Erythropoietic Stimulating Agents and Quality of a Patient’s Life: Individualizing Anemia Treatment

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Summary
Erythropoietic stimulating agents (ESAs) such as erythropoietin have been used for decades to treat the anemia of CKD. Clinical practice guidelines suggest target hemoglobin levels >10 g/dl, and average Hb levels have risen from 9.6 to 12.0 g/dl. Several studies have shown trends for higher mortality and myocardial infarction, higher BP, increased vascular access thrombosis, and strokes in patients treated to target Hb ≥13 g/dl. Patients with profound anemia suffer from symptoms of fatigue, poor energy, weakness, and shortness of breath. Such symptoms reported directly by patients, or patient-reported outcomes (PROs), may be a valuable tool to target ESA treatment in anemic CKD patients. Studies show that improvements in anemia correlate with improvements in these PRO domains in some individuals. We propose that instead of Hb targets for all patients, treatment of anemia should be directed toward improving the areas of patient-perceived quality of life most affected by anemia. PROs can be used by individual patients to prioritize the risks and benefits of ESA treatment. Patients, along with their physicians, can examine Hb level in the context of patients’ perception of their quality of life and use ESAs judiciously to improve these perceptions.


The US Food and Drug Administration (FDA) recently changed the “black box warning” for administering erythropoietic stimulating agents (ESAs), further restricting their use in treating patients for the anemia associated with CKD (1). This action, along with policy changes enacted by the Centers for Medicare and Medicaid Services (CMS), similarly reducing the indications for ESA use, occurs at the same time that the nephrology community has reduced prescription of ESAs (2). These events reflect the growing concerns for the safety and efficacy of ESAs to treat anemia in dialysis patients and those with advanced CKD. This latest chapter in the story of a medicine that enjoyed a much anticipated approval in 1989, and a meteoric rise in use through the subsequent 2 decades, marks a dramatic fall from grace, driven by a series of clinical trials that showed harm to patients when ESAs were used in increasing doses to achieve near-normal goal hemoglobin (Hb) levels (3–5). The reasons for the change in fate for erythropoietin (EPO), both its ascent to a multibillion dollar a year drug as well as its decline, say something about our rationale and processes for drug approval and drug monitoring, as well as the role that patients play in these processes.

In the 1980s, the renal community buzzed with excitement as the clinical studies of the safety and efficacy of EPO were underway. Before then, dialysis patients and those with advanced CKD often had profound anemia, and many suffered from a lack of energy, fatigue, impaired physical functioning, and inability to perform activities of daily living (6). These patients often required frequent blood transfusions when iron and anabolic steroid treatments failed to improve the clinical symptoms of anemia and Hb levels failed to increase beyond 7 or 8 g/dl. Many patients, hoping for a kidney transplant, chose to minimize blood transfusions to reduce the likelihood of developing antibodies directed at multiple HLAs, which would make a donor match difficult or impossible. This all changed in 1989, when the FDA approved EPO for use in patients with anemia of CKD. The first National Kidney Foundation Dialysis Outcomes Quality Initiative published evidence-based guidelines for anemia management, and clinicians were advised to treat anemia based on Hb level goals of 11–12 g/dl (7). Clinical performance measures to assess the success of anemia treatment were developed, using target Hb levels as measures of quality. These clinical performance measures were used by ESRD Networks, CMS, and commercial insurers, who developed “report cards” for dialysis facilities and nephrologists to show how well they managed anemia. EPO was used widely and, along with iron supplements, succeeded in increasing the average Hb level among dialysis patients from 9.6 g/dl in 1991 to 12.0 by 2005 (8). Improvements in a wide variety of symptoms were suggested to occur with EPO administration. It became rare to see dialysis patients with Hb <9 g/dl, and <3% of dialysis patients in the United States have such profound anemia (2). The following question arose. Why not treat anemia to target sex-based normal levels? The Normal Hematocrit Trial tested this question in a prospective, randomized controlled (RCT) design, examining outcomes in 1233 dialysis patients with high cardiovascular risk, treated with high dose EPO to a target “normal” hematocrit of 42% versus target hematocrit 30% (4). The trial was...
stopped before it reached its predetermined enrollment and outcome goals, when the data safety monitoring board found that mortality and myocardial infarction were trending higher in the patients treated to the high hematocrit goal (9).

Although these findings raised some concern, treating to target Hb levels near normal remained the standard of care, without adjustments to the goal (11–12 g/dl). Other adverse events related to higher Hb targets were reported, including higher BP (10) and vascular access thrombosis (4). Patients with CKD not requiring dialysis were treated in increasing numbers to goal Hb levels. However, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta study (11) showed that EPO use to target a higher Hb level resulted in earlier need to start dialysis. With the publication of the Correction of Hemoglobin and Outcomes in Renal Insufficiency RCT (3), the evidence for harm related to ESA use raised more concern for these patients and their nephrologists. This study of patients with stage 3 or 4 CKD found no benefit and possible harm when Hb targets were ≥13 g/dl. In 2009, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (5) examined the question of whether the ESA darbepoetin reduced cardiovascular events compared with placebo. There were no differences in this primary outcome between the darbepoetin- and placebo-treated groups; however, there was an increased risk of stroke for patients treated with the ESA to an Hb target ≥13 g/dl. A subsequent meta-analysis showed that ESA treatment to higher Hb targets is associated with increased hypertension, stroke, and vascular access thrombosis, as well as a trend toward increased mortality and serious cardiovascular events (12,13).

The focus of these many years to attempt near-normalization of Hb levels was driven largely by the belief that anemia exacerbates cardiovascular disease, suggested by observational studies (14). With its reduced oxygen-carrying capacity to vital organs such as the heart, anemia was thought to be a major component of the high cardiovascular mortality suffered by so many dialysis and CKD patients. Thus, what a surprise to find that driving Hb to near-normal levels with ESAs and iron did the opposite—well done RCTs showed the undeniable association of using ESAs to target high Hb levels, with increased cardiovascular complications and death (12). The studies have not shown whether high doses of ESAs alone, or the rate of increase in Hb, or using ESAs in ever higher doses in ESA-resistant anemia contributed to these unexpected complications. What is clear is that targeting Hb to levels ≥13 g/dl is associated with harm in cohort-based studies. Because the safety and efficacy of lower Hb targets have not been systematically tested, it is unclear whether targeting Hb to some level <13 g/dl is safe and whether such treatment is helpful in cardiovascular health or all-cause mortality.

As we recall the pre-ESA era, when many patients were concerned with their loss of energy, fatigue, and their perceived limitations to perform the normal activities of daily living, we need to ask the following questions: Has our focus on treating anemia been in the wrong place? Is there evidence that correction of anemia improves the symptoms suffered by patients with profound anemia, and improves the quality of their lives? Instead of asking what the goal of Hb should be, should we instead ask at what Hb level do anemia-related symptoms become less burdensome for each individual patient (15)? Our patients are heterogeneous, with different comorbidities, functional levels, psychologic structures, and expectations. It is therefore likely that the Hb level eliciting life-altering symptoms will be different for each individual. To answer this question, we need tools to ask patients directly about their symptoms and activity limitations. Recently, the international Kidney Disease Improving Global Outcomes clinical practice guideline group suggested using patient-perceived quality of life (QoL) measures as outcomes to help guide ESA treatment of anemia. This recommendation is now undergoing public review. To do this properly, we need to understand the areas in which anemia affects patients’ QoL and focus attention on the patients’ experience of these symptoms.

Outcomes that patients consider important may be different than outcomes considered important by physicians. For example, decreased left ventricular mass, an outcome that has been correlated to survival in dialysis patients, has been used as an important outcome demonstrating the efficacy of daily hemodialysis (16). However, this outcome may have little or no meaning to individual patients, who may be more concerned with their ability to walk or dress themselves. Clearly both outcomes are important. When patients rank their valuations of disease-specific health outcomes, there is considerable variability from patient to patient. Fried et al. (17) asked 357 attendees of 3 senior centers and 1 independent/assisted living facility to prioritize 4 universal health outcomes: keeping you alive, maintaining independence, reducing or eliminating pain, and reducing or eliminating other symptoms. Staying alive was ranked first by only 11%, pain or other symptom relief by 13%, and independence by 76%. The authors concluded that these findings illustrate a potential role for health outcome prioritization. When each patient determines which health outcome is most important to him or her, this outcome can be used to make a best treatment plan. Although we are accustomed to using measures of physiologic outcomes, such as incidence of strokes or vascular access thrombosis, more attention is needed for patient-reported outcomes (PROs) and patient perceptions of their QoL.

Patients will need education to understand the variables that affect their outcomes, and physicians will need to understand the importance of patients’ prioritization of PROs and the importance of integrating PROs with other outcomes measures as patient-physician joint decision making develops.

Early in the ESA era, several observational trials showed improvements in multiple domains and various measures of patients’ QoL (18–21). Most of these studies were neither randomized nor blinded and therefore are difficult to interpret; they were not fully accepted by the nephrology community. The interpretation and comparison of different studies was complicated by differences in baseline, targeted, and achieved Hb levels. For example, some studies treated patients with Hb levels <8 g/dl, whereas others treated patients with Hb levels in the 10 g/dl range. Furthermore, many different instruments were used to assess patients’ QoL—some generic and some disease or symptom specific, complicating the interpretation of the data. When the FDA reviewed these reports, they suggested that the QoL studies indicating improvements in various domains were not convincing, and they dismissed such claims and removed QoL indications from the EPO label.
Studies using PROs as outcome measures have become more sophisticated in recent years and are now attracting more attention in the nephrology community (16,22,23). The FDA has published clear directives and rigorous guidelines about how PROs should be incorporated into drug treatment studies (24). They define a PRO as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” (p 2). Given the striking impairment in QoL in CKD and ESRD patients, PROs to assess patient perceptions of their QoL have been included as key outcome measures in important clinical trials in nephrology (16,22,23) and are now mandated by CMS to be monitored in all ESRD patients (25).

Several authors recently reexamined the studies that used PROs to assess the relationship between QoL and anemia treatment in CKD and ESRD patients (26–29). When all of the data are examined, improvements in anemia correlate with improvements in selected PRO domains in some individuals. The domains that improve are patients’ perception of fatigue, energy, vitality, and physical functioning. One such early study, the Canadian Erythropoietin Study published in 1990, was an RCT conducted with 118 patients for 6 months, comparing placebo-treated patients with mean Hb 7.4 g/dL, to two ESA-treated groups achieving mean Hb levels of 10.2 and 11.7 g/dL, respectively (30). The data from this study were recently reanalyzed from a QoL perspective and the reanalysis supports an association between anemia treatment and patients’ perception of fatigue, energy, weakness, and shortness of breath (31). These reviews suggest that there is a relationship between the baseline Hb level, the increment in Hb, and the improvement in patient-perceived QoL.

These studies raise the following question: Should the goals of ESA therapy incorporate the effect of the treatment on the patients’ perception of their QoL? These PRO instruments can focus attention on the specific domains that are affected by anemia, an important refinement to generic QoL instruments that may not demonstrate as clear a response to treatment. If there are risks associated with targeting higher Hb level but patients feel better with higher levels, who should determine the appropriate Hb target? This question is complex because health care providers may be in the best position to understand the physiologic risks, whereas patients are in the best position to weigh their own symptoms and priorities. Patients will need to prioritize their concerns and problems and participate in decision making. The challenge for providers is to explain the risks and benefits in an understandable way. This can be challenging given the high incidence of low health literacy (32), depression (33), and anxiety (34) in patients with kidney disease. Such joint decision making will require that tracking and monitoring patients’ perceptions of their QoL with a variety of PROs be incorporated into routine care. For some patients, the improvements in QoL may outweigh the physiologic risks of therapy.

We propose that treatment of anemia should be directed toward improving the areas of patient-perceived QoL most affected by anemia (i.e., fatigue, energy level, sense of vitality, and physical functioning). Clinical studies are needed to determine the best specific instruments to measure these PROs. To the extent possible, the effect of anemia and its treatment should be determined individually by each patient after the risks and potential benefits are fully explained. Patients need to be encouraged to prioritize the risks versus the benefits of treatment. Studies have convincingly shown that there are significant risks associated with a target Hb of 13 g/dL with little if any evidence to show an improvement in QoL. The risks of lower Hb targets are unclear. Instead of simply targeting Hb levels, we should be looking at the Hb level in the context of the patients’ perception of their QoL and use ESAs judiciously to improve these perceptions. As the nephrology community becomes increasingly aware of the importance of the individualization of care, we need to tailor our treatment algorithms to the individual needs of each patient.

Disclosures
A.S.K. received research/consultant support from Amgen and Affymax. S.F. received research/consultant support from Affymax, Rockwell, and Medgenics. F.O.F. received research/consultant support from Amgen, Affymax, and Akebia.

References


Published online ahead of print. Publication date available at www.cjasn.org.