Impact of a Clinical Pharmacy Anemia Management Service on Adherence to Monitoring Guidelines, Clinical Outcomes, and Medication Utilization

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ABSTRACT

BACKGROUND: Anemia management clinics have demonstrated favorable impacts on clinical and economic outcomes and patient satisfaction. Clinical pharmacists are uniquely qualified to manage complex drug therapies requiring intensive monitoring. The complexity, risks associated with inappropriate treatment, and high cost of erythropoietin-stimulating agents (ESAs) make patients on these medications excellent candidates for clinical pharmacist-based management. Integrating ESA management into a clinical pharmacist-managed service has the potential to improve anemia management not only by improving patient outcomes and patient safety, but also by decreasing medication costs.

OBJECTIVES: To (a) assess adherence to monitoring guidelines, efficacy, and safety outcomes and (b) quantify medication utilization expenditures among patients using ESA therapy managed by a clinical pharmacy service compared with usual care.

METHODS: This is a retrospective longitudinal cohort study of patients with anemia caused by chronic kidney disease who were on ESA treatment for at least 6 months between January 2008 and December 2010. Adherence to monitoring guidelines, efficacy, safety, and drug utilization outcomes were compared between the 2 groups.

RESULTS: A total of 101 patients were included in the study. Of that number, 31 were managed by the pharmacist-managed anemia service, and 70 were in the usual care group. The pharmacist-managed patients had improved adherence to guidelines for hemoglobin monitoring (32.3% vs. 14.3%, $P=0.049$) and iron monitoring (61.3% vs. 30.0%, $P=0.005$) compared with similar patients receiving usual care. Time to achievement of hemoglobin target was 28 days in the pharmacist-managed group compared with 41 days in the usual care group ($P=0.135$), while the proportion of patients achieving target hemoglobin was 96.8% compared with 95.7%, respectively ($P=0.654$). Patients in the pharmacist-managed group used less epoetin alfa during the 6-month period, leading to an annualized savings of $1,288 per patient in drug expenditures.

CONCLUSIONS: A clinical pharmacist-managed anemia service resulted in improved adherence to national monitoring guidelines, equivalent quality and safety outcomes, and lower medication utilization compared with usual care.

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What is already known about this subject

- Erythropoietin therapy requires extensive monitoring to ensure desired outcomes and patient safety.
- Clinical pharmacists are uniquely qualified to manage complex drug therapies requiring close monitoring.
- Anemia management clinics have demonstrated favorable impacts on clinical and economic outcomes and patient satisfaction.
- Clinical pharmacy services (e.g., anticoagulation management, hypertension management, diabetes management) are widely established as effective care models providing superior patient care outcomes when compared with usual care.
- The impact of a clinical pharmacist-managed anemia service on adherence to monitoring recommendations, patient outcomes, and patient safety in the predialysis chronic kidney disease population is not well described in the biomedical literature.

What this study adds

- Patients receiving erythropoietin-stimulating agents who were enrolled in a clinical pharmacist-managed anemia service were more likely to complete hemoglobin and iron level monitoring recommended by national clinical practice guidelines.
- Patients managed by clinical pharmacists used less epoetin alfa, which was associated with improved safety and fewer hospitalizations related to anemia.
- Patients managed by clinical pharmacists had lower drug utilization, resulting in annualized cost avoidance of more than $1,200 per patient.

Anemia is common in patients with chronic kidney disease (CKD) and chronic inflammatory conditions and is a side effect of certain drug therapies. Erythropoietin-stimulating agents (ESAs) are commonly used to treat anemia, especially in patients with CKD; however, they are not without risks. Optimal treatment with ESAs, such as epoetin alfa and darbepoetin alfa, requires close monitoring of hemoglobin response, iron stores, comorbidities, and concurrent medications.[1,2] The addition of a boxed warning to the labeling of ESAs in 2007, following studies demonstrating that patients with CKD were at greater risk for death and serious cardiovascular events (e.g., myocardial infarction, stroke, congestive heart failure, when administered ESAs to hemoglobin targets > 12 grams per deciliter [g/dL]), further justified efforts to ensure appropriate use and monitoring of patients on ESA therapy.[3]

The National Kidney Foundation practice guidelines for ESA monitoring were published from the work of the Kidney Disease Outcomes Quality Initiative (KDOQI).[1] These guidelines recommend checking a complete blood count (CBC) and iron studies (ferritin and transferrin saturation) at baseline (prior to initiating ESA therapy) and repeating a CBC at least monthly while on therapy. These monitoring recommendations are well recognized and accepted as the standard of care; however, the optimal way to ensure that monitoring is completed, that ESA doses are appropriately titrated, and that side effects are appropriately managed has not been determined.

As medication experts, clinical pharmacists are uniquely qualified to manage complex drug therapies requiring intensive monitoring.[4,5] The complexity of management, risks associated with inappropriate treatment, and high cost of ESA therapy make patients on these medications excellent candidates for pharmacist-based management. While anemia management services have demonstrated favorable impact on clinical and economic outcomes and patient satisfaction,[6-11] these have primarily used pre/post study designs, wherein the same patient population had its ESA therapy managed by a physician and then managed by a pharmacist and compared outcomes at different points in a patient's ESA therapy course. Unique to our study, both study groups were new starts on ESA therapy, and patients were managed via a centralized clinical pharmacy service using telephonic intervention.

The objectives of this study were to assess adherence to monitoring guidelines, along with efficacy and safety outcomes, and to quantify medication utilization expenditures among patients using ESA therapy managed by a clinical pharmacy service compared with usual care.

Methods

Setting

Kaiser Permanente Colorado (KPCO) is an integrated health care delivery system providing health care to more than 530,000 members in the Denver metropolitan area. In 2005, a clinical pharmacy monitoring service was implemented at KPCO for all oncology patients receiving ESA therapy. Soon after, a separate service for patients with CKD using ESA therapy was initiated as a pilot, including only 20% of the KPCO CKD population on ESAs because of capacity issues. Both ESA services operated under a Collaborative Drug Therapy Management (CDTM) agreement, whereby a clinical pharmacist and physician establish written protocols authorizing the pharmacist to manage drug therapy for a given indication, including initiation or discontinuation of specified medications, dose adjustment, and ordering appropriate laboratory tests. Patients were monitored using a population management database (Dawn GF, 4S Systems, Ltd., Cumbria, UK). At the time this study was initiated, the target hemoglobin under both CDTM ESA protocols was between 10 and 12 g/dL, based upon current guidelines.[1]

TABLE 1 Baseline Characteristics by Intervention Status (N = 101)

Characteristic	Usual Care (n = 70)	Pharmacist (n = 31)	*P* Value[a]
Mean age (SD)	72.0 (13.3)	65.6 (14.1)	0.029
Female (%)	58.6	54.8	0.726
CKD stage by group (%)			0.667
Stage 1 (GFR ≥ 90 ml/min)	1.4	0	
Stage 2 (GFR 60-89 ml/min)	5.7	0	
Stage 3 (GFR 30-59 ml/min)	37.1	38.7	
Stage 4 (GFR 15-29 ml/min)	42.9	48.4	
Stage 5 (GFR < 15 ml/min)	12.9	12.9	
Mean baseline hemoglobin (SD)	10.0 (1.2)	9.6 (0.0)	0.148

[a]*Chi-square or Fisher's exact test.*

CKD = chronic kidney disease; GFR = glomerular filtration rate; ml/min = milliliters per minute; Pharmacist = clinical pharmacist-managed group; SD = standard deviation.

In 2008, a decision was made to expand the capacity and increase the efficiency of both ESA monitoring services by merging them into a single clinical pharmacy anemia service and transitioning into the existing workflow of the Clinical Pharmacy Anticoagulation Service (CPAS). This change was a logical transition, since the CPAS at KPCO has demonstrated success in managing patients on monitoring-intensive medications and also operates under CDTM using telephonic intervention and similar technology for patient monitoring.[5,12] The CPAS has been described in detail elsewhere.[13] The newly merged service was subsequently renamed the Clinical Pharmacy Anticoagulation and Anemia Service (CPAAS). Between 2008 and 2010, this new framework allowed ESA monitoring to gradually expand care to all patients with anemia caused by CKD. During this time, physicians began to refer new starts and existing patients on ESAs to CPAAS for enrollment into the service. Since these patients were not all receiving clinical pharmacist management, it was feasible to compare outcomes between patients who were enrolled in the clinical pharmacy service and those patients who were managed via usual care by their physicians.

Study Design

This project was a retrospective longitudinal cohort study of patients with CKD receiving ESA therapy, using data obtained via review of electronic medical records at KPCO. The study was reviewed and approved by the KPCO Institutional Review Board.

Patients

Adult patients 18 years or older with CKD (predialysis) who were newly prescribed epoetin alfa (as this was the preferred formulary agent at the time) between January 1, 2008, and December 31, 2010, were identified via electronic queries of KPCO pharmacy databases. Patients were excluded if they (a) did not have continuous KPCO membership for 90 days

TABLE 2 Adherence to Monitoring Outcomes (N=101)

Outcome	Usual Care (n = 70)	Pharmacist (n = 31)	*P* Value[a]	Adjusted *P* Value[b]
Composite hemoglobin monitoring endpoint, met all 3 criteria below (%)	10 (14.3)	10 (32.3)	0.037	0.049
Baseline hemoglobin performed (%)	57 (81.4)	29 (93.6)	0.114	0.124
First follow-up hemoglobin drawn within 28 days (%)	58 (82.9)	28 (90.3)	0.331	0.278
Follow-up hemoglobin labs drawn ≤4 weeks apart (%)	12 (17.1)	12 (38.7)	0.019	0.023
Composite iron monitoring endpoint, met both criteria below (%)	21 (30.0)	19 (61.3)	0.003	0.005
Baseline ferritin and TSAT performed (%)	31 (44.3)	23 (74.2)	0.005	0.006
Follow-up ferritin and TSAT drawn at least once during treatment period (%)	40 (57.1)	26 (83.9)	0.009	0.026
	n = 51	n = 28		
IF ferritin < 100 or TSAT < 20%: iron therapy started within 14 days (%)	23 (46.0)	21 (75.0)	0.013	0.016

[a]*Chi-square or Fisher's exact test.*
[b]*Adjusted for group differences in age.*
Pharmacist = clinical pharmacist-managed group; TSAT = transferrin saturation.

prior to and 6 months after their ESA commencement (index date); (b) were pregnant; (c) received ESA during dialysis and were managed outside of KPCO; (d) were prescribed an ESA for oncologic indications; or (e) did not complete a continuous 6-month course of an ESA. The date of the first in-office administration of ESA therapy or first purchase of an outpatient prescription was defined as the index date, and newly starting was defined as receiving no ESA therapy for 90 days prior to this date. All patients' electronic medical records were manually reviewed to confirm the accuracy of the index dates and to allocate patients to the appropriate group based upon whether or not they were enrolled in the CPAAS. Patients enrolled in the CPAAS were assigned to the pharmacist-managed group, and patients managed by their physician were assigned to the usual care group.

Outcomes

The primary study outcomes were rates of adherence to 6 monitoring recommendations based on published KDOQI guidelines for hemoglobin and iron status during the treatment period.[1] These included (a) baseline hemoglobin measured within 30 days prior to first ESA dose; (b) follow-up hemoglobin measured within 4 weeks after first ESA dose; (c) follow-up hemoglobin tests no more than 4 weeks apart during ESA therapy; (d) baseline ferritin and transferrin saturation (TSAT) measured 90 days prior to or 28 days after first ESA dose; (e) follow-up ferritin and TSAT levels measured at least once during the 6 months following ESA initiation; and (f) iron therapy initiated within 14 days of lab test if ferritin level was less than 100 nanograms per milliliter (ng/mL) or TSAT less than 20%. Composite outcomes consisting of hemoglobin monitoring (items a-c), and iron monitoring (items d-e) were also used as outcomes.

Secondary study outcomes included the proportions of (a) patients achieving target hemoglobin levels and number of days required to achieve target; (b) patients experiencing at least 1 hemoglobin higher than 12 g/dL or below 10 g/dL; (c) patients receiving at least 1 red blood cell transfusion; and (d) patients with at least 1 hospital visit defined as an anemia- or ESA-related hospitalization or emergency department visit. Anemia- or ESA-related diagnoses recorded at this hospital visit could include anemia, cardiovascular events (angina, myocardial infarction, and congestive heart failure), shortness of breath, weakness, dizziness, thromboembolism, or stroke. Additionally, the average weekly dose of ESA therapy and its associated cost were compared between groups. The 6-month cost of medication was calculated using discounted average wholesale price and extrapolated to 1 year.

Statistical Analysis

Based on estimates that clinical pharmacist-managed patients meet individual monitoring guidelines at least 70% of the time for each of the 6 monitoring endpoints, a sample size of 24 patients in the intervention group and 48 patients in the control group was needed to reach 80% statistical power to detect a 25% difference in primary outcome with a 2-sided alpha level of 0.05.

The 2 groups were assessed at baseline for demographic characteristics, including baseline lab values, age, gender, and CKD stage. The proportion of patients meeting monitoring recommendations, safety, or efficacy outcomes was compared between the pharmacist-managed and usual care groups using chi-square or Fisher's exact test as indicated. Unadjusted and adjusted analyses of the outcome variables were conducted. Patient characteristics with a $P < 0.20$ in the bivariate analysis were entered into a logistic regression model. Time to achieve hemoglobin within the target range was calculated using time-to-event analysis via the Cox proportional hazard model. Average weekly medication dose and associated costs, estimated by discounted average wholesale price, were log

TABLE 3 Efficacy and Safety Outcomes (N=101)

Outcome	Usual Care (n = 70)	Pharmacist (n = 3)	*P* Value[a]	Adjusted *P* Value[b]
Patients achieving target hemoglobin during study period (%)	67 (95.7)	30 (96.8)	0.801	0.654
Mean days to achieving hemoglobin goal (SD)	41 (44)	28 (25)	0.077	0.135
Likelihood of achieving hemoglobin goal (HR, 95% CI)		1.41 (0.91-2.17)		
Any follow-up hemoglobin > 12 g/dL (%)	38 (54.3)	15 (48.4)	0.584	0.715
Any follow-up hemoglobin < 10 g/dL (%)	42 (60.0)	20 (64.5)	0.667	0.673
Number of patients with at least 1 transfusion (%)	11 (15.7)	3 (9.7)	0.418	0.439
Number of patients with at least 1 hospital visit (%)	14 (20.0)	1 (3.2)	0.034	0.067
Reason for hospital visit (%)				
Cardiovascular event	6 (46)	1 (100)		
SOB, weakness, dizziness	8 (54)	0 (0)		
Thromboembolism, stroke	0 (0)	0 (0)		

[a]*Chi-square or Fisher's exact test.*

[b]*Adjusted for group differences in age.*

CI = confidence interval; g/dL = grams per deciliter; HR = hazard ratio; Pharmacist = clinical pharmacist-managed group; SD = standard deviation; SOB = shortness of breath.

transformed and compared using Student's t-test. All analyses were performed using SAS statistical software version 9.1.3 (SAS Institute, Inc., Cary, NC).

Results

A total of 101 patients, 31 in the pharmacist-managed group and 70 in the usual care group, were eligible for study inclusion. Baseline characteristics for the 2 groups are summarized in Table 1. Patients in the pharmacist-managed group were younger than usual care patients (mean age 65.6 years vs. 72.0 years, $P = 0.029$) but were similar in terms of indication for ESA therapy, kidney function, and baseline hemoglobin. Of the 3 individual hemoglobin-monitoring parameters, the pharmacist-managed group demonstrated superior performance for follow-up hemoglobin testing (achieved in 38.7% of patients vs. 17.1% in the usual care group, adjusted $P = 0.023$) and no difference for baseline hemoglobin and first follow-up hemoglobin (Table 2). For the individual iron-monitoring parameters, the pharmacist-managed group outperformed the usual care group for all 3 parameters (baseline iron studies, follow-up iron studies during treatment period, and initiation of iron therapy, Table 2). Significant differences were observed between groups for both composite outcomes (hemoglobin monitoring 32.2% vs. 14.3% and iron monitoring 61.3% vs. 30.0% in the clinical pharmacist-managed group and usual care group, respectively, Table 2).

A numerically greater proportion of patients in the clinical pharmacist-managed group achieved their target hemoglobin (96.8% in the clinical pharmacist-managed vs. 95.7% in usual care, $P = 0.801$, age-adjusted $P = 0.654$, hazard ratio = 1.41 [95% confidence interval = 0.91-2.17]), but this difference was not statistically significant (Table 3). The patients receiving clinical pharmacist management who achieved their target hemoglobin concentration did so in an average of 28 days compared with 41 days in the usual care group ($P = 0.077$, age-adjusted $P = 0.135$). There were no statistically significant differences in patients with a follow-up hemoglobin > 12 g/dL or < 10 g/dL, or in patients requiring a transfusion (Table 3). There was 1 patient (3.2%) with a potential ESA- or anemia-related hospital visit in the pharmacist-managed group compared with 14 patients (20.0%) in the usual care group ($P = 0.034$, age-adjusted $P = 0.067$). The average weekly ESA dose was significantly lower in the pharmacist-managed group than in the usual care group (5,509 units and 6,877 units, respectively, $P < 0.001$), as was annualized ESA expenditure ($1,288 annual savings per patient, Table 4).

Discussion

Most previous studies of anemia-monitoring services in patients with CKD have been limited by pre/post study designs or historical controls and were not limited to patients newly starting ESA therapy; therefore, any improvements in hemoglobin levels may be difficult to attribute to the intervention compared with only the effect of ESA therapy.[7-10] Nevertheless, previous studies found that a clinical pharmacist-managed anemia service improves adherence to monitoring guidelines[9] and produces superior or similar quality results to nonpharmacist management services using lower ESA doses.[7,10,14] In the current study, differences in achieving hemoglobin targets did not reach statistical significance, but this lack of significance may be because the usual care group's achievement of hemoglobin targets was very high (96%) compared with other studies in which patients achieved their hemoglobin target only 17%-44% of the time.[6,10,14]

Improvements in hemoglobin levels and ESA dose reductions in the current study may be attributed in part to better management of iron deficiency. A previous study found that a large number of patients with below-target hemoglobin levels

TABLE 4 Erythropoietin-Stimulating Agent Utilization (N = 101)

	Usual Care (n = 70)	Pharmacist (n = 31)	Difference	*P* Value[a]
Average weekly ESA dose (units)	6,877	5,509	1,368	<0.001
Annualized ESA cost per patient ($)	6,397	5,109	1,288	<0.001

[a]*T-test.*

ESA = erythropoietin-stimulating agent; Pharmacist = clinical pharmacist-managed group.

in the pre-intervention phase were also iron deficient, and most of these patients went on to achieve target hemoglobin after iron replacement.[10] Higher rates of iron monitoring and correction of laboratory-identified iron deficiencies in our study (75.0% vs. 46.0%) likely contributed not only to the high proportion of patients who achieved target hemoglobin but may have also contributed to the observed lower ESA doses in the clinical pharmacist-managed group.

Although available literature does not suggest that age contributes to differences in anemia management or outcomes, the results of the current study were age-adjusted to account for any potential difference.

We found that hospital visits related to anemia or ESA therapy occurred less frequently among patients enrolled in the pharmacist-managed group compared with usual care patients. The majority of these visits were cardiovascular related. While we may have observed lower rates of hospital visits in the pharmacist-managed group because fewer patients had a hemoglobin above the recommended upper limit of 12 g/dL or had a low hemoglobin requiring blood transfusion, these outcomes were not statistically significant; therefore, there may have been other contributing factors.

Unique to our study is the use of an existing clinical pharmacy service to provide anemia management, thereby leveraging existing organizational relationships and resources. Such an approach likely provided greater efficiency and rapid acceptance of the service by providers already familiar with the long-standing anticoagulation service compared with other similar management programs.

Limitations

This study was not without limitations. One limitation was low enrollment because of decreased global ESA utilization following new safety concerns in CKD patients in 2009.[15] Another limitation was that some patients progressed to dialysis before completing the 6-month study period and therefore had to be excluded. Thus, our estimates of cost savings are likely underestimates.

Conclusions

Patients managed by a clinical pharmacy anemia service had higher adherence to monitoring recommended by national guidelines, equivalent safety outcomes, and lower medication utilization compared with patients receiving usual care. Larger prospective studies are warranted to further assess the impact of a clinical pharmacist-managed anemia service on patient safety and efficacy outcomes.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

Debenito, Billups, Tran, and Price participated in concept and design, data interpretation, and writing the manuscript. Data were collected by Debenito, Tran, and Price, and Debenito and Billups revised the manuscript.

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