Distribution of Hemoglobin Levels Among Non-Dialysis Chronic Kidney Disease (CKD) Patients Treated with Erythropoiesis-Stimulating Agents (ESAs)

Regidor D,[1] McClellan W,[2] Sharma A,[3] Kewalramani R,[4] Bradbury B[1]

[1]Departments of Biostatistics & Epidemiology, Amgen Inc., Thousand Oaks, CA; [2]Emory School of Public Health, Emory University, Atlanta, GA; [3]Boise Kidney & Hypertension Institute, Meridian, ID;
[4]Clinical Development, Amgen, Inc., Thousand Oaks, CA

BACKGROUND

- Safety concerns raised by the CHOIR (Singh 2006[1]) and CREATE (Drueke 2006[2]) studies motivated significant regulatory and policy actions regarding the treatment of anemia with erythropoiesis stimulating agents (ESAs)
- The impact of these events on anemia management among the chronic kidney disease not receiving chronic dialysis therapy (CKD-NOD) patient population is not well understood
- Few data sources exist that capture laboratory measurements and injectable medication use among CKD-NOD patients

OBJECTIVES

- To examine trends in achieved hemoglobin levels among CKD patients receiving care in US nephrology clinics between 2005–2008, which spans the period preceding and following the major regulatory and policy changes to anemia management with ESAs

METHODS

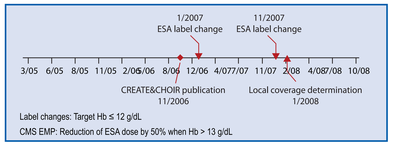
- Study design: Cross-sectional study using multiple waves of data
- Time frame: March 2005 through October 2008
- Site selection:
  - US nephrology clinics were identified from a list maintained by the American Medical Association (n~3500)
  - Study inclusion criteria:
    - Dedicated nephrology clinic
    - Treating an average of ≥ 10 CKD-NOD per week
  - Random sample of ~350 clinics were selected from pool of eligible clinics who agreed to participate
  - Approximately 4 waves were conducted in each year of the study
- Patient selection
  - Index patient was selected from computer generated random numbers or letters
    - The most recent patient record with a diagnosis of CKD (based on GFR/ICD-9) whose medical record or first three letters of his/her last name corresponded to the number or letters provided
  - Five additional patient records were identified by systematic selection:
    - Working backwards, every 10th record was evaluated for a CKD diagnosis. This process continued until 5 records were identified.
  - Diagnosis of CKD based on GFR/ICD-9
- Data collection
  - Information was abstracted from medical records by site investigators
  - Information included demographic characteristics, insurance information, laboratory data, ESA dosing

Variable definitions:

- Hemoglobin (g/dL)
  - Most recently recorded measurement as of the date of data extraction
- ESA treatment (current, former, naive)
- Patient characteristics
  - Age, gender, race (white/other), body mass index (BMI; kg/m^2), primary insurance, estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2), estimated using the MDRD equation (Levey 2000)[3], CKD stages based on K/DOQI guidelines
- Statistical analyses:
  - We characterized patient characteristics according to ESA use (current vs. naïve) stratified by study year
  - We used Mantel Haenszel chi-square analysis for categorical variables and analysis of variance (ANOVA) for continuous variables to compare patients across treatment groups
  - Trends in hemoglobin levels over time were evaluated using analysis of variance (ANOVA) with achieved hemoglobin levels as the dependent variable and calendar time (sampling wave) as the independent predictor. ~~Trends remained consistent using age and eGFR adjusted hemoglobin levels.~~

RESULTS

Sampling waves in relation to significant regulatory/policy actions



- Population characteristics (Table 1)
  - Across the four years evaluated, there were no major changes in the age, gender, race or BMI distribution of patients in either the ESA treated or the naïve patient populations. Mean eGFR levels increased slightly over the 4-year period in both ESA groups.
  - ESA trends
    - There was a decline in ESA use from 60% to 44% between 2005 and 2008 concurrent with the publication of major ESA trials in 2006(CHOIR[1], CREATE[2]) challenging high Hb targets in CKD patients
- Hemoglobin trends
  - There was an increase in the percentage of treated patients who are within the hemoglobin target range of 10–12 g/dL (59 to 66%, p-value < 0.0001) (Table 1)
  - Tracking hemoglobin trends yearly we observed differences between ESA treated and untreated patients (Figure 1) :
    - In the ESA-treated group, the mean Hb levels were fairly consistent in 2005 and 2006 at 11.3 (1.3) g/dL and 11.4 (1.3) g/dL, respectively. A downward shift was seen in 2007 [11.1 (1.2) g/dL] and continued in 2008 [10.9 (1.2) g/dL] (Figure 1a)
    - In contrast, the hemoglobin mean and standard deviation remained stable over time throughout the study period in the ESA naïve group at 12.6 (1.7) g/dL. (Figure1b)
  - Tracking hemoglobin levels by quarter over the 4-year period, we observed similar trends: (Figure 2).
    - Among untreated patients, the hemoglobin mean and standard deviation remained relatively constant throughout the four years at 12.6 (1.8) g/dL in Q1 2005 and 12.8 (1.7) g/dL in Q4 2008; p-value for trend = 0.4
    - Among ESA treated patients, the hemoglobin mean and standard deviation in Q1 2005 was 11.5 (1.3) g/dL and remained relatively constant through Q4 2006 at 11.4 (1.3) g/dL; p-value for trend = 0.6. In the second quarter of 2007, mean hemoglobin levels fell to 11.3 (1.2) g/dL , and at the end of 2008, the mean hemoglobin level was 10.8 (1.1) g/dL; p-value for trend < 0.001
  - Trends were consistent across age and race subgroups (Figure 3a & b)

Table 1. Patient Characteristics According to ESA Use By Year (2005–2008)

Patient characteristics Mean(SD) or %	2005 (n = 3424) ESA naive (N = 1240)	2005 Current ESA Use (N = 2058)	2006 (n = 3647) ESA naive (N = 1482)	2006 Current ESA Use (N = 2043)	2007 (n = 2441) ESA naive (N = 996)	2007 Current ESA Use (N = 1355)	2008 (n = 3830) ESA naive (N = 1943)	2008 Current ESA Use (N = 1689)	Difference* ESA naive (p-value)	Difference* Current ESA Use (p-value)
Age (yrs)	64.4(15.0)	69.2(13.8)	64.9(15.0)	69.1(14.2)	64.2(15.6)	69.7(13.9)	65.6(15.2)	70.1(13.9)	0.05	0.03
Female (%)	46	54	45	55	48	55	44	54	0.5	0.9
Race										
White	63	65	64	62	62	59	64	64	0.7	0.2
Other	37	35	36	38	38	41	36	36		
BMI (kg/m^2)§										
< 20	3	5	4	5	4	4	3	5	0.3	0.5
20–25	51	55	52	56	52	53	49	56		
25–35	35	31	34	30	36	34	38	29		
≥ 35	11	9	10	10	9	10	11	10		
Insurance type										
Medicare	54	68	50	63	46	60	50	60	0.04	0.006
Medicaid	8	5	12	9	11	14	10	14		
Other	38	27	38	29	42	26	40	27		
Estimated GFR†	38.4 (21.6)	25.1 (12.7)	38.6 (20.6)	25.7 (13.1)	41.7 (22.6)	26.7 (13.0)	42.6 (24.2)	26.5 (13.2)	<0.0001	0.002
CKD stage										
1/2	13	1	12	2	16	2	16	2	< 0.0001	0.04
3	48	28	49	29	52	32	54	31		
4/5	39	71	38	69	33	66	30	67		
Hemoglobin (g/dL)	12.6 (1.7)	11.3 (1.3)	12.7 (1.7)	11.4 (1.3)	12.8 (1.7)	11.1 (1.2)	12.6 (1.7)	10.9 (1.2)	0.4	<0.0001
Hemoglobin categories (g/dL)										
< 10	6	14	5	14	4	15	5	19	0.5	<0.0001
10–12	32	59	31	57	28	64	33	66		
> 12	62	27	64	29	68	21	63	16		

† based on MDRD
*Mantel-Haenszel chi-sq for categorical variables and ANOVA for continuous variables
§ Results were missing for ~26% of study population

Figure 1a: Distribution of Hemoglobin in ESA–Exposed Patients 2005–2008

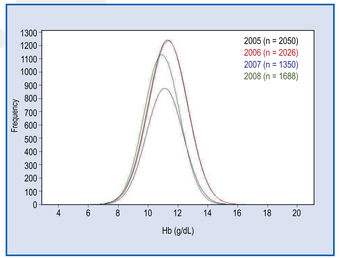


Figure 1b: Distribution of Hemoglobin in ESA–naïve Patients 2005–2008

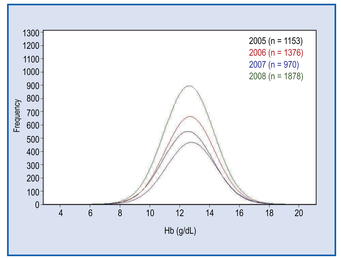
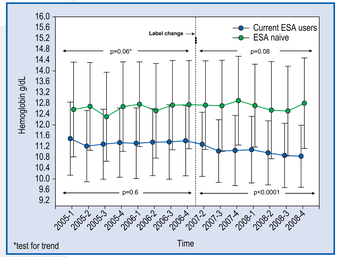


Figure 2: Mean(SD) Hemoglobin By ESA



*test for trend

Figure 3a: Mean(SD) Hemoglobin By Age — Current ESA Users

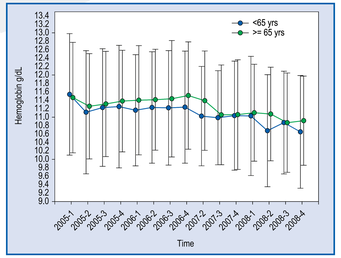
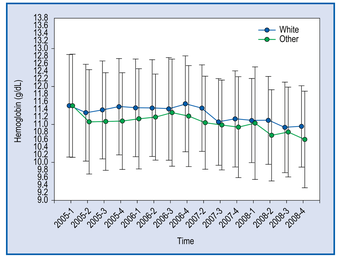


Figure 3b: Mean(SD) Hemoglobin By Race — Current ESA Users



DISCUSSION

- We studied 13,342 CKD-NOD patients receiving care in US nephrology clinics over the period March 2005 to October 2008. This period covers the two modifications to the Epoetin alfa and Darbepoetin alfa product labeling (January 2007, November 2007) and the revision to local coverage determination (LCD) which occurred in January 2008.
- Prior to the first change to the ESA label which occurred in January 2007, mean Hb levels among ESA-treated patients were 11.3 g/dL; subsequent to change, Hb levels fell to 11.1 g/dL. Following the LCD revisions, which restricted reimbursement for Hb levels above 12 g/dL, Hb levels fell further to 10.9 g/dL
- These trends in achieved Hb levels were consistent among patients over 65 years of age (Medicare eligible) and those younger than 65 (private payer), and for different race groups

LIMITATIONS

- 18% to 34% of eligible facilities at each cross-sectional wave declined participation; facilities who agreed to participate may have anemia management practices not representative of nephrology clinics across the US. Therefore, observed trends may not be generalizable to all CKD patients not on dialysis.

CONCLUSIONS

- The results from this analysis suggest that physicians have responded appropriately to recent regulatory and policy changes regarding anemia management with ESA .

REFERENCES

1. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006; 355(20):2071-2084.
2. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006; 355(20):2085-2098.
3. Levey AS, Greene T, Kusek J, and Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). J Am Soc Nephrol. 2000; 11:p.155A.

National Kidney Foundation, Nashville, TN; March 25–29, 2009