Update on Erythropoietin Treatment: Should Hemoglobin Be Normalized in Patients with Chronic Kidney Disease?

Ernesto Paoletti and Giuseppe Cannella
Divisione di Nefrologia, Dialisi e Trapianto, Azienda Ospedaliera Universitaria San Martino, Genova, Italy

The partial correction of ESRD anemia by recombinant human erythropoietin (EPO) has resulted both in generalized improvement in quality of life and physical activity and in reduced mortality and hospitalization rate. The question remains as to whether normalizing hemoglobin (Hgb) is desirable in patients with chronic kidney disease (CKD). This review provides an analysis and commentary on the available reports and, for the most part, randomized, controlled trials on the topic. In dialysis patients, normalization of Hgb is associated with improved quality of life and exercise capacity but not with reduced mortality and hospitalization rate. Moreover, no significant changes in the degree of left ventricular hypertrophy have been demonstrated. By contrast, an increased mortality rate has been reported for hemodialysis patients with overt cardiovascular disease (CVD) when randomly assigned to normal hematocrit by EPO. Data regarding patients who have CKD but are not yet on renal replacement therapy are scarce, and the effects of EPO on renal disease progression require further elucidation through controlled trials. The conclusion that can be drawn from the available studies is that Hgb >11 g/dl is the minimum required to achieve improved quality of life in patients with CKD, whereas values >12 g/dl are not recommended for patients with overt CVD. Finally, Hgb normalization might reasonably be restricted to a selected population of younger, employed, and active individuals, provided that they do not have CVD.


The partial correction of ESRD anemia by recombinant human erythropoietin (EPO) has resulted in generalized improvement in patients’ clinical conditions and outcomes. Indeed, current evidence exists that a hemoglobin (Hgb) level >11 g/dl is associated with improvement in quality of life (1), with increase in physical performance (2), with reduced risk for hospitalization, and with lower relative risk for mortality (3–5). Furthermore, partial correction of ESRD anemia has been shown to be effective in inducing a significant regression and even a renormalization of the left ventricular hypertrophy (LVH) of uremic anemic patients (6).

Consistent with this body of evidence, the National Kidney Foundation Dialysis Outcomes Initiative (K/DOQI) guidelines for the management of anemia of chronic kidney disease (CKD) recommend Hgb values between 11 and 12 g/dl (7), whereas the recently updated version of the European Best Practice Guidelines recommends a minimum target Hgb value of 11 g/dl without indicating an upper Hgb level limit (8). However, the optimal Hgb target level has not been elucidated clearly, and debate continues as to whether Hgb should be normalized in patients who have ESRD, with the aim of further improving their general and cardiovascular (CV) outcomes.

Results from Observational Studies

Quality of life further improved after normalization or near normalization of Hgb (9–11). Moreover, normalization of Hgb has been associated with greater work capacity (12), although a significant increase in maximum oxygen uptake after exercise was demonstrated only in trained individuals regardless of the level of Hgb, suggesting that factors other than anemia correction might play a role in the improvement of physical performance (13).

Hgb values >12 g/dl have been associated with significant decrease in the risk for death as compared with the 11–12-g/dl Hgb target values recommended by K/DOQI guidelines, and the same was observed for the hospitalization rate (14). However, no difference was demonstrated in the mortality rate of patients with normalized Hgb as compared with patients with Hgb in K/DOQI range when data were adjusted for covariates such as age, race, gender, body mass index, albumin concentration, urea reduction ratio, and the presence of diabetes (14). The number of hospitalizations also was not significantly different after adjustment for the same covariates (14).

Randomized, Controlled Trials Comparing Normal and Subnormal Hgb Levels

A meta-analysis by Strippoli et al. (15) on behalf of the Cochrane Renal Group evaluated the randomized, controlled trials that have compared the effects of normal and subnormal Hgb levels in renal patients. The authors found four studies in 1949 patients that compared subnormal and normalized Hgb and three studies in 255 patients that compared untreated and EPO-treated patients. The analysis found that relative risk for death from all causes was actually raised in the group with normalized Hgb as compared with lower Hgb, whereas no significant differences were evident in untreated patients as compared with treated patients. Moreover, no differences in the relative risk for arterial hypertension were demonstrated be-
between subnormal and normalized Hgb groups, whereas an increase in the development of hypertension in EPO-treated patients emerged from the studies that compared treated and untreated patients (15). The main source of the meta-analysis data, with a weighting ranging from 72 to 86% of the total, was the Normal Hematocrit Cardiac Trial published by Besarab et al. (16) in 1998. This trial was designed to ascertain whether further benefit could be gained by normalizing Hgb concentration in dialysis patients with ischemic heart disease (IHD) or cardiac failure. The study was interrupted after an interim analysis identified a borderline higher mortality rate in the group of patients who were randomly assigned to normal Hgb. Subsequent analysis of data, however, failed to demonstrate a causal relationship between the normalization of Hgb and mortality. Furthermore, the analysis of the secondary CV end points of that study, such as hospitalization for congestive heart failure (CHF) or IHD, nonfatal myocardial infarction, and the incidence of revascularization procedures, confirmed that no significant differences existed between normalized and lower Hgb groups. Therefore, the conclusion that can be drawn from study of Besarab et al. (16) is that achieving an Hgb target of almost 14 g/dl does not confer any advantage to patients with ESRD, at least in the case of patients with CV disease (CVD).

The Scandinavian Multicentric Study, which evaluated >300 patients who had ESRD and were on renal replacement therapy (RRT) and 72 patients who had CKD and were not yet on a dialysis regimen, confirmed that achieving near-normal Hgb did not reduce the risk for death from all causes or the risk for cardiac death. The latter risk actually increased slightly, although not significantly, in the group of dialysis patients with normalized Hgb concentration (11).

The Multicenter Canadian Trail evaluated the impact of Hgb normalization on cardiac outcomes in dialysis patients with asymptomatic cardiomyopathy. The achievement of normal Hgb did not significantly reduce either left ventricular mass or volume as compared with lower Hgb in patients with either pre-existing concentric LVH or left ventricular dilation (10). Indeed, maintaining subnormal Hgb concentration by EPO in dialysis patients was enough to obtain a regression of LVH provided that an adequate BP control and a reduction in pulse pressure were achieved by means of angiotensin-converting enzyme inhibitors (17).

Studies in CKD Patients Not Yet on RRT

The great majority of studies that have evaluated the effects of partial or complete correction of the anemia of ESRD have focused on patients who were undergoing RRT. By contrast, very few data are available on patients with CKD before the start of RRT. In this setting, an unfavorable scenario was demonstrated by a recent survey from the European Dialysis and Transplant Association, which showed that <30% of predialysis patients with CKD had Hgb >11 g/dl, and only 25% were on established EPO treatment (18). This report is concerning because patients who did not receive EPO in the predialysis phase had greater incidence of both CHF and IHD.

The only randomized, controlled trial of predialysis CKD is the study by Roger et al. (19), in which the impact on cardiac and renal outcomes of an early treatment with EPO that achieved higher Hgb levels as compared with late intervention with lower Hgb was evaluated in patients with stages 3 to 4 CKD. After a 2-yr observation period, the left ventricular mass did not change significantly in either group. In another study, Silverberg et al. (20) reported a significant improvement in CV outcome and even a slowing in the progression of renal insufficiency after near normalization of Hgb by means of early treatment with EPO in both patients with and without diabetes and with CHF and mild renal dysfunction.

Indeed, published reports have proposed some potential benefits of EPO treatment on renal damage and the progression of renal disease (21,22), possibly by reducing the degree of tubular damage and the extent and progression of interstitial fibrosis (23). In one such study, patients who were treated with EPO had a slower decline of renal function than did untreated patients (21), whereas near normalization of Hgb was associated with lower serum creatinine values after 1 yr of observation in another study (22). Results from these observational studies, however, are not consistent with data from Roger et al. (19), who found no difference in the rate of decline of renal function in patients with Hgb that ranged from 12 to 13 g/dl compared with patients with Hgb levels of 9 to 10 g/dl.

Problem of Hgb Variability and Costs

Although K/DOQI Clinical Practice Guidelines (7) recommend target Hgb levels between 11 and 12 g/dl, this range may be too narrow. Indeed, a great variability exists in Hgb concentration in patients with ESRD. Many factors that are linked to individual response to EPO, variability in anemia management, and even in Hgb target and action threshold are involved. As a consequence, the optimal Hgb level and upper limit of the desired range have not been elucidated clearly. Laeson et al. (24) tracked patients who had ESRD and who were enrolled in Fresenius Medical Care North America and evaluated a 3-mo rolling average Hgb level, with the aim of quantifying the degree of Hgb variability and the percentage of patients with Hgb >12 g/dl when patients were treated to avoid lower Hgb limit. Only 38% of patients had Hgb levels within the K/DOQI range for target Hgb, with >60% having Hgb <11 g/dl or >12 g/dl. Through the subsequent 9 mo, a rightward shift was observed in the curve of distribution of Hgb to meet goal. A 23% increase in patients with Hgb >12 g/dl and 33% in patients with Hgb >12.5 g/dl was needed to reduce by approximately 20% the number of patients with Hgb below the lower limit of 11 g/dl. According to these results, an upper Hgb limit of 13.6 g/dl and a level range of 11 to 13.6 g/dl seems reasonable and seems to provide a more realistic outcome expectation (24).

The strategy of increasing or even normalizing Hgb in renal patients raises financial issues. In the United States, achieving higher Hgb has been associated with a large expenditure for EPO, approaching $1.5 to 2.0 billion per year. This expense may be higher than necessary without resulting in optimal benefit for patients (25). Indeed, large EPO doses are required mostly to increase Hgb from 12 to upper levels. However, although the transition from a subnormal Hgb level to the K/DOQI guide-
lines’ Hgb target is associated with a significant increase in life expectancy, according to a Markov model simulation that evaluated the quality-adjusted life years, only a small gain is associated with further Hgb increase to 12.5 or even 14 g/dl (26). It is interesting that the cost per quality-adjusted life year gained per patient is in the region of $55,000 for transition from sub-normal Hgb to target level, whereas it approaches $800,000 for Hgb normalization. Therefore, a great increase in expenditures results in only a relatively small increase in life expectancy.

**Conclusion**

The normalization of Hgb in renal patients seems to be associated with further improvement in quality of life and physical activity but with no significant differences in mortality rate, hospitalization rate, and the extent of LVH regression. Moreover, normalizing Hgb has been associated with a higher incidence of vascular access clotting (16), whereas the effect of normalized Hgb in preserving renal function needs to be clarified. Hgb of 11 g/dl seems to be an appropriate minimum level of Hgb to target level, whereas it approaches $800,000 for Hgb normalization. Therefore, a great increase in expenditures results in only a relatively small increase in life expectancy.

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**References**


