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Special REPORT

AUGUST 2004

Inpatient Darbepoetin Alfa: Conversions, Costs, and Critical Use

Introduction

Anemia is a clinical problem that crosses healthcare specialties and disease states. Patients with chronic disease, such as cancer, kidney disease, HIV/AIDS, cardiac disease, and surgical patients, among others, are all at increased risk for anemia, which can have a negative effect on clinical outcomes as well as a strong impact on quality of life.

Increasingly, clinicians are turning to exogenously administered erythropoietic growth factors (EGFs) to treat anemia in these patient populations. There are a host of challenges in managing patients on EGF therapy, such as choice of an EGF agent, dosage conversion, and tailoring therapy for both inpatient and outpatient care. This Special Report profiles 3 healthcare systems' approach to meeting those challenges, and begins with an overview of the epidemiology and biology of anemia.

Mechanisms of Anemia

Under normal circumstances, a decrease in the blood oxygen level (hypoxia) stimulates the peritubular cells of the kidney to produce the hormone erythropoietin, which stimulates the differentiation and proliferation of red blood cell (RBC) precursors in the bone marrow. The RBCs then increase the amount of oxygen that is available to the tissues. In addition, the

higher levels of oxygen act as part of a negative feedback loop that downregulates the production of erythropoietin when it is no longer needed.

Anemia occurs when the loss of RBCs exceeds erythrocyte production. The process of erythropoiesis and the maintenance of normal hemoglobin (Hgb) levels can be disrupted by a number of disease processes and other factors. For example, patients with chronic kidney disease (CKD) often lose the ability to produce erythropoietin in the kidney. Even if sufficient erythropoietin is produced, a relative or absolute iron deficiency can limit its effectiveness in creating RBCs, since iron is an important component of Hgb. Various cancers can suppress erythropoietin production or erythropoiesis through the actions of inflammatory cytokines. In addition, certain chemotherapies and radiotherapy used to treat cancer are myelosuppressive, which can adversely affect RBC production and cause anemia. Blood loss due to injury or surgery can also reduce the number of RBCs available to transport oxygen. This anemia can be critically important in some patients, such as those with cardiovascular disease, who have increased tissue oxygen requirements.

Although transfusion is still used to manage anemia for the inpatient population, transmission of infection, immunosuppression, and the limited blood supply have encouraged healthcare providers to

reduce the reliance on transfusions. That is the driving factor for why more and more clinicians are turning to exogenously administered EGFs as their preferred method for stimulating RBC growth.

Two commercially available EGFs, epoetin alfa (Epogen, Amgen; Procrit, Ortho Biotech) and darbepoetin alfa (Aranesp, Amgen), are available in the United States. Epoetin alfa is a recombinant molecule that is chemically identical to endogenous human erythropoietin and has been available since the early 1990s. It was initially indicated for use in treating the anemia of chronic renal failure and has since been approved for patients with nonmyeloid malignancies who are receiving chemotherapy, HIV-positive patients taking zidovudine (Retrovir, GlaxoSmithKline), and anemic patients scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.^{1,2} Darbepoetin alfa, introduced in 2001, was first approved for use in patients with chronic renal failure and has since obtained an indication for patients with nonmyeloid malignancies receiving chemotherapy.³ Darbepoetin alfa and epoetin alfa have the same mechanism of action. Both are structurally similar with the exception that darbepoetin alfa possesses 2 additional carbohydrate side chains that can accommodate 8 additional sialic acid residues. Sialic acid is thought to increase the activity of EGFs.⁴ As a result, the half-life of darbepoetin alfa is approximately 3 times as long as that of epoetin alfa.⁵

Studies have shown that epoetin alfa and darbepoetin alfa are functionally equivalent when dosed properly.^{6,7} The precise conversion ratio has yet to be determined and may be 400:1, which is used in many clinical practices today. When the Centers for Medicare and Medicaid Services (CMS) determined in November 2002 that the 2 EGFs were functionally equivalent and would be reimbursed accordingly, they set a conversion ratio of 260 units epoetin alfa to 1 mcg darbepoetin alfa.⁸ Based on additional information, CMS has since raised the conversion ratio to 330 units epoetin alfa to 1 mcg darbepoetin alfa.⁹

CONVERTING EGFs IN ACUTE DIALYSIS: HUMILITY OF MARY HEALTH PARTNERS

Patients with chronic renal failure are at particular risk for anemia, because the disease often destroys the cells that produce endogenous erythropoietin. These patients are also at particular risk from anemia, because chronic renal failure is associated with high levels of cardiac disease, for which anemia is a contributing factor.¹⁰ For this reason, anemia management is very important in this patient population. Indeed, chronic renal failure was the first FDA-approved indication for both epoetin alfa and darbepoetin alfa. However, patients with renal failure often move between inpatient and outpatient settings for dialysis treatment. According to Erdal Sarac, MD, FACP, Director of Dialysis Services at Humility of Mary Health Partners (HMHP) in Youngstown, Ohio, HMHP specifies the use of darbepoetin alfa for most inpatient uses, but only epoetin alfa is used for nephrology patients in the outpatient setting. Yet the safety and efficacy of converting from outpa-

tient epoetin alfa to inpatient darbepoetin alfa and back again (the E-D-E conversion) in patients with end-stage renal disease (ESRD) had not been studied.

HMHP runs 2 facilities in Ohio. St. Elizabeth Health Center, in Youngstown, Ohio, is a tertiary, teaching, Level 1 trauma center with an average patient census of 356 patients. Drug expenditures at St. Elizabeth were \$10.1 million in 2002. St. Joseph Health Center, in Warren, Ohio, is a community, teaching health center with an average census of 117 patients. Drug expenditures at St. Joseph were \$6.1 million in 2002. In 2001, EGFs were used in 40% of nephrology cases at HMHP, and EGF use in oncology was at 58% and growing. In that year, epoetin alfa was the number-one drug expense, at \$1.1 million, representing 8.1% of the total drug expenditure.

In February 2002, shortly after darbepoetin alfa was approved for use in anemia associated with chronic renal failure, HMHP conducted a first-pass analysis of whether to change the formulary to specify the use of darbepoetin alfa. At that time, darbepoetin alfa was considered a "me-too" drug because it has the same mechanism of action as epoetin alfa. Moreover, there was little clinical experience with darbepoetin alfa reported in the literature, and the initial cost analysis was not promising. Many questions thus remained with regard to dosing, uses, and cost. However, the fact that darbepoetin alfa had increased activity and a longer half-life relative to epoetin alfa and a safety profile similar to that of epoetin alfa¹¹ prompted HMHP to take another look.

First, the pharmacy department conducted a literature review to obtain information about darbepoetin alfa and its clinical use. Based on this information, a study protocol for a 3-month trial was developed jointly by the HMHP nephrologists and health-system pharmacists to test the dosing, cost, and outcomes of darbepoetin alfa use within the inpatient dialysis unit. The study was approved by the Pharmacy and Therapeutics (P & T) Committee in July 2002 and by the Medical Executive Committee in August 2002, after which the dialysis nurses were educated on the specifics of the trial. Education of dialysis nurses was a key step in the trial, Dr. Sarac said, because they were responsible for implementing the protocol and calculating the dose conversions from epoetin alfa to darbepoetin alfa.

During the trial, epoetin alfa doses were converted to darbepoetin alfa doses according to the FDA-approved table included in the darbepoetin alfa package insert (Table 1). If the Hgb was ≥ 11 g/dL at admission, the first dose of darbepoetin alfa was to be given on the second dialysis; if the Hgb was < 11 g/dL, the first dose of darbepoetin alfa was to be given on the first dialysis. If the Hgb was ≥ 13 g/dL, the Hgb levels were monitored, and darbepoetin alfa was only given if the Hgb concentration dropped below 13 g/dL. The study assessment measures included average length of stay (LOS), Hgb levels, appropriate administration of iron, transfusions given, adverse drug reactions, clinical outcomes, and cost.

The study itself began in November 2002. The 126 patients included in the study had an average LOS of 6.85 days, during which no adverse drug reactions or

Table 1. Estimated Darbepoetin Starting Doses Based on Previous Epoetin Dose³

Previous Weekly Epoetin Alfa Dose	Darbepoetin Alfa Weekly Dose
<2,500 units	6.25 mcg
2,500–4,999 units	12.5 mcg
5,000–10,999 units	25 mcg
11,000–17,999 units	40 mcg
18,000–33,999 units	60 mcg
34,000–89,999 units	100 mcg
≥90,000 units	200 mcg

other adverse outcomes were seen. Forty percent of patients had Hgb ≥13 g/dL on admission, suggesting that anemia was being overcorrected in many patients in the outpatient setting. The first dose was given at the correct dosing level 63% of the time, and the timing of the dose was correct 75% of the time. Iron therapy was given to 64% of the patients. Since the trial was completed, Dr. Sarac said, compliance with protocol timing and dosing has improved to almost 100%, as the dialysis nurses have become more familiar with the procedures.

The values obtained from the 3-month trial with darbepoetin alfa were then compared with historical data of epoetin alfa use (Table 2). A slightly lower proportion of patients who received epoetin alfa were discharged with Hgb ≥11 g/dL, and a higher percentage of patients receiving epoetin alfa had received transfusions; however, none of the differences were significant.

The average weekly dose of darbepoetin alfa given dur-

Table 2. Results of 3-Month Nephrology Trial of Darbepoetin (Humility of Mary Health Partners)

Data	Darbepoetin Alfa	Epoetin Alfa
N	126	78
Length of stay ≤6 days	61% (range, 1–50)	68% (range, 1–57)
≤4 Hemodialysis sessions	79% (range, 1–17)	68% (range, 1–21)
Admitting Hgb ≥11 g/dL <11 g/dL,	73% 27%	65% 31%, NA 4%
Discharge Hgb ≥11 g/dL <11 g/dL	53% 40%	51% 36%, NA 13%
Blood transfusions	21%	37%

Hgb, hemoglobin; NA, not available

ing the study was 79 mcg, as compared to an historical average weekly dose of epoetin alfa of 33,900 units. These doses correspond roughly to a 400:1 conversion ratio of epoetin alfa to darbepoetin alfa. Based on the average weekly doses identified in the study and the costs as of April 1, 2003, the weekly cost of epoetin alfa was determined to be \$319, compared to a weekly cost of \$215 for darbepoetin alfa. This represents a cost savings of \$104 per patient per week, or about 33% of the epoetin alfa cost, leading HMHP to adopt darbepoetin alfa as its default EGF. Epoetin alfa doses for nephrology patients are now converted to darbepoetin alfa using a therapeutic interchange that differs slightly from that in the package insert, in that it specifies a weekly dose of 150 mcg darbepoetin alfa for patients originally receiving 60,000 to 89,999 units epoetin alfa. Newer data suggest that patients can also be safely switched back to outpatient epoetin alfa after receiving darbepoetin alfa as inpatients.

Thus, using an E-D-E conversion protocol is safe and effective for dialysis patients moving between outpatient and inpatient care. Darbepoetin alfa was therapeutically equivalent to epoetin alfa in this setting and provided significant cost savings to HMHP.

FEASIBILITY OF UTILIZING EGFs WITHIN THE INPATIENT POPULATION: SAINT BARNABAS HEALTH CARE SYSTEM

Formularies for EGF use in oncology patients tend to be 1 of 3 varieties: They specify (1) epoetin alfa for both inpatient and outpatient care, (2) darbepoetin alfa for outpatient oncology and epoetin alfa 3 times a week for inpatient care, or (3) darbepoetin alfa for both inpatient and outpatient care. Saint Barnabas Health Care System (SBHCS) in West Orange, NJ, the largest healthcare system in the state, has 3,866 acute care beds, 1,532 long-term and assisted living beds, 4,620 physicians, and \$2.3 billion in annual revenues. The system explored all 3 of these formulary options.

Robert Adamson, PharmD, Corporate Director of Clinical Services, explained that SBHCS considered whether there were compelling financial or clinical reasons for choosing one option over the other. In 2002, SBHCS spent \$13.3 million on RBC growth factors, which provided a compelling financial reason to review EGF use. Clinically, however, it was found that the process of anemia management was not optimized. According to Dr. Adamson and his colleague, Indu Lew, PharmD, Corporate Biotechnology Fellow at SBHCS, the necessary laboratory tests were not being done routinely, and therefore erythropoietic therapy was not always being initiated, titrated, or discontinued when appropriate. This necessitated the development of guidelines for anemia management before a formulary change could be considered. As a result, guidelines were developed in cooperation with SBHCS staff to ensure the routine measurement of Hgb concentrations, the evaluation of iron stores prior to the initiation of therapy, and proper iron supplementation.

Next, the use of darbepoetin alfa was considered. Darbepoetin alfa was known from clinical trials to be an effi-

caxious drug, efficacy being defined as the success of a drug in a randomized, controlled clinical trial using patients without concurrent therapy or comorbidity. As Dr. Adamson noted, "Nobody has these patients." Instead, what an institution needs to know is the effectiveness of the drug, that is, the ability of the drug to achieve the desired outcome in patients at the practice site, where patients sometimes miss appointments or skip doses. To determine the effectiveness of darbepoetin alfa at SBHCS, a drug use evaluation (DUE) was performed.

The DUE ran from July 2002 until January 2003 and consisted of a retrospective chart review of patients receiving darbepoetin alfa on an outpatient basis for chemotherapy-induced anemia. Over 16 weeks, the dose of darbepoetin alfa used, the frequency of administration, baseline Hgb, response to therapy, and time to response were recorded for each patient. The main outcome measure was the response to therapy: A partial response was defined as an increase in Hgb concentration of 1 to 2 g/dL over the course of the study, and a full response was an increase >2 g/dL or the achievement of a Hgb concentration \geq 12 g/dL.

Eighty-one patients, 59 female and 22 male, were included in the DUE. The average age of the females (59.8 years) was somewhat lower than the average age of the males (71.6 years). Most of the patients (n=78) received 200 mcg of darbepoetin alfa once every 2 weeks, although 3 patients received 100 mcg once a week. When questioned, the 3 patients who received every-week dosing said they had chosen this schedule because they felt better about coming into the clinic every week; however, the overwhelming majority of patients do not want to come in that often, so once-every-2-week dosing is generally the standard for outpatient treatment. The average baseline Hgb level was 9.3 g/dL. The majority of the participants (77.8%) had a partial or full response, with an average time to response of 41.2 days. Thus, darbepoetin alfa was clearly effective in this population and could be dosed less frequently than epoetin alfa. Darbepoetin alfa was therefore adopted as the EGF of choice for outpatient oncology areas. A therapeutic interchange was established in which patients who had been receiving weekly injections of 40,000 units epoetin alfa would now receive injections of 200 mcg dar-

bepoetin alfa once every 2 weeks. If there was no response at this dose, the dose would be increased to 300 mcg darbepoetin alfa once every 2 weeks, equivalent to 60,000 units epoetin alfa per week.

Next, SBHCS examined the use of darbepoetin alfa for inpatient treatment. Unlike outpatient treatment, in which the health system is reimbursed for the drug and the time spent administering it, inpatient reimbursements are made on the basis of Diagnosis Related Groups, which may not cover the costs of individual drugs or services provided. Therefore, cost-minimization is of increased importance in the inpatient setting.

To assess inpatient EGF use, the first step was to identify the erythropoietic length of stay (ELOS). The typical LOS calculation includes all patients, including those with short-term admissions, ie, pregnancy, pneumonia, or other acute conditions. The ELOS, by contrast, only includes patients who receive EGFs. These patients tend to be more severely ill and have more comorbidities than the average patient. A pharmacoeconomic analysis revealed that epoetin alfa would be the more cost-effective EGF if the ELOS was 4 days or less, due to a fraction of the weekly epoetin alfa dose being administered (3 times a week regimen). At 5 days, it would become more cost-effective to administer once-weekly dosing of darbepoetin alfa. The ELOS can be determined using International Classification of Diseases, 9th Revision (ICD-9) codes; other discharge codes from a billing database; or dispensing data from a computerized pharmacy system.

"In all cases, regardless of the facility or the disease category, we found that the ELOS was longer than 4 days, so it was very clear from an economic standpoint that we should go ahead with the conversion to darbepoetin alfa," Dr. Lew said.

Two inpatient conversion protocols were established to convert epoetin alfa to darbepoetin alfa, one for patients with cancer or the anemia of chronic disease, and one for patients with chronic renal failure with or without hemodialysis (Table 3). The conversions are made automatically in the pharmacy. Unlike outpatient therapy, darbepoetin alfa is dosed weekly in the inpatient setting.

The automatic conversion was built into the larger mechanism used to track laboratory values prior to administration of an EGF (Figure 1). When an order is

Table 3. Inpatient Conversion From Epoetin to Darbepoetin in the Saint Barnabas Health Care System

Oncology or Anemia of Chronic Disease		Chronic Renal Failure (\pm Hemodialysis)	
Epoetin alfa	Darbepoetin alfa	Epoetin alfa	Darbepoetin alfa
40,000 units weekly	100 mcg weekly	4,000–6,999 units 3 times a week (total weekly dose, 12,000–20,000 units)	40 mcg weekly
60,000 units weekly	150 mcg weekly	7,000–11,000 units 3 times a week (total weekly dose, 21,000–33,000 units)	60 mcg weekly

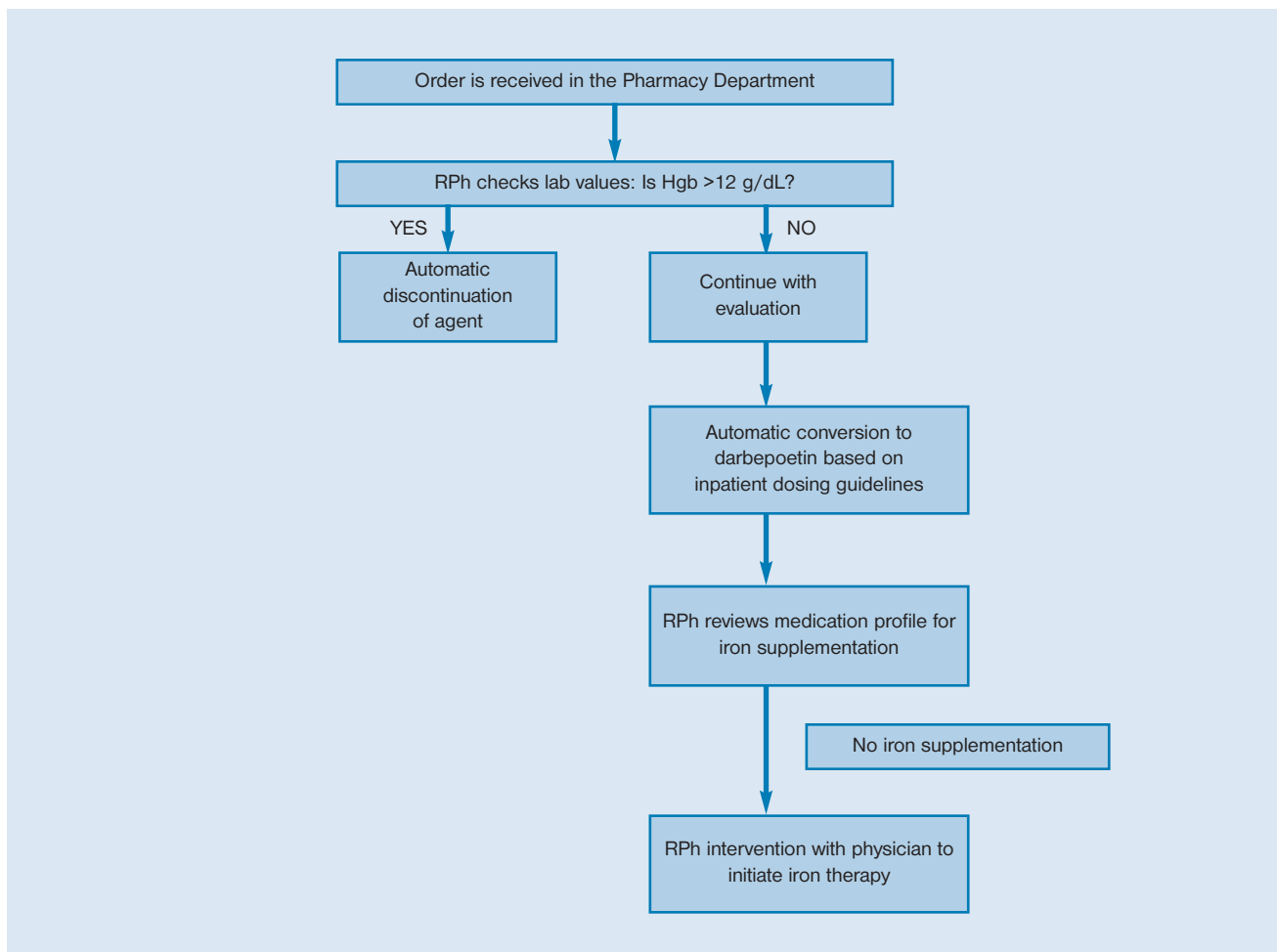


Figure 1. Anemia management at Saint Barnabas Health Care System

received in the Pharmacy Department, the pharmacist checks the laboratory values. If the Hgb concentration is >12 g/dL, the EGF is automatically discontinued. It was a big step to get this automatic discontinuation approved by the P & T Committee, said Dr. Lew, but “we don’t want to give drugs to patients who don’t need them,” she noted. If the Hgb concentration is <12 g/dL, the pharmacist reviews the medication profile for iron supplementation. If there is no record of iron supplementation, the pharmacist contacts the physician about the need to initiate iron therapy. When a patient does not respond to EGF therapy, it is frequently because of insufficient iron stores. In this case, Dr. Lew said, “you don’t have failure of the drug, you have failure of the process.”

Lastly, a discharge instruction sheet was developed to communicate the inpatient history of EGF administration to the patient’s private physician. This instruction sheet, which is filled out by a nurse and given to the patient, also includes information for the physician on when to start outpatient therapy with either darbepoetin alfa or epoetin alfa following inpatient therapy with darbepoetin alfa.

The switch to darbepoetin alfa has yielded substantial financial benefits: Although the oncology practice at SBHCS grew from 2002 to 2003, EGF expenditure de-

creased from \$13.3 million to \$11.4 million, a savings of \$1.9 million. In addition, there was better patient care in the form of improved anemia management. Currently, SBHCS is conducting a follow-up DUE in the outpatient oncology centers and is reviewing EGF use for inpatient populations as well. Importantly, they are providing feedback to users so that they can see the impact the changes had and adjust their tools as necessary. “There is so much passion and excitement at the beginning of a process,” Dr. Lew said. “But we need to have the same passion and excitement a year down the line.”

ANEMIA MANAGEMENT: THE UNIVERSITY OF PITTSBURGH MEDICAL CENTER INTENSIVE CARE UNITS

Anemia is frequent among patients in the intensive care unit (ICU). The Anemia and Blood Transfusion in the Critically Ill (ABC) trial of 3,534 patients in 146 ICUs in western Europe found that 63% of patients were anemic (Hgb <12 g/dL) on admission, and 29% had Hgb concentrations <10 g/dL; the mean Hgb concentration at admission was 11.3 ± 2.3 g/dL.¹² This high baseline prevalence of anemia is compounded by the “medical

vampirism” of frequent phlebotomy. The volume of blood drawn in the ICU averages 40 to 70 mL/day,^{12,13} much more than is drawn from patients in the general hospital population.¹⁴ This volume of phlebotomized blood accounts for 30% of the volume of blood that is transfused.¹³ Ted Rice, MS, FASHP, BCPS, Clinical Pharmacy Specialist in Critical Care at the University of Pittsburgh Medical Center (UPMC) Presbyterian Shadyside, said that UPMC is striving to develop systems to reduce the amount of blood lost to phlebotomy, such as conserving rather than discarding unused blood (especially from arterial lines) and using pediatric tubes when possible to reduce the volume of collected blood.

Despite the high incidence and severity of anemia in critical care, the conventional wisdom that it is necessary to transfuse at a high “trigger” value is being questioned. A number of clinical studies have suggested that, at least in some populations, transfusion may be associated with higher morbidity and mortality than mild to moderate anemia. The ABC trial found that mortality rates were higher for transfused patients than for nontransfused patients and that the nontransfused group showed greater improvement in organ function over time.¹² However, lower mean Hgb concentrations were associated with lower organ function, longer LOS, and higher mortality rates. Similarly, a US study of anemia and blood transfusion in the critically ill, known as the CRIT Study,¹⁵ found that the number of transfusions was independently associated with longer LOS in the ICU, longer total hospital LOS, and an increase in mortality. However, while baseline Hgb concentration did not predict LOS or mortality, a nadir Hgb concentration <9 g/dL did. “There seems to be some association between not getting blood and reducing mortality, but we do not know what the causality is,” explained Mr. Rice. “Is it because people who are more sick, who are more likely to die, are more likely to be transfused? It’s a little tricky to figure that out.”

To date, only 1 randomized, controlled trial has examined the issue of transfusion triggers in critical care.¹⁶ In

this study, performed by the Transfusion Requirements in Critical Care Investigators (TRICC), 838 patients with Hgb <9 g/dL within 72 hours of admission to the ICU were randomly assigned to a restrictive transfusion strategy (n=418), in which Hgb concentrations were kept between 7 and 10 g/dL, or to a liberal strategy (n=420), in which Hgb concentrations were maintained at 10 to 12 g/dL. Survival in the hospital was significantly higher in the restrictive transfusion group, although the overall cumulative 30-day survival rates were not statistically different between the 2 groups. The restrictive transfusion strategy particularly benefited patients younger than age 55 and those who were less ill. In contrast, the transfusion strategy did not affect 30-day mortality in patients with clinically significant cardiac disease (acute myocardial infarction and unstable angina). Therefore, a restrictive transfusion strategy appears to be at least as effective as and possibly superior to a liberal strategy, except in patients with significant cardiac disease.

Using the TRICC data as a starting point, an interdisciplinary team at UPMC discussed the adoption of transfusion criteria, and a compromise set of guidelines was established (Table 4). Although the transfusion triggers are a little more liberal than those in the TRICC study, the UPMC guidelines do incorporate the finding from the TRICC study that patients with cardiac disease should be transfused more liberally.¹⁶ In addition, patients with normal Hgb or Hct may need to be transfused if they are actively bleeding, Mr. Rice explained, since loss of blood at a normal concentration will not immediately change the concentration of Hgb or cells in the remaining blood.

Because the literature indicated that transfusions may contribute to poor outcomes, UPMC examined whether EGFs could be used to reduce the number of transfusions. A small study by Corwin et al published in 1999 supported this idea.¹⁷ This prospective, randomized, double-blind, placebo-controlled study of 160 patients in surgical ICUs gave the subjects 300 units/kg epoetin alfa (or placebo) every day on days 3 to 7 in the ICU, and every other day thereafter, unless the Hct was greater than 38%. The patients treated with epoetin alfa received half the number of transfusions (150 packed RBC [pRBC] units/80 patients) of the group receiving placebo (300 pRBC units/80 patients)—a statistically significant difference, according to the investigators.

About 6 months after the publication of this study,¹⁷ Mr. Rice and his colleagues examined EGF use at UPMC.¹⁸ One objective was to see whether the published study had had any impact on clinical practice. The use of epoetin alfa in 8 UPMC ICUs from June 30, 2000, to July 1, 2001, was reviewed retrospectively. During this period, 6,033 patients were admitted to these ICUs, only 7.5% (n=451) of whom received epoetin alfa. Sixty-two percent of those who received epoetin alfa had a preexisting reason for this treatment; the remaining 38% (n=172) had an “ICU indication,” that is, an attempt to reduce transfusion. The mean Hgb concentration of these 172 patients was 10.2 g/dL on admission (somewhat lower than in the Corwin study), and their mean LOS in the ICU was 22.3 days.

Table 4. RBC Transfusion Criteria (University of Pittsburgh Medical Center)

Patient Group/Comment	Criterion
Actively bleeding patients (may need to be transfused regardless of Hgb levels)	Acute bleeding with estimated blood loss $\geq 1,000$ mL or 20% of estimated blood volume
Patient with no medical comorbidities	Hgb ≤ 7.5 g/dL (Hct $\leq 22\%$)
Hemodynamically stable ICU patients (ACS excluded)	Hgb ≤ 7.5 g/dL (Hct $\leq 22\%$)
Non-ICU patient with cardiac, cerebral, or other major organ ischemia	Hgb ≤ 8.5 g/dL (Hct $\leq 26\%$)
Patients with unstable angina or acute myocardial infarction	Hgb ≤ 10 g/dL (Hct $\leq 30\%$)
Reinfusion of autologous blood	Hgb ≤ 9 g/dL (Hct $\leq 27\%$)

ACS, acute coronary syndromes; Hct, hematocrit; Hgb, hemoglobin; ICU, intensive care unit; RBC, red blood cell

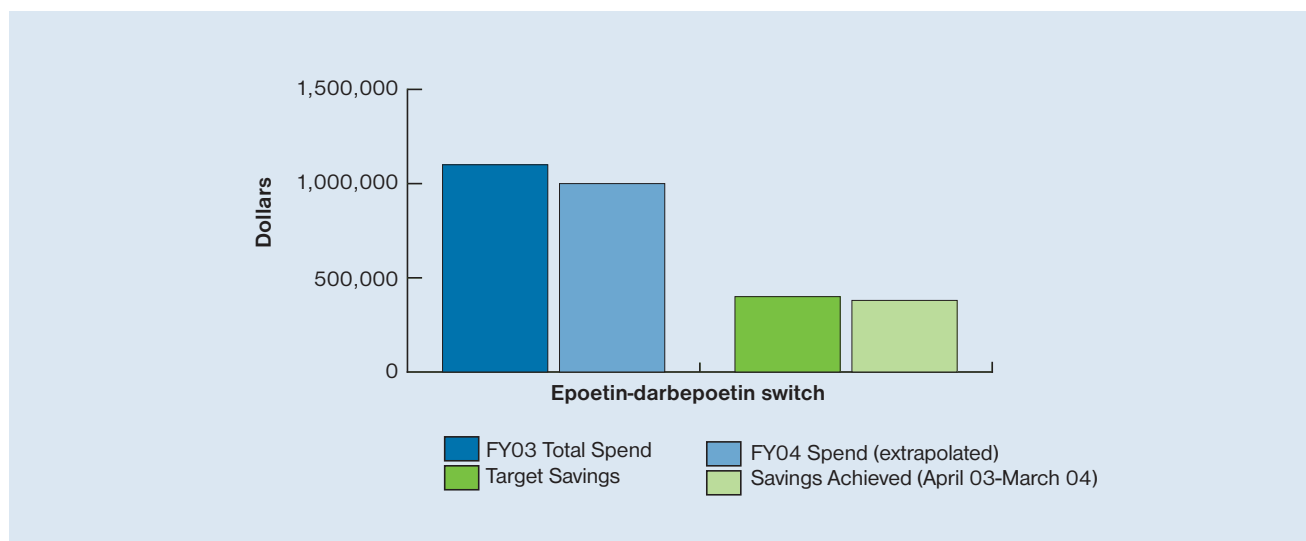


Figure 2. Graph representing a projected annual savings of \$221,778 from the University of Pittsburgh Medical Center formulary switch to darbepoetin.

FY, financial year

However, in contrast to the protocol of the Corwin et al study, epoetin alfa treatment at UPMC was initiated late (median, day 11) and at a low dose (mean, 13,500 units/week). Despite receiving epoetin alfa, 114 patients (66%) received at least 1 transfusion with a median of 2 pRBC units, indicating that the UPMC ICUs were not very successful in reducing the number of transfusions through the use of epoetin alfa.

At about the time that these data from UPMC were analyzed, a larger study was published by Corwin et al.¹⁹ In agreement with their previous results, this study found that patients started on epoetin alfa on ICU day 3 (n=650) were less likely to receive a transfusion than those receiving placebo (n=652; adjusted odds ratio, 0.65 [95% confidence interval, 0.51-0.83]). However, this corresponded to only a 10% difference in the percentage of patients receiving a transfusion (50.5% in the darbepoetin alfa group vs 60.4% in the epoetin alfa group), and, on average, \$800 to \$1,200 was being spent on epoetin alfa to save \$300 to \$400 in transfusion costs. Thus, neither the clinical data nor the economics were compelling enough for UPMC to recommend EGF use in the ICU solely for the purpose of reducing the frequency of transfusion. "The available evidence shows that we overtransfuse people," Mr. Rice explained. "We concluded that you should restrict transfusion in the ICU, but that using an EGF alone to restrict transfusion in the ICU is not logical."

Nonetheless, in response to a challenge by the CMS to evaluate the impact of a therapeutic interchange between epoetin alfa and darbepoetin alfa, UPMC performed a formulary review. The goal was to develop an interchange, provide dosing guidelines, and assess the financial effect of switching to darbepoetin alfa.²⁰ Because the 2 EGFs are therapeutically interchangeable, a cost minimization analysis (CMA) was used. A

CMA is the most restrictive form of analysis, focusing only on costs and not taking health outcomes or convenience into account, and can only be used to evaluate therapies or treatment strategies that lead to identical outcomes. At first the CMA was calculated using a conversion factor of 200 units epoetin alfa (at \$2.58) to 1 mcg darbepoetin alfa (at \$3.63), on the basis of published data.⁶ By this analysis, darbepoetin alfa would have increased costs. Therefore, the interchange was not implemented.²¹ However, a reanalysis using the CMS-recommended conversion ratio of 260:1⁸ and a subsequent 30% discount on darbepoetin alfa from Amgen led UPMC to adopt darbepoetin alfa as the preferred agent in April 2003.

Orders for epoetin alfa are automatically converted to darbepoetin alfa using a modified version of the conversion chart in the package insert: The darbepoetin alfa dose is set to 25 mcg for total weekly epoetin alfa doses $\leq 10,000$ units, and the break points between categories are shifted slightly. In this scheme the overall conversion ratio is approximately 400:1.²⁰ Compliance with the interchange has averaged 90% since April 2003. Furthermore, although the costs per total patient days varied somewhat over the 10 months for which data are available, the cost per day was reduced by 25% on average, for an expected annual savings of \$221,728 (Figure 2).²⁰ Clinical outcome analyses are still in progress.

Conclusions

Darbepoetin alfa and epoetin alfa are functionally equivalent, but the dose-equivalency curve is nonlinear and the interchange is continuing to be revised. At HMHP, on average, 1 mcg darbepoetin alfa is used to replace 400 units epoetin alfa in an inpatient dialysis unit.

Switching between outpatient epoetin alfa and inpatient darbepoetin alfa in patients needing dialysis is safe and effective, and it saves money.

The cost-effectiveness of one EGF over another depends on the ELOS, which tends to be much longer than the average LOS of all patients. If the ELOS is longer than 4 days—which it was at SBHCS—once-weekly darbepoetin alfa therapy is more cost-effective than 3-times-a-week epoetin alfa.

Although reducing transfusions in the ICU could benefit patients, EGFs are not cost-effective to use in the critical care unit for this purpose. Instead, reduced phlebotomy volume and relatively restricted transfusion triggers should

be adopted for most patients. However, switching the formulary EGF from epoetin alfa to darbepoetin alfa can provide substantial cost savings.

This report provides insights into 3 healthcare systems' approaches to managing the challenges of EGF selection and utilization. It is intended to stimulate thought and not be directly extrapolated to other practices. Institutional economic analysis of EGF use is very individual and dependent on many factors including the practice patterns, local net cost, and reimbursement of products. An unbiased economic calculator is available at www.UPA-LLC.com to allow specific and contemporary economic assessment of EGFs.

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