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Biomedical System Dynamics to Improve Anemia Control With Darbepoetin Alfa in Long-Term Hemodialysis Patients

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Abstract

Objective: To determine the value of a biomedical system dynamics (BMSD) approach for optimization of anemia management in long-term hemodialysis patients because elevated hemoglobin levels and high doses of erythropoiesis-stimulating agents (ESAs) may negatively affect survival in this population.

Patients and Methods: A model of erythropoiesis and its response to ESAs on the basis of a BMSD method (Mayo Clinic Anemia Management System [MCAMS]) was developed. Thereafter, an open-label, prospective, nonrandomized practice quality improvement project was performed with retrospective analysis in 8 community-based outpatient hemodialysis facilities. All prevalent hemodialysis patients seen from January 1, 2007, through December 31, 2010 (300-342 patients per month), were included with darbepoetin as the ESA. The primary outcome was the percentage of patients who attained the desired hemoglobin level. Secondary outcome measures included the percentage of patients with hemoglobin values above the desired range and mean dose of darbepoetin used.

Results: The 3 treatment periods were (1) standard ESA protocol in 2007, (2) transition to the MCAMS (2008 to June 2009), and (3) stability period with the MCAMS used in all hemodialysis facilities (2009 to 2010). In the first 6 months of 2007, 69% of patients were in the desired range and 26% were above the range. In comparison, during the first 5 months of 2010, 83% were in and 6% were above the range ($P<.001$). The mean monthly darbepoetin dose per patient decreased from 304 μg in 2007 to 173 μg by the second half of 2009 ($P<.001$).

Conclusion: With the introduction of the MCAMS, more patients had hemoglobin levels in the desired range and fewer patients exceeded the target range, with a concomitant 40% reduction in darbepoetin use.

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Nephrologists and other practitioners face a significant dilemma with regard to the management of anemia in patients undergoing long-term hemodialysis. On one hand, the improvement of anemia by the administration of erythropoiesis-stimulating agents (ESAs) increases the patient's sense of well-being and decreases transfusion requirements.[1-4] Conversely, elevated hemoglobin levels and high ESA doses may negatively affect survival in these patients.[5-15] Most of the widely used protocols use the most recent hemoglobin level to adjust ESA dosage and often withhold ESAs if the hemoglobin level is increasing rapidly or exceeds a predetermined threshold. This approach often leads to suboptimal dosing with persistent anemia or unnecessarily high dosing with elevated hemoglobin levels. The result may be wide fluctuations in hemoglobin levels (hemoglobin cycling), which may have a negative effect on patient survival.[16-20] These fluctuations can frustrate the clinician who wishes to use the minimum dose of ESAs to effectively treat anemia in hemodialysis patients while trying to maintain a stable hemoglobin value.

With this challenge in mind, we developed an innovative and individualized method for ESA dosing and anemia control in long-term hemodialysis patients on the basis of biomedical system dynamics (BMSD). The BMSD method is a computer-aided approach, based

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on physiologic parameters, designed to predict the outcome of any dynamic system, such as erythropoiesis.[21-23] We report the initial results of this method, which replaced an ESA dosing protocol similar to what is currently used in many hemodialysis facilities. This method has enabled us to achieve better control of anemia with a reduction in darbepoetin use and facilitated a smooth transition in ESA dose modification when the desired target hemoglobin range was altered. This approach reduces variability in hemoglobin values and offers clinicians the opportunity to achieve the important goal of individualized anemia therapy in hemodialysis patients.[12,13,15]

METHODS

Mayo Clinic Dialysis System

The Mayo Clinic Dialysis System (MCDS) includes 8 outpatient dialysis facilities (identified as A through H) with a census of 8 to 93 prevalent patients in each facility (300-342 patients). We included all prevalent patients who received at least one hemodialysis treatment and had at least one hemoglobin determination in each respective month. There were no changes in our target goals for dialysis adequacy (single-pool Kt/V >1.60) or other practices that might have knowingly affected anemia therapy during this time. All laboratory studies were performed at the Central Clinical Laboratories at the Mayo Clinic in Rochester, Minnesota.

Anemia Management Protocols

During the time of this study, ESA dosing was adjusted to our 2007 protocol (Table 1) or the Mayo Clinic Anemia Management System (MCAMS). Health care practitioners were aware of which method was being used and were free to alter ESA doses based on their assessment of each patient's unique clinical situation. All patients had hemoglobin concentrations measured every 2 weeks, and all received an oral multivitamin that contained folate and vitamin B_{12}. The physician was notified when any hemoglobin level was greater than 10.0 g/dL (to convert to g/L, multiply by 10) or if the level decreased by more than 2.0 g/dL from the previous value. The ESA doses were adjusted monthly, unless the hemoglobin level was 14.0 g/dL or higher, at which time ESA administration was temporarily suspended and resumed when the hemoglobin level was less than 12.0 g/dL. Darbepoetin was used exclusively as the ESA, although the system can be used with any ESA.

TABLE 1. 2007 Anemia Management Protocol Used to Adjust Darbepoetin Dose Before Implementation of the Mayo Clinic Anemia Management System[a]

Hemoglobin level	Protocol[b]
≤10 g/dL	Increase by 3 vial sizes
10.1-10.5 g/dL	Increase by 2 vial sizes
10.6-11.4 g/dL	Increase by 1 vial size
11.5-12.5 g/dL	No change
12.6-13.9 g/dL	Decrease by 1 vial size
>14 g/dL	Hold 2 weeks; decrease 2 vial sizes when hemoglobin <13 g/dL

[a]SI conversion factor: To convert hemoglobin values to g/L, multiply by 10.
[b]Darbepoetin vial sizes are 25, 40, 60, 100, 150, 200, and 300 μg.

Iron Management

All patients received 100 mg of intravenous iron sucrose monthly to maintain ferritin levels between 200 and 1000 μg/L (to convert to pmol/L, multiply by 2.247) and total iron-binding capacity saturation between 20% and 50%. Patients with serum iron levels less than 20 μg/L (to convert to μmol/L, multiply by 0.179) or serum ferritin levels less than 200 μg/mL were prescribed a supplemental course of intravenous iron sucrose to provide 1000 mg of iron during 5 to 10 sequential hemodialysis sessions. Parenteral iron was suspended if total iron-binding capacity saturation was greater than 50% or the ferritin level was greater than 1200 μg/mL. Serum iron studies were measured every 3 months and remeasured 4 weeks after a course of parenteral iron therapy. This protocol was in place during the entire period included in this report.

Mayo Clinic Anemia Management System

The MCAMS is proprietary software modeled on the BMSD[21-23] that simulates the dynamics of erythropoiesis and its response to ESAs for an iron-replete hemodialysis patient.[24] Five parameters that determine erythropoiesis in the presence of an ESA are used in the mathematical model: (1) the mean daily production of erythroid burst–forming units, (2) the mean survival of erythroid colony-forming units, (3)

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