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CLINICAL RESEARCH

Contemporary Practice of Anemia Treatment Among Dialysis Patients in the United States

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Introduction: The treatment of anemia is a major activity in the care of patients undergoing maintenance hemodialysis (HD). The comparative effectiveness of new pharmacologic treatments, relative to erythropoiesis-stimulating agents (ESAs), should be anticipated on the bases of controlled trials and current practice. We describe the contemporary practice of anemia treatment in a national cohort of patients undergoing maintenance HD.

Methods: We analyzed the United States Renal Data System (USRDS) data to identify adult patients undergoing in-facility HD in 2016 to 2019. Using the Consolidated Renal Operations in a Web-Enabled Network (CROWNWeb) dataset, we identified hemoglobin and ESA utilization (agent and cumulative dose) during each patient-month, as well as intravenous (IV) iron utilization, ferritin, and transferrin saturation. We compared ESA dosing during the study era to dosing in the Normal Hematocrit Cardiac Trial (NHCT), conducted in the 1990s. We assessed ESA hyporesponsiveness by estimating the prevalence of the following: (i) high erythropoietin resistance index (ERI) and (ii) either 3 or 6 consecutive months with hemoglobin $<$10 g/dl.

Results: Nearly two-thirds of patient-months had hemoglobin of 10.0 to 11.9 g/dl. Mean ESA utilization was 76.7% per month, with increasing use of pegylated epoetin beta. ESA dosing was stable; epoetin alfa dosing was slightly lower than in the low-target arm of the NHCT. The prevalence of ESA hyporesponsiveness was 22.2% if defined by high ERI, but only 2.1% to 6.0% if defined by 3 to 6 consecutive months with hemoglobin $<$10 g/dl. Median transferrin saturation was 22.3% with high ERI and persistently low hemoglobin.

Conclusion: Hemoglobin and ESA dosing distributions are stable, with epoetin alfa dosing below the low-target arm of the NHCT. Persistently low hemoglobin occurs infrequently and may reflect iron depletion.

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Effective treatment of anemia is a key goal in the ongoing care of patients undergoing maintenance HD. According to the Dialysis Outcomes and Practice Patterns Study Practice Monitor, more than 85% of patients on in-facility HD in the United States received an ESA during each month of 2020; during 3-month intervals ending in 2020, almost 90% of patients on in-facility HD received an ESA.[1] Use of ESAs increases hemoglobin, but safe use of ESAs presents a challenge. The US Food and Drug Administration has stated that "in controlled trials with [chronic kidney disease] patients, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dl."[2] This statement reflects the results of 3 key trials: the NHCT, the Correction of Hemoglobin and Outcomes in Renal Insufficiency Trial, and the Trial to Reduce Cardiovascular Events with Aranesp Therapy.[3–5] All these trials used either epoetin alfa or darbepoetin alfa, both forms of exogenous erythropoietin, although only the NHCT enrolled patients undergoing maintenance dialysis.

In the present study, we analyzed a national cohort of prevalent patients undergoing in-facility HD to characterize utilization and dosing of ESAs; the

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distribution of hemoglobin; the prevalence of ESA hyporesponsiveness; and the utilization of IV iron, as well as distributions of iron parameters. Notably, we compared contemporary practice to epoetin alfa dosing in the NHCT, which was conducted in the 1990s[3]; the low-target (i.e., 10 g/dl) arm of the trial remains the lowest-risk approach to anemia treatment with ESAs that has been identified in trials of hemoglobin targets for patients undergoing dialysis.

METHODS

Cohort

We analyzed USRDS Standard Analysis Files that were available at the end of 2021.[6] Unlike earlier studies that ascertained data regarding anemia treatment from Medicare claims, and thus were limited to the subgroup of dialysis patients with Medicare Parts A and B,[7] we ascertained data from the CROWNWeb data set. CROWNWeb is a Centers for Medicare and Medicaid Services system that includes monthly records of all patients undergoing maintenance dialysis in a Medicare-certified outpatient dialysis facility, regardless of insurance status.[8] For each calendar month from January 2016 to September 2019, we identified adult patients (age ≥18 years on the first day of the month) who underwent in-facility HD during the entire month; and to confirm the declaration of dialytic modality, whose CROWNWeb records in that month included a valid measurement of single-pool Kt/V.

Patient Characteristics

For each patient-month, we identified age (18–44, 45–64, 65–74, and ≥75 years), sex (female, male), race (White, Black, Asian, Other), Hispanic ethnicity, and rural-urban commuting area (RUCA) class (metropolitan, micropolitan, small town or rural area). Both race and Hispanic ethnicity were ascertained from form CMS-2728 (''End Stage Renal Disease Medical Evidence Report''), which is typically completed by dialysis provider staff upon initiation of maintenance dialysis. rural-urban commuting area class was derived from the ZIP code of the dialysis facility to which the patient was admitted.

Outcomes

During each patient-month, we ascertained whether an ESA was administered during HD treatments, the specific ESA (epoetin alfa, darbepoetin alfa, methoxy polyethyelene glycol [i.e., pegylated]-epoetin beta) that was administered, and the cumulative ESA dose during the month. Unlike Medicare claims, which include each ESA administration, CROWNWeb records include only the cumulative ESA dose during the month. We also ascertained the monthly measurement of hemoglobin.

To identify ESA hyporesponsiveness, we implemented 2 definitions. First, we defined hyporesponsiveness by the ERI equal to or greater than or an agent-specific threshold. The ERI was equal to the ratio of cumulative ESA dose (rescaled to a weekly basis) to body weight, subsequently divided by hemoglobin[9]; weight was set equal to the postdialysis weight included in the array of data elements used to calculate single-pool Kt/V. Agent-specific thresholds were 20 IU/wk/kg/g/dl for epoetin alfa, 0.08 mcg/wk/kg/g/dl for darbepoetin alfa, and 0.067 mcg/wk/kg/g/dl for pegylated epoetin beta.[10] Second, we defined hyporesponsiveness by a simple, clinically meaningful measure of hemoglobin less than 10 g/dl for either 3 or 6 consecutive months,[11] with the index patient-month as the final month in that series.

Finally, to contextualize ESA utilization, hemoglobin, and ESA hyporesponsiveness, we ascertained whether IV iron was administered during HD treatments, and in the case of IV iron sucrose administrations (constituting >91% of utilization during the study era), the cumulative dose during the month. We also ascertained monthly measurements of ferritin and transferrin saturation.

Statistical Analysis

We executed multiple analyses for each month in the time series from January 2016 to September 2019. First, we estimated the percentage of patients who received an ESA; the distribution of specific ESAs that were administered; and the mean, SD, and quantiles of cumulative monthly doses of epoetin alfa, darbepoetin alfa, and pegylated epoetin beta (among users of each agent). We calculated estimates among all patients and in subgroups defined by patient characteristics. In addition, to juxtapose contemporary practice with a setting in which the safety of anemia treatment was properly adjudicated among dialysis patients, we summarized ESA dosing in the 2 treatment arms of the NHCT, using data on file. Specifically, we estimated mean cumulative doses of epoetin alfa in both the low and high hemoglobin target arms of the trial, as well as mean achieved hemoglobin in those arms.

Second, we estimated distributions of hemoglobin (<9.0, 9.0–9.9, 10.0–10.9, 11.0–11.9, ≥12.0 g/dl) among all patients, in subgroups defined by patient characteristics, and in subgroups defined by concurrent use of ESAs and IV iron. Third, we estimated the prevalence of ESA hyporesponsiveness, as defined by either high ERI or consecutive months with low hemoglobin. Fourth, we estimated the percentage of patients who received IV iron and quantiles of cumulative monthly doses of iron sucrose. Fifth, we estimated distributions of ferritin (<200, 200–499, 500–799, 800–

1199, ≥1200 ng/ml) and transferrin saturation (<20, 20–29, 30–39, ≥40%). Finally, we summarized anemia-related parameters in subgroups defined by both ERI and persistence of low hemoglobin, with varying durations of time (1, 3, or 6 months).

We used SAS, version 9.4 (Cary, NC), to process USRDS data and conduct statistical analysis.

Protection of Human Subjects

USRDS data were accessed through a data use agreement with the National Institute of Diabetes and Digestive and Kidney Diseases (Bethesda, Maryland). The conduct of the study was reviewed by the Institutional Review Board of the Hennepin Healthcare Research Institute (Minneapolis, MN).

RESULTS

Between January 2016 and September 2019, the mean number of patients per month was 419,726. Among all patient-months, 11% were observed in ages 18 to 44 years, 41% in ages 45 to 64 years, 26% in ages 65 to 74 years, and 21% in ages ≥75 years. Black race, Asian race, and Hispanic ethnicity constituted 36%, 4%, and 18% of patient-months, respectively. Regarding rural-urban commuting area class, 85% of patient-months were observed in metropolitan areas, 10% in micropolitan areas, and 5% in small towns or rural areas.

On average, 76.7% of patients received an ESA during each month in the study era, with little variability among months, given a time series minimum of 74.8% and maximum of 78.5% (Figure 1). Among patient-months in 2019, ESA utilization was higher in the elderly, at 77.1% in ages 65 to 74 years and 80.1% in ages ≥75 years, compared to <74% in the non-elderly. In 2019, ESA utilization was higher among women (81.1%) than among men (72.3%). In contrast, subgroups defined by race, Hispanic ethnicity, and rural-urban commuting area class exhibited little variability. The distribution of ESAs changed between 2016 and 2019 (Figure 1). In January 2016, 54.1% of ESA users received epoetin alfa, 17.1% received darbepoetin alfa, and 29.0% received pegylated epoetin beta. By September 2019, corresponding statistics were 44.3%, 11.1%, and 44.8%. This shift in the distribution of specific ESAs occurred within all subgroups.

ESA dosing was stable during the study era. Among epoetin alfa users, the mean cumulative dose was 46,399 IU per month, or 10,671 IU per week (Figure 2a). The median cumulative dose ranged from 28,000 to 36,000 IU per month, whereas the 90th percentile cumulative dose was less than 115,000 IU per month. Among darbepoetin alfa and pegylated epoetin beta users, mean cumulative doses were 150 mcg and 152 mcg per month, respectively (Figure 2b). For both agents, 90th percentile cumulative doses were between 300 and 400 mcg per month. For all agents, ESA dosing declined with advancing age (Table 1). For example, among epoetin alfa users during 2019, the mean cumulative dose was 52,786 IU per month in ages 18 to 44 years, but only 41,028 IU per month in ages ≥75 years. Variability in ESA dosing among other subgroups was much less pronounced. Epoetin alfa dosing during the study era was slightly lower than in the low-target arm of the NHCT. In a reanalysis of trial data, with exclusion of patient-months with "zero" doses and without scaling doses

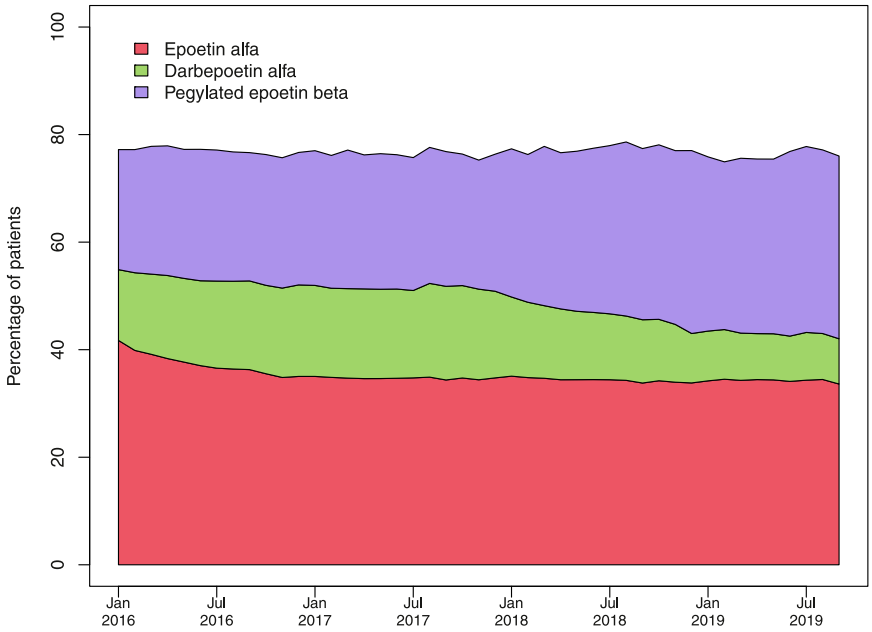

Figure 1. ESA utilization among patients undergoing in-facility hemodialysis, January 2016-September 2019.

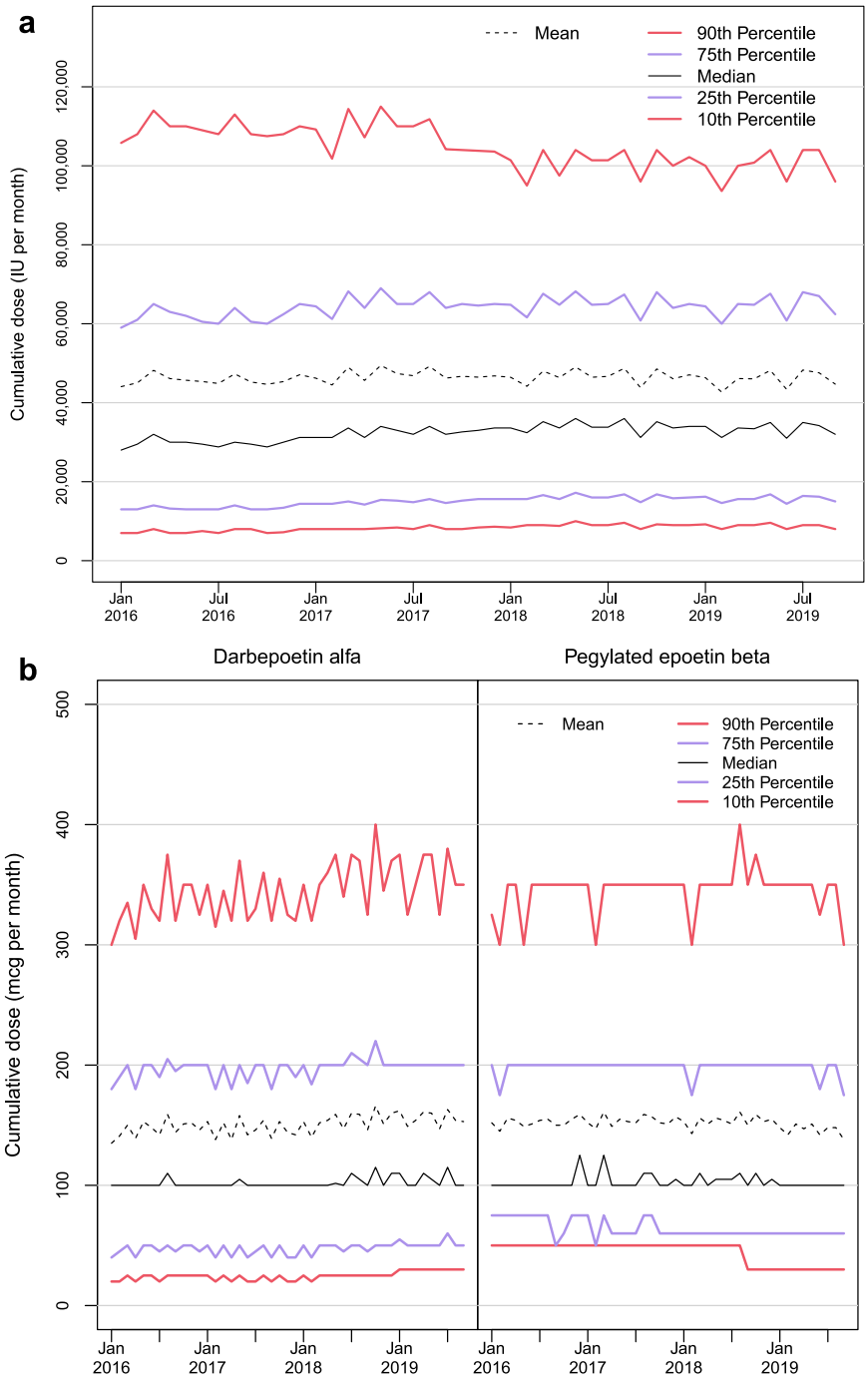

Figure 2. (a) Epoetin alfa dosing among patients undergoing in-facility hemodialysis, January 2016-September 2019. (b) Darbepoetin alfa and pegylated epoetin beta dosing among patients undergoing in-facility hemodialysis, January 2016–September 2019.

by body weight, the mean cumulative dose during follow-up was 52,466 IU per month in patients assigned to the low-target arm (13% higher than mean dosing with epoetin alfa use in contemporary practice) and 118,198 IU per month in patients assigned to the normal-target arm (155% higher). A similar pattern was evident with 90th percentile cumulative doses, which were 117,002 IU per month in the low-target arm (12% higher than 90th percentile dosing with epoetin alfa in contemporary practice) and 241,782 IU per month in the normal-target arm (131% higher).

The distribution of hemoglobin exhibited little change during the study era (Figure 3). Among patient-months in 2016, 7.1%, 15.2%, 35.1%, 28.7%, and 13.9% had hemoglobin of <9.0, 9.0 to 9.9, 10.0 to 10.9, 11.0 to 11.9, and ≥12.0 g/dl, respectively. In contrast, among patient-months in 2019, corresponding estimates were 7.7%, 15.4%, 35.8%, 27.7%, and 13.3%; an indication of a slight downward shift in the hemoglobin distribution. The percentage of patient-months with hemoglobin ≥12.0 g/dl declined with advancing age, with 15.9% among ages 18 to 44 years in 2019 and

Table 1. Erythropoiesis-stimulating agent dosing among patients undergoing in-facility hemodialysis, January 2019–September 2019

	Epoetin alfa (IU per mo)		Darbepoetin alfa (mcg per mo)		Pegylated epoetin beta (mcg per mo)	
Patient characteristic	Mean	SD	Mean	SD	Mean	SD
Overall	45,924	41,615	156	149	146	124
Age						
18–44 yrs	52,786	46,278	178	166	169	137
45–64 yrs	47,705	42,771	163	155	151	128
65–74 yrs	44,285	40,147	150	142	142	122
≥75 yrs	41,028	37,738	140	133	132	114
Sex						
Female	45,788	40,780	158	149	147	123
Male	46,036	42,288	154	149	146	126
Race						
White	44,488	40,930	153	149	144	124
Black	48,820	42,971	163	151	151	126
Asian	42,706	39,284	137	127	137	117
Other	42,917	39,271	159	152	139	120
Hispanic ethnicity						
No	47,282	42,529	162	153	148	126
Yes	41,045	37,747	132	129	137	117
RUCA class						
Metropolitan	46,016	41,613	155	148	146	124
Micropolitan	45,095	41,517	161	155	146	127
Small town or rural area	46,201	42,080	168	161	147	126

IU, international units; RUCA, rural-urban communing area.

only 9.7% among ages ≥75 years. Men were also more likely than women to exhibit hemoglobin ≥12.0 g/dl (16.0% vs. 9.7%). Subgroups defined by other patient characteristics exhibited little variability in hemoglobin distribution. However, distributions varied greatly among subgroups defined by concurrent use of ESAs and IV iron, with much higher distributions among patients who did not receive ESAs (Table 2).

Mean monthly prevalence of ESA hyporesponsiveness, as defined by elevated ERI, was 22.2% with epoetin alfa, 16.2% with darbepoetin alfa, and 19.5% with pegylated epoetin beta during the study era. The prevalence of ESA hyporesponsiveness was relatively higher with ages 18 to 44 years and Asian race, but otherwise similar among subgroups. However, the prevalence of ESA hyporesponsiveness was much lower when hyporesponsiveness was defined by consecutive months with hemoglobin <10 g/dl. In this context, the prevalence of hyporesponsiveness was 10.7% with 2 consecutive months with hemoglobin <10 g/dl, 6.0% with 3 months, 3.9% with 4 months, 2.8% with 5 months, and 2.1% with 6 months.

On average, 60.9% of patients received IV iron during each month during the study era, with some variability among months, given a time series minimum of 56.5% and maximum of 65.5%. Aside from relatively lower utilization among Asian patients at 54.6%, there was no clinically relevant variability in IV iron utilization among subgroups. Among IV iron sucrose users, mean and median cumulative doses were 183 mg and 150 mg per month, respectively. Among patient-months in 2019, 5.0%, 14.7%, 22.4%, 31.8%, and 26.1% had ferritin of <200, 200 to 499, 500 to 799, 800 to 1199, and ≥1200 ng/ml, respectively, whereas 18.7%, 35.3%, 24.8%, and 21.1% of patient-months included transferrin saturation of <20%, 20% to 29%, 30% to 39%, and ≥40%.

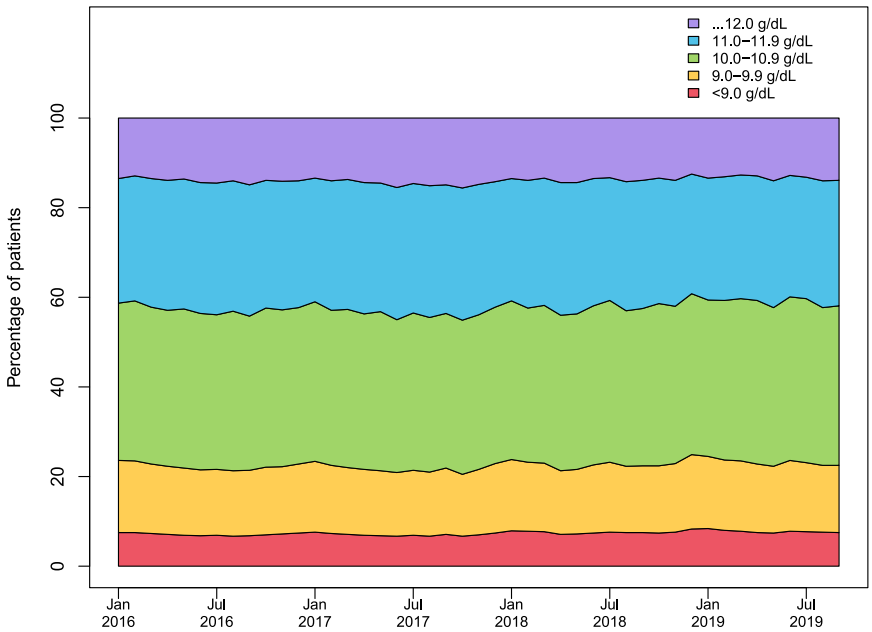

Figure 3. Distribution of hemoglobin among patients undergoing in-facility hemodialysis, January 2016–September 2019.

Table 2. Hemoglobin distribution (row percentages) among patients undergoing in-facility hemodialysis, stratified by patient characteristics, January 2019–September 2019

	Hemoglobin (g/dl)				
Patient characteristic	<9	9.0–9.9	10.0–10.9	11.0–11.9	≥12.0
Overall	7.7%	15.4%	35.8%	27.7%	13.3%
Age					
18–44 yrs	10.2%	16.3%	32.5%	25.2%	15.9%
45–64 yrs	7.8%	15.2%	34.5%	27.2%	15.3%
65–74 yrs	7.4%	15.4%	36.7%	28.3%	12.1%
≥75 yrs	6.6%	15.5%	39.0%	29.1%	9.7%
Sex					
Female	8.4%	16.9%	37.9%	27.1%	9.7%
Male	7.2%	14.3%	34.3%	28.1%	16.0%
Race					
White	7.1%	15.1%	35.9%	28.1%	13.7%
Black	9.0%	16.0%	35.3%	26.9%	12.9%
Asian	6.8%	15.9%	38.7%	28.0%	10.7%
Other	6.7%	14.4%	36.6%	27.4%	14.9%
Hispanic ethnicity					
No	8.1%	15.7%	35.7%	27.4%	13.1%
Yes	6.3%	14.5%	36.4%	28.7%	14.2%
RUCA class					
Metropolitan	7.8%	15.4%	35.8%	27.7%	13.2%
Micropolitan	7.3%	15.3%	35.8%	27.5%	14.0%
Small town or rural area	7.3%	15.5%	35.5%	27.7%	14.0%
Concurrent ESA and IV iron use					
ESA −, IV iron −	4.1%	6.0%	17.7%	28.9%	43.3%
ESA −, IV iron +	2.9%	5.7%	21.4%	37.0%	33.0%
ESA +, IV iron −	9.6%	19.6%	42.0%	24.0%	4.8%
ESA +, IV iron +	8.5%	17.5%	40.1%	27.3%	6.5%

ESA, erythropoiesis-stimulating agent; IV, intravenous; RUCA, rural-urban commuting area

Median values of anemia-related parameters during 2019, stratified jointly by ERI and persistence of low hemoglobin, are displayed in Table 3. With 1-month intervals, high ERI was evenly distributed between low and normal hemoglobin, and a larger share of patients with low hemoglobin had normal ERI. With 3-month and 6-month intervals, the prevalence of persistently low hemoglobin declined, and became increasingly represented by intervals with high ERI. With 6-month intervals, only 1.7% of intervals were characterized by both high ERI and persistently low hemoglobin; during these intervals, median hemoglobin and transferrin saturation were 8.5 g/dl and 22.3%, respectively. On the other hand, 12.1% of intervals were characterized by high ERI, but not persistently low hemoglobin; during these intervals, median ESA dose was 83,633 IU per month and median hemoglobin was 10.1 g/dl. In both sets of intervals with high ERI, the median IV iron dose was 100 mg per month.

DISCUSSION

In this study, we analyzed a nationally representative cohort of patients undergoing in-facility HD to characterize the contemporary practice of anemia treatment. We found that more than three-fourths of patients receive an ESA each month, with a steadily increasing share of users receiving pegylated epoetin beta (and decreasing shares of patients receiving epoetin alfa and darbepoetin alfa); the shift to pegylated epoetin beta reflects decisions by dialysis providers, which have aimed to reduce treatment costs. Despite flux in the distribution of specific agents that are administered, the distribution of ESA dosing has been relatively stable and, in the case of epoetin alfa, is now slightly lower than dosing in the low-target arm of the NHCT. Slightly less than two-thirds of patients in 2019 exhibited hemoglobin between 10.0 and 11.9 g/dl. Although 13.3% of patients had hemoglobin ≥12.0 g/dl in 2019, the prevalence of hemoglobin ≥12.0 g/dl was lower among ESA users, as compared with nonusers, at 4.8% among those who received only an ESA and 6.5% among those who received both an ESA and IV iron. The prevalence of

Table 3. Median anemia parameters, stratified by erythropoiesis resistance index and persistence of low hemoglobin, according to interval durations of 1, 3, and 6 months, January 2019–September 2019

	Normal ERI		High ERI	
Anemia parameter	Persistently low Hb: no	Persistently low Hb: yes	Persistently low Hb: no	Persistently low Hb: yes
1-month intervals				
Patient-mo (%)	68.7%	15.1%	8.1%	8.1%
Medications				
ESA dose (IU/mo)	18,000	26,000	94,000	99,000
IV iron dose (mg/mo)	50	50	100	100
Biochemistry				
Hemoglobin (g/dl)	11.0	9.5	10.7	9.1
Ferritin (ng/ml)	922	948	880	893
Transferrin saturation (%)	30.5	30.3	26.5	25.8
ERI (IU/wk/kg/g/dl)	4.6	8.3	27.2	32.4
3-month intervals				
Patient-months (%)	82.1%	3.1%	11.1%	3.7%
Medications				
ESA dose (IU/mo)	21,667	33,333	85,467	102,500
IV iron dose (mg/mo)	67	67	100	100
Biochemistry				
Hemoglobin (g/dl)	10.8	9.1	10.2	8.7
Ferritin (ng/ml)	929	911	873	856
Transferrin saturation (%)	30.7	28.2	25.7	23.6
ERI (IU/week/kg/g/dl)	5.9	10.7	26.6	34.3
6-month intervals				
Patient-months (%)	85.4%	0.6%	12.3%	1.7%
Medications				
ESA dose (IU/mo)	23,433	38,667	83,633	109,533
IV iron dose (mg/mo)	73	100	100	100
Biochemistry				
Hemoglobin (g/dl)	10.7	8.8	10.1	8.5
Ferritin (ng/ml)	930	803	860	822
Transferrin saturation (%)	30.7	25.0	25.2	22.3
ERI (IU/week/kg/g/dl)	6.4	12.2	26.5	37.0

ERI, erythropoietin resistance index; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous
Both ESA dose and ERI are enumerated in epoetin alfa-equivalent units, with conversion ratios of 250:1 for darbepoetin alfa and 300:1 for pegylated epoetin beta.

ESA hyporesponsiveness was sensitive to the definition of hyporesponsiveness. According to a definition that reflected ERI, prevalence exceeded 22%; however, according to an alternative definition that reflected persistently low hemoglobin, prevalence was between 2% and 6%.

Between the publication of the NHCT in 1998 and the publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy in 2009,[3,5] evidence of excess cardiovascular risk conferred by targeting normal hemoglobin concentrations in patients with chronic kidney disease and end-stage renal disease steadily accumulated. At the same time, observational studies suggested that ESA dose may be positively associated with higher risk of death,[12] although potential for confounding by indication in this research domain is substantial.[13,14] The advent of the Centers for Medicare and Medicaid Services End-Stage Renal Disease Prospective Payment System in January 2011[15] and the release of modified ESA dosing recommendations by the US Food and Drug Administration in June 2011[2] coincided with much lower ESA dosing and hemoglobin distributions among patients undergoing maintenance dialysis.[16] Although the incidence of red blood cell transfusions among dialysis patients initially increased as nephrologists and dialysis providers adjusted their approaches to anemia treatment,[17] the secular trend during the remainder of the decade has brought the incidence of transfusions to a level that is lower in 2019 than in 2009.[6] Meanwhile, the distribution of hemoglobin has essentially stabilized, with over 80% of patients having hemoglobin between 9.0 and 11.9 g/dl. As for the evolution of cardiovascular risk during the 2010s, one study reported lower than expected rates of heart failure, stroke, and venous thromboembolism during 2012, whereas another reported 5% lower adjusted risk of major adverse cardiac events in 2012 to 2016 versus 2006 to 2010.[18,19] Ultimately, the picture of anemia treatment in contemporary practice is very similar to the low-target arm of the NHCT, in which achieved hemoglobin was slightly greater than 10 g/dl and the mean cumulative dose of epoetin alfa was about 10,000 IU per week.

This study raises an important question about the prevalence of clinically relevant ESA hyporesponsiveness. There is no widely accepted definition of hyporesponsiveness,[20] despite the plethora of statistical quantities that have been proposed.[7] ERI is a popular quantity, because the ratio of cumulative ESA dose to achieve hemoglobin appears to measure the efficiency of treatment. However, ERI has limitations. First, ERI is highly correlated with ESA dose: Chait *et al*.[9] reported that 97% to 98% of variability in ERI is explained by weight-adjusted dose, illustrating the small contribution of hemoglobin to the measure.[9] Second, patients on dialysis commonly experience acute declines in hemoglobin, due to infection, hospitalization, and blood loss. These declines are likely to prompt upward titration of ESA dose, possibly satisfying epidemiologic definitions of hyporesponsiveness. As patient status improves over several months, hemoglobin increases and ESA dose decreases.[21] Accordingly, most instances of hyporesponsiveness are transient.[22]

From the perspective of the patient on dialysis, fatigue is one of the most debilitating problems.[23] Furthermore, fatigue is a "cardinal" symptom of anemia.[24] Thus, we investigated an implicit measure of ESA hyporesponsiveness, simply defined by consecutive months with hemoglobin <10 g/dl. The goal of avoiding hemoglobin <10 g/dl is not universal, but it is incorporated in clinical trials, treatment protocols,[25] and studies of ESA hyporesponsiveness.[26] The prevalence of low hemoglobin for 3 or 6 consecutive months is between 2% and 6%, again suggesting that a large share of ostensible ESA hyporesponsiveness reflects short-term complications. In the small share of patients with low hemoglobin for 6 consecutive months and concurrently high ERI, we found that transferrin saturation was low, with a median value of 22.3%, in line with an earlier study.[27] This suggests that IV iron may not be fully utilized in patients with persistently low hemoglobin. In the PIVOTAL trial, patients who were assigned to receive 400 mg of iron sucrose each month, rather than only enough iron sucrose to maintain ferritin $\geq$200 ng/ml and transferrin saturation $\geq$20%, hemoglobin increased more rapidly and cumulative ESA dose decreased. Importantly, the rate of recurrent major adverse cardiovascular events was reduced by 23%.[28] Iron dosing in the PIVOTAL trial far exceeded dosing in our study.

This study has several limitations. First, although the study era includes the most recent data that are available from the USRDS, several years (and a pandemic) have elapsed since September 2019; however, more recent CROWNWeb data have not yet been released to the research community. Further evolution of clinical practice has occurred, including growth in the utilization of iron-based phosphate binder. However, the Dialysis Outcomes and Practice Patterns Study Practice Monitor suggests that ESA utilization and the hemoglobin distribution among patients on in-facility HD have been stable. Second, we lacked data about individual ESA administrations, owing to the coarse structure of CROWNWeb data. However, the use of CROWNWeb data facilitated a true population-level view of anemia treatment, rather than a sampled view (as in the Dialysis Outcomes and Practice Patterns Study Practice Monitor) or a payer-centric view (as in USRDS analyses of Medicare claims).

In conclusion, we found that after more than a decade since the promulgation of modified dosing recommendations to improve the safe use of ESAs, the treatment of anemia in dialysis patients has shifted substantially. Prominent features of anemia treatment include ESA dosing commensurate with the lower-risk arm of the NHCT; low prevalence of not only hemoglobin greater than 12 g/dl among ESA users, but also hemoglobin persistently less than 10 g/dl; and steady progress toward lower frequency of red blood cell transfusions. ESA hyporesponsiveness, as defined by persistently low hemoglobin, may be less common than earlier studies suggested. All these observations are relevant as nephrologists and dialysis providers consider the use of novel pharmacologic therapies, including biosimilar ESAs and hypoxia-inducible factor prolyl hydroxylase inhibitors.

DISCLOSURE

EDW was an employee of the Chronic Disease Research Group at the time of study design and analysis and is currently an employee of Satellite Healthcare. WE and DTG are employees of the Chronic Disease Research Group. YH and JP are employees of Amgen and own stock.

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AUTHOR CONTRIBUTIONS

Research idea and study design was by EDW, YH, DTG, and JP. Data acquisition was by EDW and DTG; Data analysis was by EDW and WE. Data interpretation was by EDW, WE, YH, DTG, and JP. Manuscript was drafted by EDW. Review and finalization of manuscript was by EDW, WE, YH, DTG, and JP.

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