

Safety of Erythropoiesis Stimulating Agents in Patients on Dialysis: Current Issues for Nephrology Nurses

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Patients with chronic renal failure (CRF) who are on dialysis typically suffer from severe anemia. Erythropoiesis stimulating agents (ESAs) have been used for nearly two decades to treat the anemia of CRF, reduce the need for red blood cell (RBC) transfusions, and mitigate the symptoms associated with this comorbidity (Eschbach et al., 1989).

The safety of ESAs has recently been questioned by reports from clinical studies in which doses designed to raise the hemoglobin (Hb) above 13.0 g/dL were administered to patients with CRF. Results from these studies revealed an increased risk for death and serious cardiovascular events when ESAs were administered to achieve the higher target Hb level. Patient safety is paramount and, although these data were primarily from off-label uses in subjects who were not on dialysis (Bohlius et al., 2006; Drüeke et al., 2006; Leyland-Jones et al., 2005; Singh et al., 2006), it was determined that the safety implications were relevant for all clinical indications—including patients with CRF on dialysis and not on dialysis. As a result, the prescribing infor-

Clinical data have repeatedly shown that the erythropoiesis stimulating agents (ESAs) Epoetin alfa and darbepoetin alfa are safe and efficacious to treat anemia in patients on dialysis when used in accordance with the product label. The safety profile of ESAs has recently been updated based on reports from clinical investigations that studied off-label uses of ESAs at doses designed to raise the Hb to above 13.0 g/dL. This article reviews the recent safety data and the current prescribing recommendations, with an emphasis on the need to follow the guidelines found in the products' package inserts to ensure the safe and efficacious use of these agents.

mation for all ESAs has been updated to include these data.

This article reviews the clinical safety and efficacy of ESAs in patients with CRF, the revisions in the ESA prescribing information that have resulted from the recent study results, dosing recommendations for ESAs, and the implications of these data for nephrology nurses and their patients. The article emphasizes the need to follow the recommendations found in the product's package inserts to ensure the safe and effective use of these agents.

Efficacy of ESAs in Patients on Dialysis

Clinical studies have repeatedly shown that ESAs are effective in ameliorating the anemia associated with CRF in patients on dialysis. In a landmark study conducted in patients on hemodialysis (N = 333), administration of Epoetin alfa resulted in an increase in Hb from less than 10.0 g/dL to approximately 11.7 g/dL, with 97.4% of subjects achieving this level within 12 weeks. These patients had required a total of 1,030 RBC transfusions in the 6 months prior to the initiation of Epoetin alfa to maintain usual daily activities (an average of 0.52 units per patient per month). After 2 months of treatment, virtually all patients were transfusion-independent and remained so after up to 52

weeks of follow-up (Eschbach et al., 1989).

Similar results have been observed in patients on dialysis receiving darbepoetin alfa. In two multicenter dose-escalation studies, darbepoetin alfa was administered intravenously to subjects on hemodialysis (n = 75) and subcutaneously to subjects on peritoneal dialysis (n = 47). Treatment with darbepoetin alfa resulted in a dose-related increase in Hb of at least 1.0 g/dL in 60% to 80% of subjects within the first month of therapy. Hb levels subsequently increased from a baseline of 8.4 to 8.7 g/dL to a plateau of 11.0 to 13.0 g/dL at 16 weeks, and were maintained in the study Hb range of 10.0 to 13.0 g/dL for up to 52 weeks (Macdougall, Matcham, & Gray, 2003).

Safety of ESAs

When prescribed according to the recommendations found in the package inserts, adverse events associated with Epoetin alfa and darbepoetin alfa are typically mild to moderate in severity. The most commonly reported side effects in clinical trials with Epoetin alfa were hypertension, headache, arthralgias, and nausea. The most commonly reported side effects in clinical trials with darbepoetin alfa were infection, hypertension, hypotension, myalgia, headache, and diarrhea. Both medications are con-

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traindicated in patients with uncontrolled hypertension (Amgen, 2007a; Amgen, 2007b).

Cases of pure red cell aplasia (PRCA) and severe anemia, with or without other cytopenias associated with neutralizing antibodies to erythropoietin, have also been reported in patients treated with ESAs. Although PRCA is rare, any sudden loss of response to ESA therapy that is accompanied by severe anemia and a low reticulocyte count should be evaluated. If anti-erythropoietin antibody-associated anemia is suspected, ESA therapy should be held. ESA therapy should be permanently discontinued in patients with confirmed antibody-mediated anemia (i.e., patients should not be switched to another ESA) (Amgen, 2007a; Amgen, 2007b).

In March 2007, the package inserts for Epoetin alfa and darbepoetin alfa were updated to include the warning that the use of ESAs increases the risk for death and serious cardiovascular events when administered to achieve a target Hb of greater than 12.0 g/dL. This warning was prompted in large part by the results of studies in patients with anemia from CRF and cancer that were undertaken to determine whether improved outcomes would result if the Hb was increased to levels beyond the currently recommended threshold. Many of these studies were conducted in subjects who were receiving ESAs for cancer-related indications. For example, an analysis of 57 randomized controlled studies including 9,353 subjects with cancer revealed an increased relative risk for thromboembolic events of 1.67, and a survival hazard ratio of 1.08 in subjects treated with ESAs compared with subjects who had not received ESAs (Bohlius et al., 2006; Leyland-Jones et al., 2005).

Two recent studies that contributed to the changes in the prescribing information were specifically conducted in subjects with CRF. The first study was the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study that

was sponsored by Ortho Biotech. In this prospective trial of 1,432 subjects who had CRF but did not require dialysis, subjects were randomly assigned to anemia correction with Epoetin alfa to target Hb levels of either 11.3 g/dL or 13.5 g/dL. At baseline, subjects had a mean Hb level of 10.1 g/dL and a mean glomerular filtration rate of 27 mL/min; about 50% had diabetes. The primary end point was a composite of cardiovascular-related consequences, including death, myocardial infarction (MI), hospitalization for congestive heart failure, and stroke (Singh et al., 2006).

This study was terminated early after an interim analysis showed little chance of demonstrating a reduction of the composite end point for the higher Hb group compared with the lower Hb group. Final results show that subjects randomized to a Hb of 13.5 g/dL had an increased risk of death (5% versus 7.3%: $P = 0.07$) and of hospitalization for congestive heart failure (6.6% versus 9%: $P = 0.07$), and a similar occurrence of MI and stroke (3% and 2%, respectively, in both groups: $P = \text{NS}$). The authors concluded that there were potential risks associated with a target Hb of 13.5 g/dL and recommended a target of 11.0 to 12.0 g/dL (Singh et al., 2006).

The second study was the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) trial that was sponsored by Roche. This study involved 603 subjects from 22 countries with Stage 3 to 4 CRF, together with mild to moderate anemia (Hb of 11.0 to 12.5 g/dL). These subjects received Epoetin beta (a product that is not available in the United States), and were randomized to a target Hb of either 13.0 to 15.0 g/dL or 10.5 to 11.5 g/dL. The hypothesis of this study was that cardiovascular outcomes would improve if Hb was normalized in subjects with CRF. Secondary end points included left ventricular mass index, quality-of-life scores, and the progression of CRF (Drüeke et al., 2006).

In a 3-year follow-up, investigators

found no significant difference in cardiovascular event rates or all-cause mortality between the two treatment groups. The decline in kidney function was not significantly different between groups ($P = 0.40$), although more subjects in the higher group required dialysis by the end of the study ($P = 0.03$). The only factors that differed between groups were general health and physical function, which improved significantly ($P = 0.003$ and $P < 0.001$, respectively) in the higher Hb group compared with the lower one. The authors concluded that complete correction of anemia does not reduce the risk of cardiovascular events (Drüeke et al., 2006).

These study results added to the data on the potential safety risks of targeting higher Hb levels that had originally been reported by a randomized, prospective trial of 1,265 subjects on hemodialysis who had clinically evident cardiac disease (i.e., ischemic heart disease or congestive heart failure). In this study, subjects were assigned to a target maintenance Hb of either 14.0 ± 1.0 g/dL or 10.0 ± 1.0 g/dL. As the study progressed, a trend toward higher mortality was observed in subjects randomized to the higher group (35% versus 29%). Although the difference in outcomes did not reach the prespecified statistical stopping boundary, the study was halted. The reason for the increased mortality was not determined (Besarab et al., 1998).

As a result of these cumulative data, the safety of ESAs and the recommended target Hb range were reexamined by both the Food and Drug Administration (FDA) and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI™), the sponsor of Clinical Practice Guidelines, including anemia of CRF. The FDA determined that a warning should be inserted in the prescribing information of all ESAs to include the statement that ESA therapy increases the risk for death and serious cardiovascular events when administered to a target Hb of greater than 12.0 g/dL. A specific target Hb level was also

removed from the prescribing information, and was replaced by the statement that the healthcare team should use the lowest dose of Epoetin alfa or darbepoetin alfa that will gradually increase the Hb concentration to the lowest level sufficient to avoid the need for RBC transfusions and not exceed 12.0 g/dL (Amgen, 2007a, Amgen, 2007b).

In light of these new clinical studies and the changes in the prescribing information for Epoetin alfa and darbepoetin alfa, KDOQI™ updated its *Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease*. This re-analysis included an evaluation of data from six randomized controlled trials that were not included in the last guideline revision in May 2006. On the basis of this assessment, the Work Group issued a revised draft recommendation, stating that “the target Hb should generally be in the range of 11.0 to 12.0 g/dL in patients with CKD.” This recommendation was based on the Work Group’s opinion that selection of a target Hb for an individual patient should include consideration of potential benefits (including avoidance of transfusion) and potential harm (including the risk of life-threatening adverse events). The Work Group also noted that Hb levels may vary in patients on dialysis, and stated that the target Hb should not be above 13.0 g/dL (National Kidney Foundation, 2007). A comparison of the previous and current target Hb recommendations is provided in Tables 1 and 2.

Dosing Recommendations for ESAs in Patients on Dialysis

To ensure the safe and efficacious use of ESAs, it is important that clinicians follow the dosing recommendations outlined in the prescribing information for Epoetin alfa and darbepoetin alfa (see Table 3). As previously stated, Epoetin alfa and darbepoetin alfa should be administered at the lowest dose required to gradually increase and maintain the Hb at a level sufficient to avoid the need for

Table 1
Comparison of Previous and Current Hb FDA-Approved Recommendations for Patients on Dialysis

	Previous Hb Recommendation	Revised Hb Recommendation
Epoetin alfa prescribing information	<ul style="list-style-type: none"> Target Hb range of 10 to 12 g/dL. 	<ul style="list-style-type: none"> Use the lowest dose that will achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.
Darbepoetin alfa prescribing information	<ul style="list-style-type: none"> Target Hb not to exceed 12 g/dL. 	<ul style="list-style-type: none"> Use the lowest dose that will achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusion and not to exceed 12 g/dL.

Table 2
Comparison of KDOQI™ Hb Recommendations for Patients with CRF

	Previous Hb Recommendation	Revised Hb Recommendation
NKF-KDOQI™	<ul style="list-style-type: none"> Hb should be 11.0 g/dL or greater. In the opinion of the Workgroup, there is insufficient evidence to recommend routinely maintaining Hb levels at 13.0 g/dL or greater in patients receiving ESAs. 	<ul style="list-style-type: none"> The selected Hb target should generally be in the range of 11.0 to 12.0 g/dL. The Hb target should not be above 13.0 g/dL.

Table 3
Recommended ESA Dosing Guidelines for Patients on Dialysis

Dosing/Administration Parameters	Epoetin alfa	Darbepoetin alfa
Starting dose	50 to 100 Units/kg administered IV three times a week	0.45 mcg/kg administered IV or SC once weekly
Maintenance doses	Individually titrate to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusions and not to exceed 12.0 g/dL.	Individually titrate to achieve and maintain the lowest Hb level sufficient to avoid the need for RBC transfusions and not to exceed 12.0 g/dL.

RBC transfusions and avoid Hb levels above 12.0 g/dL. Note that the Hb level at which a blood cell transfusion should be administered is based on individual patient characteristics, and is, therefore, up to the discretion of the treating physician. The prescribing information for ESAs does not

provide guidance on transfusion policies, and the revised prescribing information does not specify a Hb concentration at which physicians should consider an RBC transfusion (Amgen, 2007a; Amgen, 2007b).

Decisions to titrate ESA doses should be based on individual patient

parameters. At the onset of therapy, the dose should be increased by approximately 25% if the Hb does not increase by 1.0 g/dL after 4 weeks of therapy and Hb remains at a level not sufficient to avoid the need for RBC transfusions. In cases where the Hb remains below the level the nephrology team feels is necessary to avoid RBC transfusions, or when longitudinal laboratory data show a downward trend in Hb, the patient should be assessed for the presence of an underlying condition that may be affecting Hb (such as iron deficiency or bleeding). These conditions should be corrected whenever possible, and clinical judgment should dictate whether a change in the ESA dose is necessary. When appropriate, the ESA dose may be titrated upward by approximately 25% at 4-week intervals until the desired Hb is attained (Amgen, 2007a; Amgen, 2007b).

In cases where longitudinal trends in laboratory values show that Hb levels are increasing and approaching 12.0 g/dL, the ESA dose should be reduced by approximately 25%. If the Hb continues to increase, the ESA dose should be temporarily withheld until the Hb begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. The patient's response should be monitored carefully—especially during the dose titration phase—and the ESA dose should be reduced by approximately 25% if the Hb increases by more than 1.0 g/dL in any 2-week period (Amgen, 2007a; Amgen, 2007b).

Implications for Nephrology Nurses

The new safety data reemphasize the importance of adhering to the upper Hb limit of 12.0 g/dL that has consistently been recommended in the prescribing information for Epoetin alfa and darbepoetin alfa. Nephrology nurses, in collaboration with the healthcare team, will need to ensure that anemia management protocols are updated, if necessary, to

Table 4
Factors That Can Contribute to Hb Variability in Patients on Dialysis

Patient Factors/Comorbidities	Intercurrent Events	Practice Patterns
<ul style="list-style-type: none"> • RBC lifespan • Chronic inflammation • Secondary hyperparathyroidism • AIDS/HIV • Hepatitis C • Cancer/malignancies • Hematologic disorders 	<ul style="list-style-type: none"> • Infection • Acute inflammation • Hospitalization • Iron deficiency • Bleeding/hemolysis • Pure red cell aplasia • Medications • Interdialytic weight gain 	<ul style="list-style-type: none"> • Protocol design (i.e., comprehensive, integrated protocol) • Protocol compliance • Patient adherence • Lab monitoring • Hb level

ensure that the current ESA dosing recommendations are being followed.

The goal of maintaining a stable Hb is also complicated by the host of factors (see Table 4) that cause inevitable fluctuations in Hb levels in patients on dialysis (Breiterman-White, 2005; Breiterman-White, 2006). As a result, ongoing modifications in the anemia prescription are necessary for most patients, and nursing analysis of longitudinal trends in Hb (e.g., three to six Hb readings over a period of several weeks to months) is crucial to ensure that these conditions are detected proactively, thereby providing accurate data to guide ESA dosing decisions. The following case example illustrates how nursing assessment and intervention are key to avoiding excessively low or high Hb levels.

Case Study

K.C. is a 62-year-old male with ESRD caused by diabetes mellitus. He has been on hemodialysis for 6 years. His Hb had been maintained at an adequate level to avoid RBC transfusions with a prescription that included Epoetin alfa (6,800 Units administered IV three times a week) and routine maintenance doses of IV iron. Laboratory trends showed a slow decrease in Hb, and a nursing assessment subsequently revealed an inflamed and infected pressure ulcer on the back of the patient's leg. Following hospitalization for debridement of the ulcer, the patient returned

to the dialysis facility with a Hb that was more than 1.0 g/dL below the pre-hospitalization level. Antibiotics were prescribed, and a wound care protocol was initiated to ensure proper healing of the ulcer.

The decrease in Hb prompted the nurse to confer with the physician and recommend a proactive 25% increase in the dose of Epoetin alfa to mitigate the decline in Hb and minimize the risk for blood transfusion. The change in dose was discussed with the patient, who questioned the dose increase based on information he had heard regarding the safety of ESAs. The nurse and patient discussed the recommended treatment plan, including the potential negative ramifications of letting the Hb continue to fall (i.e., an increased risk of RBC transfusion) and data showing that these medications are safe and effective when used in accordance with the recommended prescribing information. The dose of Epoetin alfa was subsequently increased, and Hb monitoring was changed to twice weekly during the period of dose titration (note that twice weekly Hb monitoring was done during the original registration trial).

The Epoetin alfa dose was maintained, and the Hb slowly began to increase, reaching prehospitalization levels and stabilizing after about 10 weeks. Several months later the nurse noted that longitudinal laboratory trends revealed a slow increase in the Hb level. The dose of Epoetin alfa

was subsequently decreased by 25% to ensure that the Hb did not exceed 12.0 g/dL. The Hb level decreased slightly before stabilizing at the pre-hospitalization level.

This case illustrates how acute events such as hospitalization, infection, and inflammation can precipitate a sudden decline in Hb. While the preferred course is to correct the underlying event, it can sometimes take months to completely resolve a condition that is affecting Hb. In such cases, a proactive increase in the dose of ESA may be required to maintain Hb at a level that will minimize the risk for RBC transfusion. As shown in this case, it is also vital that the anemia management protocol contain provisions for frequent Hb monitoring and longitudinal trend assessment to ensure that the ESA dose is proactively decreased once the condition resolves.

Conclusions

The class of drugs known as ESAs has been used for nearly 20 years, and Epoetin alfa and darbepoetin alfa have improved anemia management in millions of patients worldwide. Darbepoetin alfa and Epoetin alfa are safe medicines when used in approved patient populations in accordance with FDA-approved dosing recommendations; the information contained in the approved labeling accurately reflects the current state of knowledge about the proper use of these important products.

Nurses and other members of the nephrology team are urged to follow the recommendations found in the prescribing information for Epoetin alfa and darbepoetin alfa to ensure that the use of ESAs continues to be both safe and efficacious. Ongoing nursing assessments and interventions will continue to be crucial in the management of anemia—ensuring that patients avoid the potential safety risks associated with inappropriately high or low Hb levels while continuing to experience the benefits associated with ESA therapy.

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