients with lower Hct. This study is consistent with recent USRDS data which reported that higher haemoglobin levels at initiation, >11 g/dl, appear to be associated with an ~3.6% lower overall cost of care in the first year on dialysis [1] and highlights the potential cost benefits of anaemia correction in patients with CKD.

Conclusions

To date, the timing and quality of care of patients with CKD has received only limited attention. It is evident that there is room for improvement in the management of patients during the pre-dialysis period. In particular, very few patients receive regular anaemia treatment with epoetin before the initiation of dialysis.

A large-scale observational study of ESRD patients conducted in the USA has highlighted the benefits of consistent epoetin treatment given for at least 1 year before the initiation of dialysis. Patients had higher Hct levels at first renal replacement therapy, a lower rate of mortality once dialysis was started and a decreased incidence of hospitalization in the pre-ESRD to ESRD transition period. Consistent epoetin treatment was also associated with lower overall costs of care, particularly during the month dialysis was started. It is possible that the improved outcomes associated with consistent epoetin treatment may reflect both higher Hct levels in these patients, and

![Fig. 4. Total allowable Medicare expenditure per member per month in patients grouped according to level of epoetin use during the 2-year pre-dialysis period (St Peter et al. [25] with permission).](image-url)
also more consistent medical care in the pre-dialysis period. Nevertheless, the promising results from this study warrant further investigation of consistent epoetin treatment versus consistent clinical care prior to dialysis requirement.

The implication of this study may directly apply to the ever-increasing number of patients coming to dialysis and those who have evidence of CKD. Improvement in care during the pre-dialysis period, including the timely treatment of anaemia with the administration of epoetin, if needed, has the potential to improve the long-term outcome of patients. Taking this into account, KDIGO guidelines have been published recently to address the need to manage CKD patients from an early stage [7]. Moreover, the reduction in overall costs associated with the early treatment of renal anaemia may decrease the burden on the already overstretched healthcare system.

References