**IV Iron Use in Patients With Higher Serum Ferritin: Case Study on Anemia in Kidney Disease**

**Kristin Larson**

The following case study, along with an in-depth discussion, addresses the issues of anemia management practices in patients on hemodialysis that incorporate a balanced approach to erythropoiesis-stimulating agent (ESA) and intravenous (IV) iron therapy, use the lowest effective dose of ESA, and provide IV iron therapy in patients with higher serum ferritin levels have become important treatment considerations.

**Case Study**

**Patient Overview**

B.W. is a 75-year-old white woman with end stage renal disease (ESRD) on hemodialysis. She recently reported feeling greater fatigue and weakness than usual. Her hemoglobin (Hb) levels had been steadily declining despite escalating doses of an erythropoiesis-stimulating agent (ESA). Her Hb level now measures 10.4 g/dL, indicating that she is anemic.

**Medical History and Assessment**

The patient has been on maintenance hemodialysis for 3.5 years. She has a 10-year history of diabetes mellitus, which is controlled with diet. A diagnostic workup in September 2007 yielded an Hb of 11.5 g/dL, serum ferritin of 650 ng/mL, and transferrin saturation (TSAT) of 28% (see Table 1). At this time, the patient was on an aggressive ESA dosing regimen of 18,000 units per week administered intravenously. She was receiving a low weekly maintenance intravenous (IV) iron dose of 31.25 mg. Her blood pressure was elevated at 130/85 mmHg. Her weight was recorded as 58.97 kg. There were no obvious signs of infection.

In October and November 2007, laboratory testing revealed that the patient was anemic, as her Hb level steadily declined below the 11 to 12 g/dL target range recommended by the anemia management protocol (see Table 1). In December 2007, her Hb level further decreased to 10.4 g/dL. The patient’s TSAT level had decreased to 24%, whereas her serum ferritin level had gradually increased to 1025 ng/mL. At this time, her ESA dose had increased to 27,000 units per week and her maintenance IV iron dose had remained constant.

**Goal**

To identify anemia management practices for safely and effectively achieving appropriate hemoglobin (Hb) targets, reducing ESA requirements, addressing elevated serum ferritin levels, and overcoming obstacles to effective erythropoiesis.

**Objectives**

1. Evaluate a case study involving an increase in maintenance IV iron to improve Hb levels and overall patient outcomes.
2. Understand how to interpret updated KDOQI and FDA recommendations that address emerging information about ESAs, Hb targets, IV iron, and patients with elevated serum ferritin levels.
3. Discuss the relevance of this information for treating patients on hemodialysis who have anemia and recent evidence that IV iron administration is an effective solution for such patients.
Diagnostic Considerations and Treatment Options

To determine the best course of treatment for this patient, an anemia management team considered various factors and treatment scenarios.

Should the ESA dose be increased? To rapidly bring the patient’s Hb back into the desired target range, some anemia management protocols recommend increasing the patient’s ESA dose. In this patient, however, further increases in her ESA dose was not a viable option for several key reasons. First, the patient’s ESA dose was already on an upward trend without a corresponding hematologic response, indicating ESA hyporesponsiveness. A patient’s erythropoietic response can be reduced in the presence of inadequate iron stores, even with ongoing ESA therapy. Second, the patient was already receiving a high ESA dose of 27,000 units per week, and the use of high ESA doses can raise safety concerns. According to guidance from the National Kidney Foundation’s (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) and the U.S. Food and Drug Administration (FDA), the lowest effective ESA dose should be used (FDA, 2007a; NKF, 2006).

Should the IV iron dose be increased? Some clinicians may be reluctant to administer IV iron when serum ferritin levels are as high as those of this patient (i.e., 1025 ng/mL), citing that the KDOQI guidelines state that “there is insufficient evidence to recommend routine IV iron administration when serum ferritin is greater than 500 ng/mL” (NKF, 2006). Some clinicians misinterpret this statement as an indication to withhold IV iron when serum ferritin levels are greater than 500 ng/mL. However, the KDOQI guidelines do not suggest a specific upper serum ferritin level at which to withhold IV iron therapy, nor do they recommend withholding IV iron when serum ferritin exceeds 500 ng/mL. Rather, they advise weighing the patient’s clinical status, Hb level, ESA dose, and TSAT level when making iron treatment decisions at these higher serum ferritin levels. With this in mind, automatically limiting or withholding IV iron from this patient would be inappropriate.

It is important to consider that patients treated with ESA, particularly those similar to this patient who was receiving high ESA doses, may experience iron-restricted erythropoiesis, one form of iron deficiency (Adamson & Eschbach, 1989; Eschbach, Egrie, Downing, Browne, & Adamson, 1987; Tarrng, Huang, Chen, & Yang, 1999; Wish, 2006). In iron-restricted erythropoiesis, ESA therapy triggers a supraphysiologic rate of erythropoiesis such that red blood cell (RBC) production outpaces the rate at which iron can be released from storage and transferrin-bound circulating iron can be delivered to the erythroid marrow to support Hb synthesis. As ESA therapy increases the demand for iron, transferrin-bound iron becomes depleted and Hb production cannot be sustained. Iron-restricted erythropoiesis is characterized by elevated serum ferritin and low TSAT levels, which were observed in this patient. Therefore, increasing the maintenance dose of IV iron in this patient is a practical treatment option.

Another consideration is that a high serum ferritin level, low TSAT level, and elevated C-reactive protein (CRP) level (a measure of inflammation) could point toward reticuloendothelial (RE) blockade. An elevated CRP is associated with inflammation and erythropoietin resistance during hemodialysis (Sezer et al., 2004). Therefore, there was a possibility that inflammation was interfering with this patient’s ability to mobilize iron, thereby hindering effective erythropoiesis. Serum ferritin greater than 800 ng/mL, as observed in this patient, has been found to correlate strongly with inflammation and increased CRP levels (Kalantar-Zadeh, Rodriguez, & Humphreys, 2004). Therefore, assessing the patient’s CRP level would be a reasonable step in managing her anemia.

Treatment

After thoughtfully considering all of these factors, the anemia management team decided to look more closely at the patient’s entire clinical picture. They searched for a possible cause of the decreasing Hb levels, such as a gastrointestinal bleed, clotting in the dialyzer, and excess bleeding from the vascular access.

Table 1
Case Study: Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th></th>
<th>2008</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>September</td>
<td>October</td>
<td>November</td>
<td>December</td>
</tr>
<tr>
<td>ESA dose, U/wk</td>
<td>18,000</td>
<td>21,000</td>
<td>25,000</td>
<td>27,000</td>
</tr>
<tr>
<td>IV iron dose, mg/wk</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.5</td>
<td>10.9</td>
<td>10.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>650</td>
<td>760</td>
<td>840</td>
<td>1025</td>
</tr>
<tr>
<td>TSAT, %</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>January</td>
<td>February</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>ESA dose, U/wk</td>
<td>15,000</td>
<td>15,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV iron dose, mg/wk</td>
<td>125</td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.3</td>
<td>11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ferritin, ng/mL</td>
<td>800</td>
<td>620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSAT, %</td>
<td>27</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ESA = erythropoiesis-stimulating agent; IV = intravenous; Hb = hemoglobin; TSAT = transferrin saturation.
site, and also queried the patient for any unexplained bleeding, such as blood in the urine or bleeding from the nose or uterus. They also examined trends in the patient’s laboratory results and determined that the patient’s upward-trending ESA doses and simultaneously falling Hb levels, combined with her elevated serum ferritin and low TSAT levels, signaled ESA hyporesponsiveness.

Because insufficient available iron is a response-limiting factor for ESA therapy, the team investigated whether the patient was experiencing iron-restricted erythropoiesis and/or inflammation-mediated RE blockage. To help make this determination, the team ordered a CRP test in December. The patient’s CRP level was 25 mg/L, indicating inflammation (although signs of inflammation were not readily observed). In patients undergoing hemodialysis, a CRP value greater than 20 mg/L usually indicates an inflammatory state (Barany, Divino-Filho, & Bergström, 1997; Qureshi et al., 1998). After ruling out an active infection as the cause of the inflammation, the anemia management team increased the patient’s maintenance IV iron dose to 125 mg/wk to facilitate the release of iron stored in the RE system and jumpstart effective erythropoiesis.

**Follow-up and Outcomes**

In February 2008, after 1 month on the increased maintenance IV iron dosing regimen, the patient’s Hb increased to 11.8 g/dL, which was within the protocol’s target range (see Table 1). Her serum ferritin level decreased to 620 ng/mL, perhaps signaling resolution of an inflammatory state (Barany, Divino-Filho, & Bergström, 1997; Qureshi et al., 1998). After ruling out an active infection as the cause of the inflammation, the anemia management team increased the patient’s maintenance IV iron dose to 125 mg/wk to facilitate the release of iron stored in the RE system and jumpstart effective erythropoiesis.

**Key Discussion Points From Case Study**

**Lessons in Maintaining Appropriate Hb Levels**

The improvement observed in this patient following an increase in her IV iron maintenance dose raises several important issues for nephrology nurses to consider. One critical issue is the question of which treatment approach to take when formerly optimal Hb levels in a patient treated with ESA fall below the target range, as observed in the case study patient. In such cases, a strategy of many anemia management protocols has been to greatly increase the ESA dose to rapidly bring the patient back into the target Hb range. This strategy, however, assumes that erythropoietin deficiency is the sole cause of the Hb decline, when other contributing factors, such as insufficient iron, are possible. In fact, when a patient responds to IV iron with an increase in Hb or a decrease in ESA, outcomes that were observed in the case study patient, iron-restricted erythropoiesis and/or inflammation-mediated RE blockage should be suspected.

Insufficient iron is a common problem for patients on hemodialysis. They can lose an estimated 1.5 to 3 g of iron annually, in part because of ongoing blood losses related to frequent blood tests or access surgery, blood retention in dialyzers and tubing, or gastrointestinal and other sources of bleeding (Eschbach, 2005; Fishbane, Mittal, & Maesaka, 1999; NKF, 1997; Sakiewicz & Paganini, 1998). When these patients receive ESAs, increased utilization of iron for erythropoiesis further depletes their iron stores. Although a rapid increase in Hb might be achieved by giving a higher dose of ESA, this approach is ineffective if the patient is experiencing iron-restricted erythropoiesis. Administering large ESA doses will further exacerbate the lack of iron and lead to ESA hyporesponsiveness (Besarab, Frinak, & Yee, 1999; Eschbach et al., 1987; Fishbane & Maesaka, 1997; Sunder-Plassmann & Hör, 1997).

A decision to boost an ESA dose can lead to overshooting the Hb target, which is associated with increased risks. When anemia managers overshoot a patient’s Hb target, they sometimes attempt to compensate by withholding ESA therapy to restabilize the patient’s Hb level. This inconsistency in ESA dosing can cause the patient’s Hb levels to seesaw, an undesirable effect because fluctuating Hb levels are associated with poor patient outcomes (Besarab, 2006; Fishbane & Berns, 2005; Yang et al., 2007). A retrospective analysis of the association between Hb fluctuations and mortality in 19,150 patients on dialysis from the Fresenius Medical Care database in 1996 found that Hb variability strongly predicted death, independent of absolute Hb values and trends over time (Yang et al., 2007). The risk of death increased 33% with each 1-g/dL increase in Hb variability, even after adjusting for age, duration of ESRD, average Hb level, serum albumin, ESA dose, and several other factors. The researchers suggested that Hb variability may cause alterations in cardiac and autonomic nervous system function that affect patients’ survival.

A study of chain, hospital-based, and independent dialysis providers in 2003 found that, when Hb levels exceed the recommended Hb target, only 70% of the providers adjust ESA doses in accordance with KDOQI guidelines and FDA labeling instructions (Collins, Ebben, & Gilbertson, 2007). This leaves open the possibility that a large percentage of dialysis providers do not adequately adjust their ESA doses to the recommended Hb levels and may consistently be overshooting Hb targets and putting their patients at risk. Before initiating any ESA dose increases, it is wise to carefully evaluate the whole patient to determine underlying causes of the decrease in Hb level. Nurses can take an active role in this initiative by regularly monitoring iron markers to deter-
mine whether a patient’s iron status is sufficient to meet the increased iron demands of ESA therapy (Fishbane, Kowalski, Imbriano, & Maesaka, 1996). It is also important for nurses to be familiar with indicators of iron-restricted erythropoiesis, which include a normal or elevated serum ferritin level and a low TSAT level (Fishbane & Maesaka, 1997; Kopelman, Smith, Peoples, Biesecker, & Rizkala, 2007; Lin, Chang, Tan, & Leu, 2001; NKF, 2001; Wish, 2006). A patient’s TSAT, which indicates the amount of iron circulating in the body, may be reduced (generally less than 20%), a sign that circulating iron is being utilized more quickly than transferrin can replenish it with iron released from storage (Lin et al., 2001; Wish, 2006).

Nurses should heed signs that acute or chronic inflammation or infection is interfering with erythropoiesis. For example, an elevated CRP and/or a high erythrocyte sedimentation rate can indicate RE blockade, an extreme form of iron-restricted erythropoiesis that is associated with inflammatory states (Wish, 2006). In RE blockade, an inflammation-mediated process blocks the release of iron to transferrin in RE storage. Low TSAT and normal or elevated serum ferritin may be present in this scenario, because serum ferritin and TSAT increase and decrease, respectively, when inflammation occurs (Kalantar-Zadeh et al., 2004; Wish, 2006). According to the KDOQI guidelines, increased serum ferritin, decreased TSAT, decreased Hb, and increased ESA dose are characteristics of patients with inflammation-mediated RE blockade (NKF, 2006). Interestingly, the case study patient met all these criteria and benefited from an increase in IV iron.

Weighing these factors can help nurses to determine whether IV iron supplementation is required. Nurses’ findings in this area can help to avert unnecessary ESA dose increases and ultimately help to improve patient outcomes as well as contribute to the reassessment of protocols if necessary. Supplying IV iron may be the solution needed to help patients overcome iron-restricted erythropoiesis and/or inflammation-mediated RE blockade — and to safely help bring outlying Hb levels back into the target range (Coyne et al., 2007; Wish, 2006).

Hb Targets: Serious Safety Lessons

There are serious issues that underscore the importance of regular monitoring of laboratory parameters to identify the underlying cause when anemia management goals, such as optimal Hb targets, are not reached. One of these issues is that patients with suboptimal Hb levels are more likely to have decreased quality of life, impaired cardiac function, increased hospitalization stays, and greater risk of death (Gilbertson et al., 2008; NKF, 2006). In an analysis of Medicare data on 159,720 patients on hemodialysis who were treated with ESA and who survived the first 6 months of 2004, it was found that persistently low Hb levels were associated with the highest risk of death. The longer a patient’s Hb level remained below 11 g/dL, the greater the risk of death (Gilbertson et al., 2008). In a 2006 observational study of 58,058 patients receiving hemodialysis in a large dialysis organization, declining Hb levels and the need for higher ESA doses were associated with decreased survival (Regidor et al., 2006).

Recent evidence has shown increased safety risks with higher Hb levels in patients with CKD, particularly with the use of high-dose ESAs to target high Hb levels. The outcomes of two leading trials, Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta (CREATE), suggested that targeting Hb levels above 13.0 g/dL with an ESA in patients with CKD increases the risk of life-threatening adverse events (Drieke et al., 2006; Singh et al., 2006).

In the CHOIR study, 1,432 patients with CKD were randomized to receive more than 10,000 units of epoetin alfa per week, with 715 of these patients assigned an Hb target of 13.5 g/dL and 717 patients assigned an Hb target of 11.3 g/dL. Patients who were targeted to the higher Hb level had a significantly increased risk of death compared with those in the lower Hb target group (7.3% vs 5.0%; \( P = .07 \)). They also had a higher rate of hospitalization for congestive heart failure (9.0% vs 6.6%; \( P = .07 \)). Their composite end point of death, stroke, myocardial infarction, and congestive heart failure rate was worse (17.5% vs 13.5%; \( P = .03 \)), and they had an increased number of serious adverse events (see Table 2) (Singh et al., 2006).

Table 2

<table>
<thead>
<tr>
<th>End Point</th>
<th>High-Hb Group</th>
<th>Low-Hb Group</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite events (death, stroke, MI, CHF)</td>
<td>125 / 715 (17.5%)</td>
<td>97 / 717 (13.5%)</td>
<td>.03</td>
</tr>
<tr>
<td>Death</td>
<td>52 / 715 (7.3%)</td>
<td>36 / 717 (5.0%)</td>
<td>.07</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>64 / 715 (9.0%)</td>
<td>47 / 717 (6.6%)</td>
<td>.07</td>
</tr>
<tr>
<td>Any serious AE associated with ESA</td>
<td>10 / 688 (1.5%)</td>
<td>3 / 688 (0.4%)</td>
<td>.05</td>
</tr>
<tr>
<td>Serious AE: CHF</td>
<td>77 / 686 (11.2%)</td>
<td>51 / 688 (7.4%)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Note: Hb = hemoglobin; MI = myocardial infarction; CHF = congestive heart failure; AE = adverse event; ESA = erythropoiesis-stimulating agent.

Source: Singh et al., 2006.
In the CREATE study, 603 patients with CKD were randomized to receive epoetin beta. Of these patients, 301 were assigned to a target Hb of 13.0 to 15.0 g/dL and 302 to a target Hb of 10.5 to 11.5 g/dL. This study used a less aggressive ESA dosing regimen than the CHOIR study, but it too demonstrated a higher incidence of adverse events among patients with the higher Hb target, in addition to a greater incidence of progression to dialysis [see Table 3] (Drüeke et al., 2006).

The outcomes of the CHOIR and CREATE trials were released shortly after the updated KDOQI clinical practice recommendations and guidelines for anemia in CKD were published in May 2006. Therefore, the KDOQI publication did not account for the results of these trials and included a lower-limit Hb target of at least 11 g/dL and an upper-limit Hb target of 13 g/dL (NKF, 2006). Although the guidelines cited insufficient evidence to recommend maintaining an Hb greater than 13 g/dL, it did not suggest that physicians hold ESA doses when Hb was at this level or even higher. Instead, the KDOQI Work Group recommended decreasing ESA doses and using clinical judgment when maintaining an Hb of at least 13 g/dL, particularly in patients on hemodialysis or with cardiovascular disease (NKF, 2006).

In March 2007, after considering evidence from CHOIR and CREATE as well as ESA studies in patients with cancer, the FDA issued a safety advisory about ESAs and approved labeling changes for these drugs (FDA, 2007a). The FDA recommended using the lowest ESA dose possible to gradually increase the Hb concentration to avoid the need for transfusions. The FDA also recommended measuring Hb twice weekly after initiating ESA treatment until Hb is stabilized and withholding ESA if Hb increases beyond 12 g/dL or increases by 1 g/dL in any 2-week period (FDA, 2007a). The inherent message in the FDA recommendations was that physicians should scale back ESA doses.

The FDA recommendations, combined with the evidence from CHOIR and CREATE, sparked serious concerns in the nephrology community about how to safely use ESAs to achieve target Hb levels in anemia management. In the midst of the controversy, the NKF published an update to its guidelines on Hb targets in September 2007 (NKF, 2007). The update was based on a review of evidence that included the data from CHOIR, CREATE, and other trials comparing mortality rates and adverse events in patients assigned to higher and lower Hb targets. The update recommends an Hb target between 11 and 12 g/dL in patients with CKD who are treated with ESA, whether or not on dialysis (NKF, 2007). The update advises that the Hb target should not be above 13 g/dL in these patients. The guidelines state that targeting a higher Hb with an ESA has a greater possibility of causing harm than improving quality of life or decreasing transfusions (NKF, 2007).

In November 2007, the FDA further expanded its earlier advisory and labeling changes by approving revised boxed warnings and other safety-related product labeling changes for ESAs (FDA, 2007b). The revised boxed warnings for ESA dosing in patients with CKD who have anemia state that ESAs should be used to maintain the Hb from 10 to 12 g/dL. Maintaining higher Hb levels, according to the revised warnings, increases risk of death and serious cardiovascular reactions such as stroke, heart attack, or heart failure. The revised labeling includes directions for adjusting ESA doses and monitoring Hb levels in patients with CKD who do not respond to ESA therapy with an adequate Hb increase. The FDA also removed several quality-of-life claims that had been made previously with ESAs (FDA, 2007b). Table 4 summarizes the recent recommendations of both the FDA and NKF regarding Hb targets.

Although these developments have provoked anxiety among those who manage anemia in kidney disease, there are several treatment approaches through which nurses and fellow caregivers can continue to safely and effectively manage anemia in their patients.

### Treatment Considerations

#### Balancing IV iron and ESA.

The numerous issues surrounding Hb levels and ESA use highlight the need to balance ESAs with IV iron therapy. Effective erythropoiesis requires both iron and erythropoietin. Erythropoietin drives erythropoiesis by activating RBC production in the bone marrow, but iron plays an equally important role because it is utilized by the cells and incorporated into Hb during the process of RBC development. If there is insufficient iron available during this process, perhaps owing to a condition like iron-restricted

<table>
<thead>
<tr>
<th>End Point</th>
<th>High-Hb Group (n = 715)</th>
<th>Low-Hb Group (n = 717)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td>125 (17.5%)</td>
<td>97 (13.5%)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52 (7.3%)</td>
<td>36 (5.0%)</td>
<td>.07</td>
</tr>
</tbody>
</table>

**Table 3**

**Increased AE and Progression to Dialysis With ESA in High-Hb Group: CREATE**

**Note:** AE = adverse event; ESA = erythropoiesis-stimulating agent; Hb = hemoglobin.

**Source:** Drüeke et al., 2006.
erythropoiesis, microcytic, hypochromic RBCs will develop (Petroff, 2005).

An anemia management protocol that promotes a balance between IV iron and ESA therapy is one that avoids unwarranted withholding of IV iron based on serum ferritin levels, provides needed iron in a continuous, systematic manner, and makes certain that IV iron and ESA therapy are safely and appropriately dosed. An anemia management protocol with these characteristics can help to ensure that iron will be readily available when needed for effective erythropoiesis (Pruett, Johnson, & O’Keefe, 2007).

Likewise, nephrology nurses who understand the importance of IV iron and ESA therapy for effective erythropoiesis can incorporate this knowledge into anemia management practices. By accurately assessing the iron status of the patient and using the information gained to help devise an optimal IV iron and ESA dosing strategy, they can help the patient avoid unnecessarily high doses of ESA, receive needed iron, achieve effective erythropoiesis, and maintain target Hb levels (Besarab et al., 1999; Eschbach et al., 1987; Fishbane & Maesaka, 1997; Sunder-Plassmann & Hörl, 1997).

Reducing ESA requirements with IV iron. The safety issues and increased iron demands associated with higher ESA doses call attention to the need to treat patients with the lowest effective ESA dose. Evidence supports the ability of IV iron administration to facilitate reduction in ESA doses. There are several clinical trials that demonstrate IV iron’s capacity for reducing patients’ ESA requirements, among them the Dialysis Patients’ Response to IV Iron With Elevated Ferritin (DRIVE) trial and its 6-week follow-up extension known as DRIVE-II (Coyne et al., 2007; Kapoian et al., 2008). DRIVE was a 6-week, open-label, randomized study that demonstrated the efficacy of IV iron (sodium ferric gluconate) in improving anemia in patients on hemodialysis having Hb levels of 11 g/dL or less, a serum ferritin of 500 to 1200 ng/mL, and a TSAT of 25% or less and receiving adequate ESA doses. Patients in DRIVE were randomized to receive IV iron (1 g administered as 125 mg doses over 8 consecutive hemodialysis sessions) or no IV iron (control). Both groups received a 25% increase in ESA at the beginning of week 1. The ESA dose was then held constant for the next 6 weeks. Compared with the no iron group, the IV iron group had a greater Hb increase, a greater percentage of patients with an Hb response (defined as at least a 2 g/dL increase in Hb at any study point), and a faster time to Hb response (Coyne et al., 2007). DRIVE participants were enrolled in DRIVE-II, which observed patients for 6 weeks as they resumed routine management of ESA and IV iron therapy. DRIVE-II results showed that the IV iron group experienced a mean ESA dose decrease of about 21% from the

### Table 4

<table>
<thead>
<tr>
<th>KDOQI: 2006</th>
<th>Lower Limit of Hb</th>
<th>Upper Limit of Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 11 g/dL (evidence-based guideline; strength of evidence is moderate)</td>
<td>• Insufficient evidence to recommend maintaining Hb level of 13 g/dL or higher in ESA-treated patients (clinical practice recommendation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Should decrease but not hold ESA dose with Hb level of 13 g/dL or higher</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Use clinical judgment when maintaining Hb level of 13 g/dL or higher, particularly in patients undergoing HD and patients with CVD</td>
<td></td>
</tr>
<tr>
<td>KDOQI: 2007</td>
<td>• 11-12 g/dL (clinical practice recommendation)</td>
<td>• 13 g/dL (clinical practice guideline; strength of evidence is moderate)</td>
</tr>
<tr>
<td></td>
<td>• Targeting a higher Hb with an ESA poses greater possibility of harm than help</td>
<td></td>
</tr>
<tr>
<td>FDA: March 2007</td>
<td>• Use the lowest ESA dose possible to gradually increase Hb concentration</td>
<td>• 12 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If Hb increases beyond 12 g/dL or rises by 1 g/dL in any 2-week period, withhold ESA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Measure Hb twice weekly after ESA initiation until Hb stabilized</td>
</tr>
<tr>
<td>FDA: November 2007</td>
<td>• 10-12 g/dL</td>
<td>• 12 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintaining higher Hb levels increases risk of death and serious cardiovascular reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor patients with CKD who do not respond to ESA with adequate Hb increase</td>
</tr>
</tbody>
</table>

**Note:** KDOQI = Kidney Disease Outcomes Quality Initiative; FDA = United States Food and Drug Administration; Hb = hemoglobin; ESA = erythropoiesis-stimulating agent; CVD = cardiovascular disease; HD = hemodialysis; CKD = chronic kidney disease.

**Sources:** NKF, 2006; NKF, 2007; U.S. FDA, 2007a; U.S. FDA, 2007b.
DRIVE dose to the end of DRIVE-II, which was significant ($P = .003$) (see Figure 1). Additionally, the final ESA dose of the control group was significantly higher than that of the IV iron group ($P = .017$) (Kapoian et al., 2006). In addition, dramatic decreases in ESA requirements have been reported with several anemia management protocols that were revised to incorporate the DRIVE treatment paradigm, allowing patients with serum ferritin above 500 ng/mL to receive the IV iron dose deemed clinically necessary, instead of withholding iron at this level (Bralow, 2007; Pruett, Johnson, & O’Keefe, 2007). In one dialysis facility, a revised protocol called for a 1 g repletion course of IV iron (sodium ferric gluconate) in patients with TSAT less than 30%, serum ferritin less than 1500 ng/mL, and Hb of 8 to 15 g/dL. Implementation of the new protocol resulted in an approximately 30% decrease in ESA requirements (Amerling, Eason, & Juergensen, 2007). Before the new protocol, 70% of patients had no change in ESA dose, 16% had an increase in ESA dose, and only 14% had a decrease in ESA dose.

One study reported significantly greater cost savings resulting from reduced ESA requirements with the administration of 1 g of IV iron (sodium ferric gluconate) over 12 weeks in patients with high serum ferritin and low TSAT as defined by DRIVE, compared with administration of an ESA alone. Total cost per patient receiving IV iron plus an ESA was $3,524 per each g/dL increase in Hb, whereas the total cost per patient receiving an ESA alone was $5,065 per each g/dL increase in Hb (Pizzi, Bunz, Goldfarb, Coyne, & Singh, 2007).

These data, considered with the reduced ESA requirements of our case study patient after her maintenance IV iron dose was increased, provide useful information for nephrology nurses to consider. Nurses can encourage their anemia management teams to recognize the value of these data and follow a treatment protocol that allows patients to be treated with the lowest effective ESA dose and ensure that patients achieve their Hb targets safely and effectively.

**Stabilizing Hb levels with an appropriate IV iron maintenance regimen.** Intermittent IV iron may be sufficient for some patients on hemodialysis, but a maintenance IV iron dosing protocol is essential for most of these patients. The KDOQI guidelines acknowledge the importance of iron for effective erythropoiesis and support iron repletion and maintenance IV iron to achieve and maintain target Hb levels (NKF, 2006). Regularly scheduled maintenance doses of IV iron that are based on the individual needs of patients on hemodialysis have several benefits. They help to replace the ongoing iron losses experienced by these patients. They help to sustain iron repletion and maintain sufficient iron for RBC development. By making iron readily available when needed during RBC development, they also help to prevent iron-restricted erythropoiesis and ESA resistance. In addition, regularly scheduled maintenance IV iron

**Figure 1**

**IV Iron Group Had Reduced ESA Requirements as Observed in the Drive-II Extension Study**

<table>
<thead>
<tr>
<th>Mean ESA Dose, IU/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>50,000</td>
</tr>
<tr>
<td>45,000</td>
</tr>
<tr>
<td>40,000</td>
</tr>
<tr>
<td>35,000</td>
</tr>
<tr>
<td>30,000</td>
</tr>
</tbody>
</table>

**DRIVE Dose**

- Control Group
- IV Iron Group

**Note:** ESA = erythropoiesis-stimulating agent; DRIVE = Dialysis Patients’ Response to IV Iron with Elevated Ferritin.

**Source:** Kapoian et al., 2008.
doses can help to ward off the use of inappropriately high ESA doses by enabling patients to maintain stable levels of Hb (Besarab, 2006; Michael et al., 2007). As discussed previously, many anemia management protocols call for large ESA dose increases when a patient’s Hb drops below 11 g/dL. Across large dialysis providers, there is a 10% to 50% cumulative probability of overshooting the Hb target to a level greater than 14 g/dL within 6 months of initiating an ESA after achieving a first Hb of 11 g/dL (Collins, Dunning, Zhang, & Gilbertson, 2006). Because there are safety concerns associated with overshooting the Hb target, it is good practice to begin reducing ESA doses if Hb levels start trending upward, and nurses should address Hb levels that are consistently above target with fellow staff members. Nurses might encourage the rest of the team to understand that ESAs are only one component of anemia management and “to recognize the important role of maintenance IV iron in stabilizing Hb levels.” The ultimate outcome may be that the anemia management protocol needs to be reevaluated and a more appropriate maintenance IV iron regimen incorporated.

IV Iron for Managing Anemia at Higher Serum Ferritin Levels and Overcoming Iron-Restricted Erythropoiesis

About 60% of patients on hemodialysis in the United States have a serum ferritin greater than 500 ng/mL and about 20% have low TSAT (less than 21%) (Centers for Medicare & Medicaid Services, 2005). The mistaken notion that patients with higher serum ferritin levels will not benefit from IV iron therapy has been contested by the results of the DRIVE study. DRIVE demonstrated that IV iron is effective for managing anemia in patients with elevated serum ferritin and low TSAT and receiving adequate ESA doses (Coyne et al., 2007). A subsequent analysis showed that neither the serum ferritin nor TSAT level could predict response to IV iron in the DRIVE study population (Singh et al., 2006). These results suggest that the only way to determine clinical response in patients with elevated serum ferritin and low TSAT is to administer a trial course of IV iron. The KDOQI guidelines advise clinicians to administer a trial of IV iron therapy to patients with serum ferritin levels above 500 ng/mL and low TSAT if they judge this approach to be appropriate (NKF, 2006).

DRIVE also demonstrated that a course of IV iron was effective in overcoming iron-restricted erythropoiesis (Coyne et al., 2007). A significant increase in serum ferritin and TSAT levels, indicating more readily available iron for erythropoiesis, occurred in the IV iron group. Serum ferritin levels decreased in the no iron group. There was also a decrease in CRP levels in the IV iron group, but none in the no iron group. The study specifically recruited patients who met the KDOQI criteria for inflammation-mediated RE blockade, and all of these results demonstrated that a course of IV iron helped the patients to effectively overcome this condition (Coyne et al., 2007; NKF, 2006).

Thus, nurses should consider that administering a course of IV iron can be the most efficient method of managing iron-restricted erythropoiesis and possibly inflammation, particularly in patients with elevated serum ferritin and low TSAT.

IV Iron Administration and Concerns Associated With Infection

Although caution should be used in patients with an active infection, concerns about patients on hemodialysis experiencing an increased risk of infection with recommended IV iron regimens is not found in the literature. One prospective, multicenter study involving 988 adult patients on hemodialysis investigated incidence and risk factors for bacteremia (Hoen, Paul-Dauphin, Hestin, & Kessler, 1998). After observing the patients for 6 months each, it was determined that the only factors independently associated with infection were vascular access through a catheter, immunosuppressive therapy, a history of bacteremia, and anemia. Interestingly, 5% of the study patients had serum ferritin levels greater than 1000 ng/mL, but there was no association between risk of bacteremia and serum ferritin level or cumulative iron dose.

Nephrology nurses who are concerned about IV iron use and infection can follow these practical management techniques: (1) examine the patient for a more probable cause of infection, such as catheter use, rather than IV iron use; (2) withhold IV iron therapy in patients who have an active infection and restart iron treatment after the infection has resolved; and (3) monitor the patient for deteriorating health status, and any signs should prompt an investigation for a possible source, including IV iron.

Conclusion

When faced with a blunted response to ESA therapy in patients on hemodialysis, nurses have several avenues for effectively managing anemia and safely and appropriately balancing IV iron with ESA therapy. These include identifying the root causes of ESA hyporesponsiveness before increasing ESA doses further; recognizing the signs of iron-restricted erythropoiesis; evaluating measures of iron status; and assessing the potential causative roles of infection, inflammation, malnutrition, and hemodialysis-related iron losses. Nurses should also remember that elevated serum ferritin does not preclude the necessity of IV iron and, when iron-restricted erythropoiesis or inflammation-mediated RE blockade is suspected, a trial of IV iron is the most efficient method for facilitating the release of stored iron. If a patient does not respond to IV iron with an increase in Hb or decrease in ESA dose, sources of inflammation should be further investigated. Implementing such strategies can
help to avert unnecessary ESA dose increases and potential risks – and ultimately help to improve patient outcomes.

References


IV Iron Use in Patients with Higher Serum Ferritin: Case Study on Anemia in Kidney Disease

Kristin Larson, MSN, ANP, GNP, CNN

Posttest – 1.5 Contact Hours

Posttest Questions

(See posttest instructions on the answer form, on page 194.)

1. Which of the following are possible signs of inflammation-mediated reticuloendothelial (RE) blockade?
   a. Increased serum ferritin only
   b. Increased serum ferritin and decreased TSAT only
   c. Increased serum ferritin, decreased TSAT, and decreased Hb only
   d. Increased serum ferritin, decreased TSAT, decreased Hb, and increased ESA dose

2. According to the current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, what should clinicians do when a patient’s serum ferritin is greater than 500 ng/mL?
   a. Evaluate the patient’s clinical status and withhold the dose of intravenous (IV) iron.
   b. Evaluate the patient’s clinical status, Hb, ESA dose, and TSAT, and consider a course of IV iron.
   c. Withhold the dose of IV iron and increase the ESA dose.
   d. After trending the patient’s IV iron and ESA dose, increase both.

3. Which of the following can cause a patient’s Hb to fall short of the recommended targets for anemia management, despite adequate or even high ESA doses?
   a. Inflammation-mediated RE blockade only
   b. Inflammation-mediated RE blockade and iron-restricted erythropoiesis only
   c. Inflammation-mediated RE blockade, iron-restricted erythropoiesis, and insufficient iron only
   d. Inflammation-mediated RE blockade, iron-restricted erythropoiesis, insufficient iron, and inadequate ESA dose

4. Which of the following statements about higher ESA doses is true?
   a. They can drive the development of iron-restricted erythropoiesis.
   b. They consistently help patients achieve appropriate Hb levels.
   c. They are generally recommended by the U.S. Food and Drug Administration (FDA) and the KDOQI Work Group.
   d. They are associated with minimal risks and adverse events.

5. Which statement is true about the group of patients in the DRIVE study (Goyne, 2007) who received IV iron?
   a. They had a greater Hb increase.
   b. They required an increased ESA dose.
   c. They had a decrease in serum ferritin.
   d. They experienced less negative cardiovascular outcomes.

6. Which of the following statements reflects current FDA guidance about the use of ESAs to target higher Hb levels in anemic patients with CKD?
   a. Avoid ESAs in anemia management.
   b. Do not use ESAs if patients have cardiovascular disease.
   c. Quality-of-life improvements with ESAs outweigh the risks associated with their use in targeting higher Hb levels.
   d. The use of an ESA to maintain Hb levels higher than 12 g/dL increases risk of death and serious cardiovascular reactions such as stroke, heart attack, or heart failure.

7. When managing a patient with a blunted response to ESA therapy, what is the first course of action to take?
   a. Administer a higher ESA dose and check the patient’s Hb level in 2 weeks.
   b. Identify the root causes of ESA hyporesponsiveness, including the possibility that the patient lacks sufficient iron for effective erythropoiesis.
   c. Target Hb levels between 11-13.0 g/dL as a goal of anemia management.
   d. Increase the ESA dose and give the patient IV iron.

8. Which of the following is a good practice regarding iron markers?
   a. Iron markers should be routinely measured to determine if a patient has an adequate supply of iron to meet the increased iron demands driven by ESA therapy.
   b. Iron markers should be measured once annually because iron deficiency is not a concern in hemodialysis patients.
   c. Iron markers do not need to be measured if the patient’s ESA dose is less than 2 g/dL in a 1-week period.
   d. Iron markers do not need to be measured unless the patient’s Hb level decreases more than 2 g/dL in a 1-week period.

9. What are the Hb target ranges recommended by KDOQI and the FDA, respectively?
   a. 10 to 12 g/dL, 11 to 12 g/dL
   b. 11 to 13 g/dL, 10 to 12 g/dL
   c. 11 to 12 g/dL, 11 to 13 g/dL
   d. 11 to 12 g/dL, 10 to 12 g/dL

10. Which of the following describes a goal that nephrology nurses should support in their anemia management practices for patients who are receiving ESAs?
    a. Trend patient’s Hb levels only.
    b. Trend patient’s Hb levels and ESA doses only.
    c. Trend patient’s Hb levels, ESA doses, and IV iron doses only.
    d. Trend patient’s Hb levels, ESA doses, and IV iron doses and balance IV iron and ESA therapy.
ANSWER/EVALUATION FORM
IV Iron Use in Patients with Higher Serum Ferritin:
Case Study on Anemia in Kidney Disease
Kristin Larson, MSN, ANP, GNP, CNN

Complete the Following:
Name: ____________________________________________________________
Address: __________________________________________________________
__________________________________________________________________
Telephone: ______________________ Email: _____________________________

CNN: ___ Yes   ___ No   CDN: ___ Yes   ___ No   CCHT: ___ Yes   ___ No

Payment:
ANNA Member: ____ Yes   ____ No    Member #___________________________
☐ Check Enclosed  ☐ American Express  ☐ Visa  ☐ MasterCard
Total Amount Submitted: _________________
Credit Card Number: _______________________________ Exp. Date: _______
Name as it Appears on the Card: ______________________________________

Special Note
Your posttest can be processed in 1 week for an additional rush charge of $5.00.
☐ Yes, I would like this posttest rush processed. I have included an additional fee of
$5.00 for rush processing.

Note: If you wish to keep the journal intact, you may photocopy the answer sheet or access this posttest at
www.annanurse.org/journal

Posttest Answer Grid (Please circle your answer choice):
1. a  b  c  d   3. a  b  c  d   5. a  b  c  d   7. a  b  c  d   9. a  b  c  d
2. a  b  c  d   4. a  b  c  d   6. a  b  c  d   8. a  b  c  d   10. a  b  c  d

Evaluation
1. The objectives were related to the goal.  1  2  3  4  5
2. Objectives were met
a. Evaluate a case study involving an increase in maintenance IV iron to improve Hb levels and overall patient outcomes.
   1  2  3  4  5
b. Understand how to interpret updated KDOQI and FDA recommendations that address emerging information about ESAs, Hb targets, IV iron, and patients with elevated serum ferritin levels.
   1  2  3  4  5
c. Discuss the relevance of this information for treating patients on hemodialysis who have anemia and recent evidence that IV iron administration is an effective solution for such patients.
   1  2  3  4  5
3. The content was current and relevant.  1  2  3  4  5
4. This was an effective method to learn this content.  1  2  3  4  5
5. Time required to complete reading assignment: _________ minutes.

GOAL
To identify anemia management practices for safely and effectively achieving appropriate hemoglobin (Hb) targets, reducing ESA requirements, addressing elevated serum ferritin levels, and overcoming obstacles to effective erythropoiesis.

I verify that I have completed this activity:

_____________________________________________
(Signature)

Comments ______________________________________
_____________________________________________
_____________________________________________

Suggested topics for future articles? ___________________
_____________________________________________
_____________________________________________

ONLINE SUBMISSIONS THROUGH A PARTNERSHIP WITH HDCN.COM ARE ACCEPTED ON THIS POSTTEST AT $20 FOR ANNA MEMBERS AND $30 FOR NONMEMBERS. CNE CERTIFICATES WILL BE AVAILABLE IMMEDIATELY UPON SUCCESSFUL COMPLETION OF THE POSTTEST.