Anemia Management in Adult Chronic Hemodialysis Patients Using Darbepoetin Alfa Protocol

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BACKGROUND: Data on darbepoetin alfa for anemia management in patients with chronic kidney disease (CKD) is scarce when compared with epoetin alfa. Clinical experiences of using darbepoetin alfa, dosing guide, and average weekly requirements are discussed in this article.

METHODS: A retrospective data analysis of 150 adult chronic hemodialysis patients was conducted for the period January 2005–May 2006. Darbepoetin alfa administration used convenient pre-filled syringes. Dose was titrated up or down in small increments to target hemoglobin (Hgb) levels of at least 11 and less than 13 g/dL. Hgb levels were measured twice monthly with the goal of maintaining 80% of patients at the target of 11 g/dL or greater. Intravenous iron was administered to maintain serum ferritin levels between 100 and 600 ng/mL and transferrin saturation between 20% and 45%. Other parameters monitored included average weekly darbepoetin alfa dose.

RESULTS: The average percentage of patients maintained at an Hgb level of 11 g/dL or greater was: January–June 2005, 76.5% (95% CI, ± 2.56); July–December 2005, 82% (95% CI, ± 2.12); and 2006, 78.6% (95% CI, ± 2.96). The percentage of patients with an Hgb > 12 g/dL was 21%–46%. The average weekly darbepoetin alfa doses decreased from 70 ± 3 μg (January–June 2005) to 62 ± 2 μg (June–December 2005) and further decreased to 55 μg (95% CI, mean ± 1.12) in 2006.

CONCLUSIONS: Darbepoetin alfa is effective for anemia management in CKD patients. The average weekly darbepoetin alfa requirement for anemia management to target an Hgb level of 11 g/dL or greater for most adult chronic hemodialysis patients is 55 μg or less.

Anemia management is important, as it affects the quality of life for many dialysis patients. According to the United States Renal Data System (USRDS), many new dialysis patients have anemia, with hemoglobin (Hgb) levels less than 10 g/dL, and only about 30% of patients have Hgb levels in the recommended range of the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).[1,2]

Epoetin alfa (Epogen, Procrit) has been available for more than a decade and has been the standard therapy for anemia management in patients with renal failure. More recently, darbepoetin alfa (Aranesp), a modified version of epoetin alfa, became available. Darbepoetin alfa differs from epoetin alfa in that it contains additional *N*-glycosylation sites, giving it a more favorable pharmacokinetic profile, including an extended duration of action and a longer half-life.[3]

The Centers for Medicare and Medicaid Services (CMS) did not reimburse for its use in end-stage renal disease (ESRD) patients until 2004.[4] Although both darbepoetin alfa and epoetin alfa are very efficacious,[5,6] there is a lack of experience with the use of darbepoetin alfa in ESRD patients. In addition, the clinical impact of darbepoetin alfa in this patient population is not as well known as that of epoetin alfa. Both agents are very costly, and prior to CMS reimbursement for darbepoetin alfa, not many practitioners prescribed it for their patients.

However, the potential advantages of darbepoetin alfa's pharmacokinetic profile and more favorable financial costs following the CMS issue of a temporary reimbursement code for darbepoetin alfa usage in ESRD support its use. This allowed our dialysis center at Holy Name Hospital, Teaneck, New Jersey, to take a proactive approach as we slowly introduced darbepoetin alfa to our patients in the middle of 2004. Through multidisciplinary efforts of pharmacists, nurses, and physicians, we gained valuable clinical experience with using darbepoetin alfa in ESRD patients and eventually developed a simplified darbepoetin alfa protocol for anemia management in adult chronic hemodialysis patients.

This article describes our experiences and the protocol developed by the

multidisciplinary team for the use of darbepoetin alfa for anemia management in adult chronic hemodialysis patients.

Patients and Methods

We conducted a retrospective data analysis of 150 adult ESRD patients receiving chronic hemodialysis for the period January 2005–May 2006. The darbepoetin alfa protocol was developed and implemented using convenient prefilled 25-, 40-, 60-, 100-, 150-, and 200-μg darbepoetin alfa syringes.[5] Dose was titrated up or down in small increments (see *Table I* for guide to standardized doses) to make adjustments to target hemoglobin (Hgb) level between 11 and <13 g/dL (see *Table II* for dose adjustments and goals).

Hgb level was measured twice a month with the goal of maintaining 80% of patients at an Hgb level of 11 g/dL or greater. Intravenous iron was administered to maintain serum ferritin levels between 100 and 600 ng/mL and transferrin saturation between 20% and 45%. Other parameters monitored included average weekly darbepoetin alfa dose. All data were tracked on spreadsheets and graphs generated throughout the entire evaluation period. The method was approved by Holy Name Hospital board.

Statistical Analysis

Mean monthly Hgb level and mean weekly darbepoetin alfa dose (± standard deviations) with 95% CIs were calculated.

Results

In the first 6 months of 2005, an average of 76.5% of all 150 patients (95% CI, mean ± 2.56) maintained an Hgb level of 11 g/dL or greater. During the second 6 months of 2005, an average of 82% of the patients (95% CI, mean ± 2.12) maintained an Hgb level of 11 g/dL or greater. In 2006, an average of 78.6% of the patients (95% CI, mean ± 2.96) maintained an Hgb level of 11 g/dL or greater (*Figure 1*).

The potential advantages of darbepoetin alfa's pharmacokinetic profile may support its usage in ESRD patients.

During the entire period, 21%–46% of patients had an Hgb level greater than 12 g/dL (*Figure 2*). The average weekly darbepoetin alfa dose decreased from 70 ± 3 μg during the first half of 2005 to 62 ± 2 μg in the second half of 2005 and further decreased to 55 μg (95% CI, mean ± 1.12) in 2006 (*Figure 1*). More than 80% of patients maintained serum ferritin levels between 100 and 600 ng/mL, and 70% of patients maintained transferrin saturation (TSAT) between 20% and 45% throughout the entire evaluation period.

Protocol Management

The protocol utilizes convenient pre-filled syringes of 25, 40, 60, 100, 150, and 200 μg of darbepoetin alfa.[5] This helps to eliminate the waste associated with odd doses, reduces dose calculation errors, and eliminates incorrect amounts of the drug being given to patients. Because of the long half-life of darbepoetin alfa, it may be administered at weekly or 2-week intervals. All patients were to receive darbepoetin alfa, which was administered via intravenous push, either Monday or Tuesday depending on their dialysis schedule. An Hgb level was drawn twice a month or, when a dose held, it was drawn weekly.

Dose was adjusted up or down in small increments (one step at a time) as recommended in the guide to standardized doses in *Table I*, which also indicates the amounts of increases or decreases (in micrograms) in a 4-week period. Alternate doses (e.g., 25/40 μg) were also utilized to accomplish a gradual increase in dosing. *Table II* details dose adjustments and goals based on Hgb levels, with the goal of maintaining Hgb levels of ≥11 and <13 g/dL.

Patients who required minimal darbepoetin alfa to maintain target Hgb were given 25 μg every other week. Darbepoetin alfa therapy was put on hold if Hgb level increased to 13 g/dL or greater and resumed at a lower dose when Hgb fell below 13 g/dL based on the dose guide in *Table I*. For patients receiving darbepoetin alfa 25 μg, every other week, if Hgb level reached 13 g/dL or greater, doses were held and resumed at the same dose when Hgb fell below 13 g/dL. For doses greater than 60 μg per week, dose was decreased to 60 μg per week if Hgb increased above 12 g/dL.

If Hgb level decreases more than 2 g/dL, further assessment is warranted, such as a workup for active bleeding, ruling out an acute illness or other factors, and prompts physician attention. If there is an absolute iron deficiency, defined as a serum ferritin level less than 100 ng/mL and a TSAT less than 20%, the darbepoetin alfa dose should not be increased until iron is being administered concurrently, as iron is

TABLE I. Guide to standardized darbepoetin alfa doses.

Standard Doses of Darbepoetin Alfa	Total Micrograms Administered in a 4-Week Period
25 μg, IV push, every other week	50 μg
40 μg, IVP, every other week	80 μg
25 μg, IVP, every week	100 μg
40 μg alternating with 25 μg, IVP, alternating weeks	130 μg
40 μg, IVP, every week	160 μg
60 μg alternating with 40 μg, IVP, alternating weeks	200 μg
60 μg, IVP, every week	240 μg
100 μg alternating with 60 μg, IVP, alternating weeks	320 μg
100 μg, IVP, every week	400 μg

TABLE II. Dose adjustments and goals.

- Achieve and maintain a target Hgb level ≥ 11 g/dL and < 13 g/dL. Avoid increasing Hgb > 1 g/dL over a 2-week period.
- Dose is adjusted every 2 weeks or, for weekly doses ≥ 60 μg, every 4 weeks.

Parameters (Hgb in g/dL)	Clinical Intervention	Clinical Reasons
• Hgb 10–10.9 g/dL and increased from previous Hgb • Hgb 11–12 g/dL and increased < 1 g/dL from previous Hgb • Increased ≥ 1 g/dL and current Hgb < 10 g/dL	MAINTAIN current dose	Hgb is increasing, on target, or below target; no dose adjustment is required
Hgb 12.1–12.9 g/dL	• DECREASE current dose, follow Table I, standardized doses guide (except on lowest dose, 25 μg, every other week)* • If current dose > 60 μg/week, decrease to 60 μg/week	Current Hgb is higher than manufacturer's recommended range; decrease dose to keep Hgb from continuing to increase
Hgb ≥ 13 g/dL	• (1) Hold dose; (2) monitor Hgb weekly; (iii) resume at next DECREASED dose (follow Table I, standardized doses guide) when Hgb decreases to <13 g/dL • If current dose > 60 μg/week, decrease to 60 μg/week	Hgb level above product labeling is not recommended and high Hgb level is associated with adverse events
If Hgb increased ≥ 1 g/dL from previous Hgb and current Hgb is ≥ 10 g/dL	• DECREASE current dose, follow Table I, standardized doses guide • If current dose is > 60 μg/week, decrease to 60 μg/week	Not recommended to increase Hgb too fast; decrease dose to avoid Hgb increasing above recommended range
Hgb < 11 g/dL and decreased or same as previous Hgb	INCREASE current dose, follow Table I, standardized doses guide	Hgb is suboptimal; increase in dose is recommended
If Hgb decreases ≥ 2 g/dL in a 2-week period	Further assessment is required; assess for iron, folic acid, or vitamin B12 deficiencies; infections; inflammatory or malignant process; occult blood loss; hemolysis; aluminum toxicity; osteofibrosis cystica; evaluate for evidence of pure-red-cell aplasia (PRCA).	

Notes

- Do not INCREASE dose if patient has absolute iron deficiency, until patient is CONCURRENTLY receiving iron.
- If INCREASE to an alternate dose, begins with higher dose.
- If DECREASE to an alternate dose, begins with lower dose.
- If dose INCREASE is needed for every-other-week dosing, administer dose the following week and do not wait 2 weeks.

*If currently on the lowest dose, 25 μg, every other week, and Hgb level > 13 g/dL, (1) hold dose; (2) monitor Hgb weekly; (3) resume at the same dose when Hgb decreases to < 13 g/dL.

essential for effective hemoglobin synthesis.[2] When a dose increase is required with alternate or every-other-week dosing, the patient would start with the higher of the alternating doses. For example, if the current dose is 25 μg weekly and increases to 40/25 μg weekly, the next dose due is 40 μg, alternating with 25 μg the following week and vice versa. If there is a dose increase with every-other-week dosing, the dose should be given the following week, rather than waiting for 2 weeks.

Discussion

We began the conversion of epoetin alfa to darbepoetin alfa in the middle of 2004, starting with a small number of adult chronic hemodialysis patients (n = 50). At the time of conversion (baseline), 79% of these patients had Hgb levels of 11 g/dL or greater, and about 70% had serum ferritin levels between 100 and 600 ng/mL and TSAT between 20% and 45%. During this period, the percentage of patients with Hgb levels 11 g/dL or greater ranged from 70% to 78%, and by the end of 2004 approximately 78% of patients had Hgb levels 11 g/dL or greater (data on file and presented in abstract and poster).[7]

We then slowly converted all patients (n = 150) to darbepoetin alfa. The results, shown in *Figure 1*, illustrate the outcomes were better than with our previous epoetin alfa data, which were just around or below the 80% mark (data on file, presented in abstract, poster and published in letter form).[7,8] In the interest of product labeling, we also tracked the

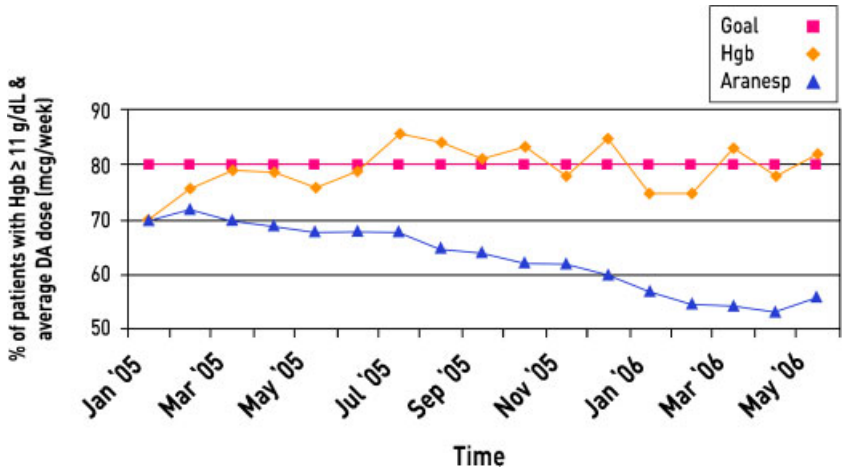

FIGURE 1. *Percentage of study patients with Hgb ≥ 11 g/dL and average darbepoetin alfa dose (mcg/week).*

percentage of patients who had Hgb levels greater than 12 g/dL, which averaged 21%–46%; about 5% of the patients had Hgb levels of 13 g/dL or greater. During the initial period, the mean darbepoetin alfa dose was 70 ± 3 μg weekly. In the second half of 2005, the average dose decreased to 62 ± 2 μg weekly, and in 2006, the average dose decreased further to 55 μg (95% CI, 53.88, 56.12 μg). This is comparable to our previous weekly epoetin alfa doses[8] and the manufacturer's recommended conversion ratio.[5]

Several studies have shown that the weekly darbepoetin alfa requirement is approximately 30 μg or less. However, doses ranged from a low of 0.075 μg/kg a week to as high as 0.75 μg/kg a week, depending on the patient's condition.[9-11] Two of these studies were performed in Canada and Europe and their erythropoiesis-stimulating agent (ESA) usage tended to be lower than that in the United States patient population. Around midyear 2005, based on the above and present data, more than 70% of patients received doses of 60 μg per week or less; and fewer than 25% of patients received doses above 60 μg per week. The protocol was revised if patients required doses greater than 100 μg per week, as several things must be done prior to increasing the dose. Dose increases were to be made no more frequently than once every 4 weeks, as supposed to every 2 weeks with lower doses.

Adequate iron support is essential and must be replaced if needed and assessed for reasons that may interfere with darbepoetin alfa responsiveness such as bleeding, infection, or other factors. Physicians may override these criteria if the patient has valid reasons that may require a higher darbepoetin alfa dose. Since the time we implemented this change, there was a decrease in weekly darbepoetin alfa doses, from 70 ± 3 to 62 ± 2 μg, and interestingly, the percentage of patients with Hgb levels greater than 11 g/dL remained in the 80% range. This is an indication that patients with Hgb levels below target may not be related to darbepoetin alfa therapy but could be a result of any number of medical factors. The percentage of patients who achieved an Hgb level of 11 g/dL and above did not decrease. Patients were therefore adequately dosed. Patients receiving higher doses either were hyporesponsive to darbepoetin alfa, had issues with iron utilization, or had other comorbid conditions that hampered darbepoetin alfa responsiveness.

In 2006, more than 80% of patients received doses 60 μg per week or less, and fewer than 20% of patients received doses greater than 60 μg per week. The protocol was revised again to a cutoff of 60 μg per week. Interestingly, the percentage of patient remained at targeted Hgb levels and was unchanged after several months, and the average weekly darbepoetin alfa dose continued to decrease, as shown in *Figure 1*. Weekly doses ranged from 12.5 to 100 μg per week, and only 4.5% of patients received doses of 150 or 200 μg per week. The average weekly dose remains less than 55 μg per week. We do think that the average weekly dose required to maintain a target Hgb for most patients is lower, but the average was skewed because of a small number of outliers who received higher doses.

Our data confirmed KDOQI findings, which showed that most anemic CKD patients responded to erythropoiesis-stimulating agent and that most required ESA doses (epoetin alfa) of less than 30,000 units per week, which is approximately 60 μg or less of darbepoetin alfa per week.[2] It was also reported in the literature that for an average 70-kg person, required maintenance doses may be less than 32 μg per week.[5] A small percentage of patients require higher doses, but most should respond in about 6 months.[2] After the dose was capped at 60 μg per week, the number of patients with Hgb levels greater than 12 g/dL decreased, as seen in *Figure 2*.

Clinicians should be aware of the increased mortality associated with elevated hemoglobin levels beyond recommended target. Data from the Correction of

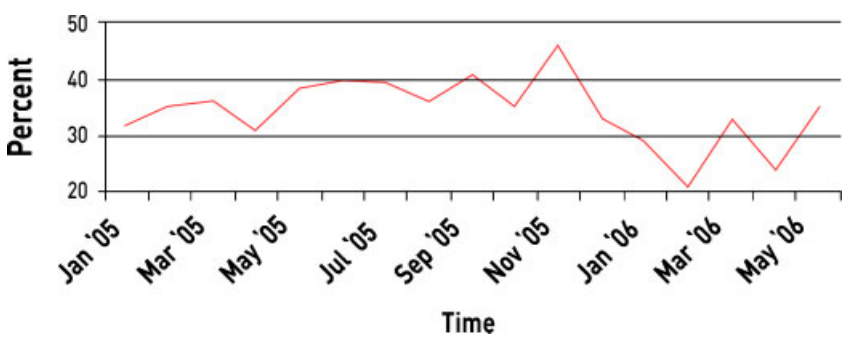

FIGURE 2. *Percentage of study patients with Hgb > 12 g/dL.*

Anemia Management Using Darbepoetin Alfa

Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study showed there was a significantly higher incidence of composite end-point events consisting of mortality, stroke, heart attack, and increased hospitalization because of congestive heart failure. The CHOIR study investigated patients treated to attain hemoglobin levels of 13.5 or 11.3 g/dL.[12] The study was terminated short based on the recommendation of its data safety monitoring board. This data reinforced the validity of maintaining hemoglobin within the levels recommended on product labeling, and currently the Food and Drug Administration has an approved product label stating that the treatment goal should not exceed a hemoglobin level of 12 g/dL.[5,6]

We found that a low Hgb level was not always a product of inadequate administration of darbepoetin alfa, but more likely a result of external factors such as acute bleeding or other acute illness.

We made multiple revisions to the protocol prior to the current working version. There were mishaps with protocol compliance, and physicians often increased doses more frequently than suggested because of a sudden drop in Hgb for a variety of reasons, such as bleeding, iron deficiency, acute illness, and surgery. Physicians also tended to increase doses higher than allowed and as a result, Hgb level rose too high once patients' conditions resolved. We discovered that increasing patients' doses higher than the protocol suggested often resulted in Hgb levels above KDOQI targets. Such patients with doses higher than recommended were the majority of patients who had Hgb levels 13 g/dL or greater, indicating that a low Hgb level is not always a product of inadequate administration of darbepoetin alfa but is more likely to be a result of external factors such as acute bleeding or other acute illnesses.

All these factors contributed to the fluctuation in Hgb levels. It was difficult to maintain all patients at the target Hgb at all times, as the conditions of these patients were complex conditions with multiple comorbidities. Several studies confirmed the difficulty of maintaining patients in the target range and that most dialysis patients experienced hemoglobin cycling.[13-15] The average weekly darbepoetin alfa dose decreased after the last revision capping the dose at 60 μg weekly.

Although the reported darbepoetin alfa doses were lower[9-11] than those at our clinic, they were consistent with our previous epoetin alfa doses, which were based on the manufacturer's conversion recommendation. Interpatient variation may account for the different dosages and factors such as physician-prescribed doses outside the recommended range, causing Hgb variability. Additional benefits of darbepoetin alfa over epoetin alfa include less frequent injections and fewer dose adjustments being required.

The limitations of our data include the retrospective nature of the study, occasional non-compliance with the protocol, missed doses, patient complication issues such as acute illnesses, and other unknown factors that may have caused patients to be hyporesponsive to darbepoetin alfa therapy.

Conclusion

A simplified and standardized darbepoetin alfa dose protocol was successfully used to manage the anemia of adult patients undergoing chronic hemodialysis. The results suggest that using this approach is not only feasible and practical for a busy dialysis center but also effective in maintaining approximately 80% of patients with Hgb levels of 11 g/dL or greater. Most adult chronic hemodialysis patients required an average weekly darbepoetin alfa dose of 55 μg or less.

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