Evaluation of the use of erythropoietin-stimulating agents in a hospital setting to assess the necessity of a protocol-driven anemia management service

Shivali K. Patel, PharmD^a , Michael R. Griggs, PharmD^a, Yehya M. Ghoneim, RPh^a, Cindy K. Malhotra, PharmD^a, Andrew Z. Fenves, MD^{b,c} , and Susan C. Jacob, PharmD^a

^aDepartment of Pharmacy, Massachusetts General Hospital, Boston, Massachusetts; ^bDepartment of Medicine, Massachusetts General Hospital, Boston, Massachusetts; ^cDepartment of Medicine, Harvard Medical School, Boston, Massachusetts

ABSTRACT

Erythropoietin-stimulating agents (ESA) have revolutionized the management of anemia. However, these agents are not always utilized with proper monitoring parameters, which can present significant safety concerns, unwarranted drug expenditures, and decreased ESA efficacy. This retrospective study assessed the utilization of all ESAs in non-intensive care unit hospitalized patients at a large academic medical center from August 18, 2018, to August 31, 2018, using established guideline-based assessment criteria. Among the 167 doses of ESA evaluated, 86% ($n = 144$) were utilized in accordance with guideline-based assessment criteria regarding laboratory monitoring of iron studies. However, 24% ($n = 40$) of ESA doses were administered to patients with active, untreated iron deficiency at the time of administration. Although most ESA doses were utilized in accordance with the guideline-based criteria, interventions can be implemented to further improve anemia treatment. Implementing a protocol-driven anemia management service is one strategy that can improve patient care, advance patient safety, and be cost-beneficial.

KEYWORDS Anemia; cost savings; erythropoietin-stimulating agents; kidney disease; protocol; utilization

Erythropoietin-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa, stimulate the production of red blood cells through their interaction with the erythropoietin receptor and have revolutionized the management of anemia.^{1,2} Large medical centers often utilize thousands of ESA doses annually, which results in high drug costs. Several studies have demonstrated that optimizing laboratory monitoring can result in decreased ESA utilization since the clinical efficacy of ESAs is dependent on adequate vitamin and mineral stores in the body. Underlying deficiencies in iron, vitamin B12, and folate can cause hyporesponsiveness to ESA therapy. Treatment of the underlying cause of ESA hyporesponsiveness is highly recommended over progressively increasing the ESA dose.^{3,4} Implementing measures to support optimal use of ESAs can be cost beneficial in several ways. Literature suggests that a protocol-driven anemia management service can improve adherence to national monitoring guidelines and lead to

substantial cost savings in drug expenditures.^{5–10} Utilizing cost-effective measures to correct iron, vitamin B12, and folate deficiencies prior to ESA administration can prevent unwarranted use of ESA and maximize its clinical efficacy.³ The purpose of this study was to assess the prescribing patterns of ESAs for non-intensive care unit (ICU) hospitalized patients at a tertiary medical center and help develop interventions for improvement.

METHODS

This retrospective study assessed the utilization of ESAs in non-ICU hospitalized patients from August 18, 2018, to August 31, 2018, at a 1035-bed tertiary academic medical center. This study was undertaken as a quality improvement initiative at the Massachusetts General Hospital, and as such was not formally supervised by the institutional review board per their policies. The utilization of ESAs was assessed based

Corresponding author: Susan C. Jacob, PharmD, Department of Pharmacy, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114 (e-mail: scjacob@mgh.harvard.edu)

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Table 1. Guideline-based assessment criteria for erythropoietin-stimulating agent use

Congruence with guidelines	Criteria
Congruent	<ul style="list-style-type: none"> • Appropriate FDA-approved indication for an ESA • Iron studies (serum iron, transferrin saturation, and ferritin) obtained within 1 month prior to ESA administration • Vitamin B12 and folate levels obtained prior to initiating treatment with ESA for patients on hemodialysis • Repletion of any iron, vitamin B12, or folate deficiencies prior to ESA administration
Incongruent	<ul style="list-style-type: none"> • Untreated iron, vitamin B12, or folate deficiencies prior to ESA administration • No iron studies (serum iron, transferrin saturation, and ferritin) obtained within 1 month of ESA administration • Hemoglobin level >10 g/dL for nondialysis or >11 g/dL for dialysis patients • Active thrombus (pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction) • Uncontrolled blood pressure $\geq$180/110 mm Hg prior to administration

ESA indicates erythropoietin-stimulating agent; FDA, Food and Drug Administration.

on criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) and National Comprehensive Cancer Network best practices guidelines (*Table 1*).^{11,12}

Data were collected for patient demographics, ESA agent, ESA dosage regimen, number of ESA doses received during hospitalization, treatment indication, renal status, blood pressure, presence of an active thrombus, repletion of any laboratory deficiencies prior to the administration of ESA, and ESA prescribing through a clinical order set. Data on laboratory hemoglobin, iron, transferrin saturation, ferritin, folate, and vitamin B12 levels were also collected. In addition, we examined whether patients undergoing hemodialysis were receiving supplementation with a water-soluble renal multivitamin. Notably, we did not have access to laboratory results obtained at outpatient dialysis centers. Data were collected using the electronic medical record and documented on a secure online database system (REDCap). ESA cost information was calculated using average wholesale pricing. Data were analyzed using descriptive statistics as indicated based on distribution.

RESULTS

The study included 54 patients who received treatment with a total of 167 ESA doses during this time period. Ninety-five percent of ESAs were prescribed via a clinical order set. *Table 2* illustrates baseline patient demographics.

Most doses (86%; $n = 144/167$) were prescribed in congruence with best practice guidelines since laboratory iron status was obtained within 1 month prior to ESA administration (*Table 3*). However, 24% ($n = 40$) of ESA doses were utilized in patients with active, untreated iron deficiency at the time of administration. Moreover, only 67% of patients undergoing hemodialysis were receiving supplementation with a water-soluble renal multivitamin during their treatment. All ESA doses were administered in congruence with the guideline-based assessment criteria regarding indication, hemoglobin level, blood pressure, and presence of an active thrombus. Pertinent laboratory values of patients and information related to ESA utilization are detailed in *Tables 3* and *4*.

Table 2. Baseline demographics of the 54 study participants

Baseline patient demographics	n (%) or mean (range)
Male	32 (59%)
Weight (kg)	77.5 (36.1–137.6)
Length of admission (days)	17 (1–238)
Renal status	
ESRD on HD	48 (89%)
CKD <u>not</u> on HD	3 (5.5%)
Normal (chemotherapy-induced anemia)	3 (5.5%)
Total ESA doses during admission	7 (1–69)
Continuation of prior ESA therapy	24 (44%)

CKD indicates chronic kidney disease; ESA, erythropoietin-stimulating agent; ESRD, end-stage renal disease; HD, hemodialysis.

Using average wholesale pricing, approximately \$14,000 was spent during the 2-week study period on ESA utilized without obtaining laboratory iron studies within 1 month of ESA administration. This is an estimated \$355,000 annual drug expenditure for ESA use without adequate iron monitoring. Furthermore, approximately \$24,000 worth of ESA doses was administered to patients with active, untreated iron deficiency during the 2-week study period. This accounts for an estimated \$624,000 spent annually on guideline-incongruent ESA utilization due to active, untreated serum deficiencies.

DISCUSSION

This study provides data on baseline prescribing of ESAs for non-ICU hospitalized patients at a tertiary medical center. Our results demonstrated that adequate laboratory monitoring of ESA therapy is not consistently implemented and that approximately one-third of patients administered an ESA while on hemodialysis were not receiving supplementation with a water-soluble multivitamin. Continuation of water-soluble multivitamin supplementation for patients on

Table 3. Pertinent laboratory values of patients

Laboratory marker	Mean	Range	Standard deviation	Normal values	Timing before ESA administration			
					<1 mo	2 mo	3–6 mo	>6 mo
Iron (μg/dL)	81	17–1552	226	Female: 35–145; Male: 50–150	68%	15%	6%	11%
Vitamin B12 (ng/L)	1001	312–2000	552	180–914	26%	0%	12%	62%
Folate (μg/L)	32	2.8–2223	266	≥4.0	27%	4%	5%	64%
Transferrin saturation (%)	27	7–76	15	Female: 12–44; Male: 15–50	68%	15%	6%	11%
Ferritin (μg/dL)	852	75–4400	782	Female: 11–307; Male: 24–307	68%	15%	6%	11%

Table 4. ESA utilization during the study period

Variable	Category	n (%)
Total ESA doses administered (n)		167
ESA agent	Epoetin alfa	155 (93%)
	Darbepoetin alfa	12 (7%)
Indication for ESA	Anemia of CKD on HD	154 (93%)
	Anemia of CKD not on HD	7 (4%)
	Chemotherapy-induced anemia	4 (2%)
	Acute kidney injury	2 (1%)
Labs obtained during hospital admission	Iron	144 (68%)
	Vitamin B12	44 (26%)
	Folate	44 (26%)
	Transferrin saturation	144 (68%)
	Ferritin	144 (68%)
Prescribed via a clinical order set		130 (95%)

CKD indicates chronic kidney disease; ESA, erythropoietin-stimulating agent; HD, hemodialysis.

hemodialysis is recommended even during hospitalization. These multivitamins have minimal adverse effects and their absence may contribute to disease-related complications as well as ESA hyporesponsiveness.^{3,4}

In an effort to optimize patient care and limit unwarranted use of ESAs, we sought to evaluate the utilization of these expensive medications based on specific best practices put forth by national guidelines. Although this study demonstrated a significant unwarranted expenditure on ESAs, some limitations of this study include its single-center design, short study period, and unavailability of laboratory monitoring data associated with each ESA administration. It should also be noted that the use of ESA depends on several factors, and our guideline-based assessment criteria may not apply to all patients. This study utilized relatively strict assessment

criteria for evaluation. The KDIGO guidelines recommend checking iron status at least every 3 months during ESA therapy. We chose to monitor iron status using transferrin saturation and ferritin within 1 month prior to ESA administration, as these markers are acute-phase reactants that may fluctuate during certain illnesses. However, we were unable to verify if serum laboratories were checked at outpatient dialysis centers and if individual providers were aware of such laboratory results prior to prescribing an ESA. As noted, 24% of patients had prior ESA therapy before hospitalization. It is therefore quite likely that these patients had their iron studies and other laboratory work performed in the outpatient setting. However, this information is often not readily available. In fact, our institution currently does not have an off-site outpatient dialysis facility. By conducting this study, we found a valuable opportunity for a quality improvement initiative that includes implementing direct communication with outpatient dialysis centers and creating a pathway for which medical centers can gain easier access to patient records at outpatient dialysis centers. Integration of data within the electronic medical record is one avenue that should be explored. In hopes of further limiting unwarranted expenditures on ESAs, future studies should evaluate decreasing the number of ESAs available in the hospital formulary.

Ultimately, the plan is to utilize the results of this study to demonstrate the benefit of a protocol-driven anemia management service in optimizing patient care and limiting unwarranted expenditures on ESAs. This protocol would be developed in collaboration with medical providers, pharmacists, and other health care providers. We anticipate the role of the pharmacist in anemia management to include screening patients for anemia, developing guidelines for the treatment of anemia, ordering appropriate laboratory monitoring, initiating supplementation with a water-soluble renal multivitamin for patients undergoing hemodialysis, conducting patient education to promote adherence to therapy, and verifying that all medications are dosed appropriately based on a patient's renal status. Previous studies have demonstrated that pharmacist involvement in anemia management can improve patient outcomes.^{5–10} In addition to recommending the allocation of full-time equivalent hours for pharmacists

who specialize in anemia management, we plan on implementing a revised electronic clinical order set for ESA that incorporates prompts for optimal monitoring parameters and guidelines for correcting serum deficiencies. Revisions to the hospital policy on ESA and provider education sessions on optimal prescribing of ESA have also been implemented. The utilization of ESAs will be reassessed following the implementation of these interventions in order to determine the impact of the interventions and if further evaluation is necessary.

In conclusion, most ESA doses were utilized in accordance with the guideline-based assessment criteria developed for this study. Interventions can be implemented to further improve anemia treatment. It is critical to monitor laboratory values and provide clinical justification for the use of ESAs to optimize patient care and limit excessive treatment costs.

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ORCID

Shivali K. Patel <http://orcid.org/0000-0003-1325-0095>

Andrew Z. Fenves <http://orcid.org/0000-0003-2817-3280>

Susan C. Jacob <http://orcid.org/0000-0003-1256-5757>

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