Original Paper

Implications of a Reduction in the Hemoglobin Target in Erythropoiesis-Stimulating Agent-Treated Hemodialysis Patients

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Key Words

Anemia · Chronic kidney disease · Erythropoietin · Hemodialysis · Iron · Kidney failure

Abstract

Background: Patients treated with erythropoiesis-stimulating agents (ESAs) to a hemoglobin (Hb) level >12.0 g/dl have increased risk of multiple complications, including death. The optimal Hb target for ESA use has not been established. We hypothesized that reducing the target Hb would prevent levels >12 g/dl and lead to significant cost savings. **Methods:** Our target Hb range was reduced to 9–11 g/dl from 10–12 g/dl. Thirty-five chronic hemodialysis (HD) patients received erythropoietin (EPO) and intravenous iron from January to December 2009. Data analysis included: Hb level, EPO dose, transferrin saturation and ferritin levels. EPO was administered via subcutaneous injection weekly or twice weekly. **Results:** The mean monthly Hb level changed from 11.2 to 10.6 g/dl. The percentages of patients with mean Hb >10.0, 12.0 and 13.0 g/dl were 82 ± 6.5 , 10 ± 5.6 and $1.8 \pm 1.9\%$, respectively. Weekly EPO dose decreased from 9,500 to 5,600 units, a 40% reduction per dose per patient and costs. The savings exceeded USD 60,000 per year for 35 patients. More than 80% of patients had transferrin saturation >20% and ferritin >200 ng/ml throughout the entire period. **Conclusions:** Lowering the target Hb range to 9–11 g/dl in HD patients achieved quality anemia management, avoided values >12.0 g/dl and resulted in cost savings. A minimal reduction in quality of life and no change in cardiovascular morbidity or mortality would be expected. The study has important implications in the new American bundled reimbursement model.

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Introduction

Anemia is a frequent complication of chronic kidney disease (CKD) and if unmanaged can lead to severe consequences. Erythropoiesis-stimulating agents (ESA) are frequently employed in the management of CKD-induced anemia. ESAs are recombinant protein products intended to improve the outcome of CKD-related anemia [1]. However, treating patients with ESAs to higher hemoglobin (Hb) targets is associated with an increased risk of adverse effects, including death [2–5]. In previous studies, mortality has been associated with rapid ESA dose increases and rapid rises in Hb levels [6]. There is controversy surrounding what the optimal target Hb level in CKD patients should be. The black box warning of the Food and Drug Administration (FDA) was not to exceed Hb level >12 g/dl in ESA-treated patients [7], whereas the National Kidney Foundation-Kidney Disease Outcome Quality Initiative Anemia Guidelines recommend a Hb target range from 11 to 12 g/dl and not to exceed 13 g/dl [8]. (Recently the FDA issued a new guideline suggesting that ESAs be used only to reduce the frequency of transfusions [9].) Managing CKD-induced anemia to achieve a narrow target range is difficult due to Hb fluctuations. Recent data also suggest that the adverse effects associated with ESA treatment of CKD patients are dose dependent, with larger ESA doses, rather than the Hb target dose, being associated with mortality and adverse events [2–4, 6]. ESAs are very expensive drugs and mismanagement of anemia associated with CKD can increase costs. We hypothesize that in the context of uncertainty about the optimal Hb target, reducing the target Hb range in ESA-treated patients would prevent Hb levels >12 g/dl and at the same time lead to cost savings.

Subjects and Methods

After publication of the results of CHOIR [3] and CREATE [4] in 2006 and the issuance of FDA black box warnings in 2007, we lowered the Hb target range in our hemodialysis (HD) unit from 10–12 to 9–11 g/dl in late 2008. Our rationale was that the optimal Hb target was not established and that higher Hb targets were potentially unsafe. At the time of that decision, the results of TREAT were not yet available, but since we participated in the study, we were aware that the control group received rescue darbepoetin when hemoglobin fell <9 g/dl, which seemed a reasonable strategy [5]. Although in our relatively small unit we could not determine the optimal Hb target, we thought we should err on the side of safety and reduce the target. After reviewing the effect of treatment of anemia in CKD patients on healthcare-related quality of life [10], we thought the benefit of higher Hb targets was relatively small given the potential risks. We monitored the effect of this change in policy though our sample size would not suffice to establish if the change would lead to superior results. The policy change and monitoring were applied to all patients and did not constitute a research program, and therefore review by the institutional review board was not required.

The facility is a Department of Veterans Affairs Medical Center located in New York City. Patient demographics include mostly males, many >65 years old, receiving chronic HD, with diabetes and hypertension being the leading causes of kidney failure. We prospectively collected and retrospectively reviewed and analyzed data for 35 chronic adult HD patients who received EPO and intravenous iron from January to December 2009. Data analyzed included: Hb levels, EPO dose, transferrin saturation and ferritin levels. EPO was administered, as before, via subcutaneous injection weekly or twice weekly [11]. Ferric gluconate was administered intravenously to maintain transferrin saturation >20% and ferritin >200 ng/ml. Iron was also given to some patients with ferritin >500 ng/ml as per DRIVE (Dialysis Patients' Response to IV Iron with Elevated Ferritin) Study [12].

Fig. 1. Mean Hb levels in 2009.

Fig. 2. Average EPO dose in units per week in 2009.

Table 1. Number of Hb determinations >12.0 and >13.0 g/dl in 2009 versus 2007

	≤12.0 g/dl	>12.0 g/dl	≤13.0 g/dl	>13.0 g/dl	Total
Determinations of Hb, n					
In 2007	301	119*	382	38*	420
In 2009	377	43	413	7	420
Total	678	162	795	45	840

* $p < 0.001$ vs. 2009 (χ^2 test).

Results

The average 2009 monthly Hb levels fell from 11.2 g/dl in January to 10.6 g/dl in December. The percentage of patients with average monthly Hb in 2009 >10.0, 12.0 and 13.0 g/dl were 82 ± 6.5 , 10 ± 5.6 and $1.8 \pm 1.9\%$, respectively (fig. 1). The proportion of patients with values >12.0 and >13.0 g/dl was lower in 2009 compared with 2007 ($p < 0.001$, χ^2 test; table 1). The average weekly EPO doses decreased from 9,500 in January to 5,600 units in December (fig. 2). The reduction was approximately 40% per dose per patient, which translated to a 40% reduction in costs of treatment. The savings exceeded USD 60,000 for 35 patients in 2009 or approximately USD 1,750 per patient per year based on the costs to the Department of Veterans Affairs of USD 182 for 20,000 units of EPO. More than 80% of patients had transferrin saturation >20% and ferritin level >200 ng/ml throughout the entire period.

Discussion

The management of CKD-induced anemia continues to have several controversial components: optimal Hb levels, ESA doses, potential adverse outcomes and costs. Clinicians rely on various clinical practice guidelines to help guide anemia management. However, these

guidelines utilize data that include observational trials and expert opinions [8]. The most effective Hb target in patients with CKD remains to be determined and there is little evidence to support higher target Hb levels without the risks associated with ESAs. We revised the anemia guideline in our HD unit in order to address concerns about ESA utilization.

Prior to 2009, patients were treated with ESAs to a target Hb range of 10–12 g/dl, as recommended by the FDA anemia guidelines. This relatively narrow range and Hb variability led to many patients ($38 \pm 11.5\%$ in December 2008) occasionally having Hb levels >12 g/dl. Of those that had Hb levels >12 g/dl ($28 \pm 8.5\%$), $10 \pm 3\%$ of patients had Hb levels >13 g/dl. Due to these high percentages of patients achieving Hb >12 g/dl levels, we revised the target Hb range to 9–11 g/dl. By reducing the Hb target, we hoped to decrease the number of patients having Hb levels raised >12 g/dl.

The data demonstrate that by reducing Hb levels to 9–11 g/dl, we decreased the chance of having Hb levels rise to values >12 g/dl (fig. 1). At the same time, there was a decrease in ESA usage: from January to December 2009, the average EPO dose per week decreased from 9,500 to 5,600 units. This result yielded an approximately 40% reduction in ESA usage per dose per week. In 2009, we saved more than USD 60,000 for the approximately 35 patients we cared for.

Reducing the cost of treatment with ESAs is extremely important as the Center for Medicare and Medicaid Services (CMS) is moving toward a bundled reimbursement structure. The anticipated bundling of intravenous drugs including ESAs and intravenous iron into the dialysis composite rate is likely to lead to reductions in ESA utilization [11]. Given the results of TREAT [5], it is likely that reductions in Hb targets will be recommended by Kidney Disease: Improving Global Outcomes, CMS and FDA [12, 13]. The CMS is also looking at performance measures to ensure that ESA-treated patients achieve high-quality anemia management and the risk associated with adverse events linked to higher Hb levels and ESA doses is decreased. According to the FDA, patients treated with ESAs should be closely monitored and have their Hb levels cautiously raised to avoid transfusion [9].

In patients with CKD, estimating the ESA dose that is both safe and effective in maintaining adequate Hb levels is challenging. Our study demonstrates that CKD patients on average required EPO doses $<10,000$ units per week and that approximately $82 \pm 6.5\%$ of patients achieve Hb levels >10 g/dl. Our findings are important in the light of previous findings that keeping ESA dose equivalents $<16,000$ units per week may decrease the risk of mortality in HD patients. A benefit of weekly doses $>16,000$ units has not been demonstrated [14]. The National Kidney Foundation also recognizes the importance of individualizing the treatment of anemia. The treatment target should not be based on Hb level alone, but should carefully consider the individual patient's clinical status. In general, patients with CKD should maintain a target Hb concentration to avoid blood transfusion. The exact target Hb concentrations should be tailored to the patient's need, gender, age, ethnicity, activity and co-morbid conditions. Treatment with ESAs has improved patients' lives. However, recent studies have found that higher Hb targets cause harm. Practitioners have realized the value of ESAs in the management of anemia, but the high cost and new safety concerns should remind practitioners to reexamine ESA use [9, 15].

Our study is not without limitations. Outcomes were analyzed retrospectively and we used administrative data from a single dialysis center. We did not track iron utilization but administered iron per protocol to all patients to ensure that iron deficiency, whether absolute or functional, was not present [12]. We would predict that cumulative doses and costs associated with iron administration were lower with the lower Hb target, further contributing to the economic benefit. Hb variability and ESA dosing could be associated with other underlying patient characteristics. We cannot establish whether reducing the Hb target is associated with higher or lower mortality rates, with prevention of left ventricular hypertrophy or with reductions in health-related quality of life.

Conclusion

Treating patients with ESAs to higher Hb targets is associated with an increased risk of adverse effects, including death. Lowering the target Hb range to 9–11 g/dl in HD patients treated with EPO achieved quality anemia management with significantly fewer numbers of patients with a dangerous Hb rise >12 g/dl and at the same time resulted in cost savings.

Disclosure Statement

Dr. Goldfarb is a consultant for Takeda.

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