# Dose Conversion Relationship Between Epoetin alfa (EPO) and Darbepoetin alfa in Hospital-Based Dialysis Centers (HBDCs)

Amit Sharma MD, FACP, FASN;[1] Jerry Yee, MD;[2] Irfan Khan, PhD;[3] Jeffrey Petersen, MD;[3] Shravanthi R Gandra, PhD, MBA[3]

[1]Boise Kidney and Hypertension Institute, Meridian, ID; [2]Henry Ford Hospital, Detroit, MI; [3]Amgen Inc., Thousand Oaks, CA

## BACKGROUND

- Epoetin alfa (EPO) and darbepoetin alfa are erythropoiesis-stimulating agents (ESA) that are used to treat anemia in patients with chronic kidney disease (CKD).
- Clinical trial data from a registrational, multicenter, randomized, double-blind, noninferiority study in hemodialysis patients demonstrated that the dose conversion relationship between epoetin alfa and darbepoetin alfa is nonproportional across the dosing spectrum;[1-3] comparatively lower darbepoetin alfa doses are needed at higher epoetin alfa doses.
- At the population level, converting patients from EPO to darbepoetin alfa within a health system has economic implications and can be evaluated by assessing the dose relationship between the two ESAs.
- Previous reports comparing the dose relationship between EPO and darbepoetin alfa (reported as dose ratios [DR]) at the population level have significant methodological limitations:[3-10]
  - Used cross-sectional designs:
    - Do not represent the same patients who underwent conversion from one ESA to the other.
    - Compare mean doses for patient groups using each ESA.
    - Were therefore vulnerable to confounding.
  - Do not adjust for the nonproportional dose relationship between the two ESAs.
  - DRs reported in the literature range from 217:1 to 287:1 EPO (Units [U]):darbepoetin alfa (micrograms [µg]).
- Accurate methods that use appropriate populations and take into account the non-proportional dose relationship between EPO and darbepoetin alfa to estimate the dose conversion ratio (DCR) between the two ESAs in a real-world setting are important but lacking.

## OBJECTIVES

- The objective of this study is to:
  - Describe two methods for calculating the DCR between EPO and darbepoetin alfa
  - Report a population mean DCR value for a chronic hemodialysis (HD) patient population converted from EPO to darbepoetin alfa treatment

## METHODS

### Data Source

- Twenty-five hospital-based dialysis centers (HBDCs) that converted their patient population from EPO to darbepoetin alfa during the study time frame of January 1, 2004 to December 31, 2005.

### Analysis Dataset

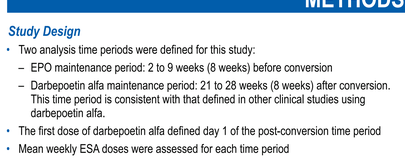
- Retrospective chart reviews of chronic dialysis patients being treated at the 25 HBDCs were conducted; after application of eligibility criteria, patient data were used from 23 HBDCs
  - Retrospective chart reviews were performed in fourth quarter of 2006
  - Longitudinal data from chart reviews were collected for approximately 26 randomly sampled patients from each of the 23 HBDCs. Data collected were:
    - Gender
    - Age
    - Dates of all dialysis sessions during the study time frame
    - Administered EPO or darbepoetin alfa dose for each dialysis session, including identifier for any dose withheld for clinical reasons
    - Hemoglobin (Hb) records by date

## METHODS (Continued)

### Study Design

- Two analysis time periods were defined for this study:
  - EPO maintenance period: 2 to 9 weeks (8 weeks) before conversion
  - Darbepoetin alfa maintenance period: 21 to 28 weeks (8 weeks) after conversion. This time period is consistent with that defined in other clinical studies using darbepoetin alfa.
- The first dose of darbepoetin alfa defined day 1 of the post-conversion time period
- Mean weekly ESA doses were assessed for each time period
  - EPO dose: the average of all weekly EPO doses over the EPO maintenance period
  - Darbepoetin alfa dose: average of all weekly darbepoetin alfa doses over the darbepoetin alfa maintenance period

### Figure 1. Patient Selection




### Primary Analysis Endpoint

- The primary analysis endpoint was to calculate a population mean maintenance DCR for chronic HD patients who converted from EPO to darbepoetin alfa treatment and were subsequently maintained on darbepoetin alfa.

### Statistical Analysis

- Descriptive statistics were used for continuous (mean, median, standard deviation [SD], 95% confidence interval [CI], and interquartile range [Q1, Q3]) and categorical (count and percent) variables.
- We determined the DCR using two specific methods.
  - ***Regression-based method***
    - Methodology consistent with the one previously submitted to Centers for Medicaid & Medicare Services (CMS), and used by CMS during their 2003 and 2004 deliberations of the DCR reimbursement policy for darbepoetin alfa.[11]
    - Includes ordinary least squares regression analysis.
    - Ln-transformed darbepoetin alfa dose over the darbepoetin alfa maintenance period was regressed on the Ln-transformed EPO dose over the EPO maintenance period.
    - The regression line can be represented by the equation:

$$D = \beta(E) + \alpha$$

D = predicted Ln-transformed darbepoetin alfa dose derived from E
E = Ln-transformed EPO dose
α = y-intercept
β = slope of regression line

  - ***Ratio-based method***
    - Consists of an arithmetic mean approach. Calculated as follows:

*DCR per patient =*

$$\frac{\text{Patient's mean weekly EPO dose}}{\text{Patient's mean weekly darbepoetin alfa dose}}$$

$$\text{Mean population level DCR} = \frac{\sum \text{(DCR per patient)}}{n}$$

n = total number of patients in the analysis

### Sensitivity Analysis

- Sensitivity analyses using both methods were conducted for patients whose mean Hb levels remained within ± 0.5 g/dL or within ± 0.8 g/dL between the EPO and darbepoetin alfa maintenance periods
- All outlier data (extreme values in doses) were included in the analysis

### DR Estimation Using Previously Published Methodology[7]

- Finally, we used a method similar to one previously reported[7] to estimate the DCR for the population. This method uses cumulative EPO and darbepoetin alfa doses for all patients as follows:

$$\text{Mean population level DCR} = \frac{\text{Cumulative EPO dose for all patients over the EPO maintenance period}}{\text{Cumulative darbepoetin alfa dose for all patients over the darbepoetin alfa maintenance period}}$$

## RESULTS

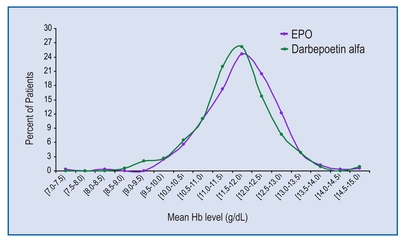
### Table 1. Patient Demographics, Hb Levels, and ESA Doses Over the Respective Maintenance Periods

| | Total (N = 337) |
|---|---|
| Sex, n (%) | |
| Male | 179 (53%) |
| Female | 158 (47%) |
| Age Groups, % | |
| 19 to 34 years | 5.9% |
| 35 to 49 years | 13.9% |
| 50 to 64 years | 26.1% |
| 65 to 89 years | 51.9% |
| ≥ 90 years | 2.1% |
| Hb level over the EPO maintenance period, g/dL | |
| Mean (SD) | 11.7 (0.9) |
| Median (Q1, Q3) | 11.8 (11.2, 12.2) |
| Hb level over the darbepoetin alfa maintenance period, g/dL | |
| Mean (SD) | 11.6 (0.9) |
| Median (Q1, Q3) | 11.6 (11.1, 12.1) |
| Maintenance EPO dose, U/week | |
| Mean (95% CI) | 18157 (16093, 20220) |
| Median (Q1, Q3) | 12125 (7088, 20875) |
| Maintenance darbepoetin alfa dose, µg/week | |
| Mean (95% CI) | 62.5 (56.3, 68.7) |
| Median (Q1, Q3) | 40 (25, 80) |

## RESULTS (Continued)

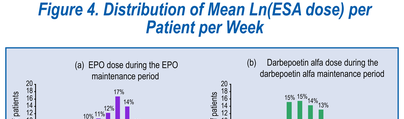
### Figure 2. Distribution of Mean Hemoglobin Levels During the Respective Maintenance Periods

### Figure 3. Mean Dose Per Week During the (a) EPO and (b) Darbepoetin alfa Maintenance Periods




### Figure 4. Distribution of Mean Ln(ESA dose) per Patient per Week

### Figure 5. Regression Analysis of Ln-Transformed EPO and Darbepoetin alfa Doses




### Table 2. DCR Results in the Primary and Sensitivity Analysis

| | DCR (EPO dose per 1 µg darbepoetin alfa) | |
|---|---|---|
| | Regression-based method | Ratio-based method |
| Overall | | |
| N | 337 | 337 |
| DCR (95% CI) | 320 (298, 344) | 350 (319, 381) |
| Patients with Hb within ± 0.5 g/dL[a] | | |
| N | 122 | 122 |
| DCR (95% CI) | 313 (282, 348) | 330 (289, 375) |
| Patients with Hb within ± 0.8 g/dL[a] | | |
| N | 179 | 179 |
| DCR (95% CI) | 311 (283, 342) | 333 (294, 372) |

[a]Hb comparison between the darbepoetin alfa and EPO maintenance periods

### DR Estimation Using Previously Published Methodology[7]

$$\frac{\text{Mean maintenance EPO dose}}{\text{Mean maintenance darbepoetin alfa dose}} = \frac{18157}{62.5}$$

DR (95% CI) = 290 (286, 294)

## DISCUSSION

- DCRs (95% CI) of 320 (298, 344) and 350 (319, 381) were calculated using the two empirical methods described in this analysis (regression-based method and the ratio-based method, respectively). Both DCRs are greater than the DCR obtained using previously described methodology (DCR [95% CI]: 290 [286, 294]).
- Most of previous publications[3-10] compared 2 nonmatched cohorts, with each cohort receiving only 1 of the products, instead of directly studying the effect of converting from one product to the other. Important unaddressed factors in these analyses include dosing frequency, the stage of treatment (i.e., whether at initiation or during maintenance), patient age, and Hb outcomes. Additionally, none of these studies considered the nonproportional relationship between EPO and darbepoetin alfa. As shown, a similar analysis applied to our data results in a lower DR for the study sample used in this analysis, even though our study included patients converted from EPO to darbepoetin alfa.
- The two methods described in this analysis address the non-proportional dose relationship between EPO and darbepoetin alfa.
- Additionally, both mathematical approaches are robust:
  - The regression-based method allows one to mathematically linearize the non-proportional dose relationship between EPO and darbepoetin alfa.
  - The ratio-based method allows the inclusion of outlier doses.
- Given the need to balance rigor with the applicability of a methodology, the ratio-based method may be a more practical approach of implementing and assessing the economic value of converting a HBDC patient population.
- Providers can easily utilize these methods to assess the economic implications for converting a dialysis patient population in a HBDC:
  - For a dialysis patient population that has already been converted, the DCR described here allows for comparison of dose requirements.
  - For a dialysis patient population that has not been converted, a DCR above 300:1 could be expected.

### Limitations

- Only HBDCs represented in this study.
- A large number of HBDCs declined to participate because of insufficient time and resources to complete study requirements. This may have resulted in selection bias.
- Other patient-related factors that could influence ESA dosing were not collected for the two maintenance periods. However, patient demographics were the same at both time points, and Hb outcomes were not clinically different with the use of either ESA.

## CONCLUSIONS

- The two methods for DCR estimation presented here recognize the nonproportional dose relationship between the EPO and darbepoetin alfa, and provide payers with an empirical way of comparing ESA utilization for pharmacoeconomic evaluation. Unlike previous cross-sectional comparisons, the present study employed methods in which each patient served as his/her own control.
- Among HD patients converted from EPO to darbepoetin alfa and titrated to achieve comparable Hb outcomes in this real world hospital setting, the estimated sample mean maintenance DCR was 320 U EPO:1 µg darbepoetin alfa using regression analysis of log-transformed doses, and 350 U:1 µg when individual patients' DCRs were averaged

## REFERENCES

1. Nissenson AR. Dosing darbepoetin alfa. *Am J Kidney Dis.* 2002;40(4):872.
2. United States Aranesp® (darbepoetin alfa) prescribing information. Amgen Inc., Thousand Oaks, CA, USA
3. Nissenson AR, Swan SK, Lindberg JS, *et al.* Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis.* 2002;40(1):110-18
4. Cremieux PY, *et al. Curr Med Res Opin.* 2006;22(12):2329-2336.
5. Duh MS, *et al. Drugs Aging.* 2006;23(12):969-976.
6. Duh MS, *et al. Clin Ther.* 2006;28(9):1443-1460.
7. Hymes J, *et al. Curr Med Res Opin.* 2007;23(8):1931-1937.
8. Papatheofanis F, et al. *Am J Ther.* 2007;14(4):322-327.
9. Papatheofanis FJ, *et al. Curr Med Res Opin.* 2006;22(3):837-842.
10. Vekeman F, et al. *Am J Health Syst Pharm.* 2007;64(18):1943-1949.
11. *CMS. Federal Register* 2004;69:65796-65797.

### Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
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