**Dose–Conversion Ratio for Epoetin Alfa and Darbepoetin Alfa in Chemotherapy Patients with Anemia and Cancer**

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**ABSTRACT**

**Objective:** We sought to quantify the dose–conversion ratio (DCR) between epoetin alfa (EPO) and darbepoetin alfa (DARB), based on a randomized, prospective clinical trial. This study was designed to compare the effectiveness of EPO at a starting dose of 40,000 units once weekly versus DARB at a starting dose of 200 mcg every two weeks in patients with chemotherapy-induced anemia.

**Methods:** This retrospective secondary analysis used data from an open-label, randomized, multicenter, head-to-head trial comparing EPO with DARB in patients 18 years of age or older with anemia and a solid tumor who were undergoing chemotherapy. Patients received subcutaneous injections of either EPO 40,000 units once weekly or DARB 200 mcg every two weeks for up to 16 weeks. Cyclic chemotherapy was scheduled for a minimum of 12 weeks.

The DCR was defined as relative doses between EPO and DARB needed to achieve equivalent effectiveness of treatment. Both cumulative and average weekly doses were used in the dose calculation. The effectiveness measure was the area-under-the-hemoglobin-change curve over the 16-week treatment (Hb AUC16), calculated according to patients' weekly and monthly Hb change values, respectively. We chose the cumulative dose and the weekly Hb AUC16 as the base case scenario, and we conducted sensitivity analyses using the average weekly doses and monthly Hb AUC16. We used the Delta method and the nonparametric bootstrap procedure to determine the 95% confidence interval (CI) around the DCR point estimate.

**Results:** A total of 346 patients (172 receiving EPO, 174 receiving DARB), formed the study population. There were no significant differences between these groups with respect to sex, race, age, body mass index, or baseline Hb level. The base case scenario corresponded to a DCR of 199:1 (range, 190:1–207:1) in sensitivity analyses. The 95% CIs derived from each method were comparable. The upper boundary of the DCR confidence limits was systematically lower than 300:1.

**Conclusion:** This study indicated a DCR of 199:1 between EPO and DARB; 199 units of EPO achieved a level of hemato-logical effectiveness equivalent to 1 mcg of DARB, as measured by Hb AUC16. The DCR 95% CI observed in our analysis (range, 113:1–303:1) was lower than the 330:1 DCR adopted by the Center for Medicare & Medicaid Services in 2004 and 2005.

**Key words:** Epoetin alfa, darbepoetin alfa, chemotherapy-induced anemia, dose conversion ratio, area under the curve

**INTRODUCTION**

Anemia is a common complication of myelosuppressive chemotherapies in patients with cancer.1 When untreated, chemotherapy-induced anemia (CIA) may adversely affect the patient's quality of life and ability to function because of symptoms such as fatigue, weakness, shortness of breath, and impaired mental function.2-4

Red blood cell (RBC) transfusions can be used to correct anemia, but they are also associated with serious complications and risks.5-7 In April 1993, epoetin alfa (EPO) first entered the U.S. market as the only biopharmaceutical product approved by the Food and Drug Administration (FDA) for the treatment of CIA. EPO is biologically indistinguishable from endogenous erythropoietin.

In July 2002, the FDA approved darbepoetin alfa (DARB), a hyperglycosylated analogue of recombinant human erythropoietin, for patients with CIA. Both agents share a similar mechanism of action by binding to the erythropoietin receptor on erythroid progenitors to stimulate erythropoiesis, thereby increasing RBC production and hemoglobin (Hb) levels.8-16

Hb levels indicate the severity of anemia, and they are used, along with additional patient-specific characteristics, in decision-making regarding transfusions.17

Based on the FDA-approved CIA indication, the recommended starting dose for EPO is 40,000 units once weekly or 150 units/kg three times per week; the starting dose for DARB is 2.25 mcg/kg once per week or 500 mcg every three weeks. However, several studies suggest that DARB 200 mcg once every two weeks is the most commonly prescribed initial regimen.18,19

When substituting one of these erythropoietic agents for the other in patients with CIA, we must determine the DARB dosage needed to achieve a level of effectiveness equivalent to that of EPO (i.e., the ratio of units of EPO to micrograms of DARB).

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This is generally known as the dose–conversion ratio (DCR). Determining the DCR is important not only from the perspective of patient care; it is also crucial for developing an accurate comparison of treatment cost and for efficiently allocating limited resources in the health care system.

Thus far, DCRs have varied considerably, depending on the source. The variations stem mainly from the differences in the effectiveness measure used to quantify equivalency between the two agents.

A DCR of 200 units of EPO to 1 mcg of DARB was suggested, based on the ratio of the protein mass of the two molecules as well as on a phase 3 double-blind, placebo-controlled, randomized registration trial of DARB conducted by Vansteenkiste and colleagues. Using results by Glaspy et al., who had conducted a phase 1/2 dose-finding study involving 429 patients, Scott reported a DCR of 300:1 and 380:1, respectively, by using the change in Hb from the baseline to the end of the study and the proportion of patients achieving a hematopoietic response during the study as the respective effectiveness measure.

In a meta-analysis of published prospective clinical trials of EPO or DARB for the treatment of CIA, Rosberg et al. observed that the estimated DCRs ranged from 126:1 to 139:1 for three-times-weekly EPO and from 187:1 to 191:1 for once-weekly EPO, compared with once-weekly and twice-weekly DARB. The authors used the normalized area-under-the-hemoglobin curve (Hb AUC) as a measure of treatment effectiveness. The equi-table payment ratios (units of EPO to micrograms of DARB), adopted by the Centers for Medicare & Medicaid Services (CMS) for reimbursement purposes were 260:1 in 2003 and 260:1 in 2004–2005.

Because the definition of treatment effectiveness has a direct impact on DCR calculation, it is essential that the most informative measure be used. One of the authors of this article (Duh et al.) found Hb AUC to be an objective, clinically meaningful, comprehensive summary statistic to quantify the clinical benefits of erythropoietic agents. Hb AUC has an important advantage of accounting for the complete hematological profile over the entire course of treatment rather than at an arbitrary discrete time point, as with the hematopoietic response measure.

None of the DCRs reported to date have been based on randomized, head-to-head studies directly comparing EPO and DARB. Because the previous research used data from different source populations using EPO or DARB, the DCR could not be inferred conclusively.

The objective of our analysis was to calculate the DCR between EPO and DARB using Hb AUC as the effectiveness measure based on the first head-to-head clinical trial that was designed and powered to compare the effectiveness of the two agents in patients with CIA. EPO was initiated at 40,000 units once weekly, and DARB was initiated at 200 mcg every two weeks.

**METHODS**

**Study Population**

This secondary retrospective analysis used data from an open-label, randomized, multicenter, head-to-head trial comparing EPO and DARB. To be included in the trial, patients had to be 18 years of age or older and had to meet the following criteria:

- histologically confirmed solid malignancy
- baseline hemoglobin level of 11 g/dl or lower
- cyclic chemotherapy scheduled for a minimum of 12 weeks
- informed consent obtained
- fewer than two prior chemotherapy regimens received for metastasis
- adequate hematological, renal, and hepatic function
- life expectancy of more than six months
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

Patients were excluded from the study for any of the following reasons:

- receipt of a transfusion within 28 days before randomization
- receipt of erythropoietic agents within the previous three months
- history of stem cell or bone marrow transplantation
- radiation treatment
- anemia that was unrelated to chemotherapy

Randomization was stratified according to the study site and the type of chemotherapy (i.e., platinum-based or non–platinum-based) (Table 1). The full details of the study design are published in their entirety elsewhere.

**Dose Adjustments**

Subjects were assigned to receive subcutaneous injections of either EPO or DARB for up to 16 weeks. The EPO doses were initiated at 40,000 units once weekly, with a potential dose escalation to 60,000 units once weekly if the increase in Hb was less than 1 g/dl after four weeks of treatment. DARB was started at 200 mcg every two weeks, with a potential for the dose to increase to 300 mcg every two weeks if the increase in Hb was less than 1 g/dl after six weeks of therapy.
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Dose adjustments for non-responders were based on recommendations of the National Comprehensive Cancer Network (NCCN)\textsuperscript{30} and the American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) treatment guidelines.\textsuperscript{31} If Hb values rose to more than 13 g/dl, the study drugs were withheld until the Hb fell below 12 g/dl; therapy was then resumed with the dose reduced by 25%.

Investigators were also instructed to make a similar dose reduction if a rapid Hb response occurred—an increase of more than 1.3 g/dl in a two-week period with EPO and less than a 1-g/dl increase in a two-week period with DARB—whether or not patients received RBC transfusions.

**Calculating the Dose–Conversion Ratio Point Estimate**

The DCR, defined as relative doses between EPO and DARB needed to achieve equivalent treatment effectiveness, was formulated as follows:

\[
\text{DCR} = \frac{\text{EPO Dose}}{\text{Hb AUC of EPO}} : \frac{\text{DARB Dose}}{\text{Hb AUC of DARB}}
\]

We used two alternative measures for EPO and DARB doses:

- the cumulative dose (the total amount of study drug received over the 16 weeks of the study)
- the average weekly dose (the cumulative dose divided by the number of weeks of treatment)

The effectiveness measure employed was the area-under-the-hemoglobin-change curve from the baseline value to week 16 of treatment (Hb AUC\textsubscript{16}).

Figure 1 illustrates a simplified version of the Hb AUC calculation assuming monthly Hb change data. In this analysis, Hb AUC\textsubscript{16} was derived via the trapezoidal rule, which summed up the area under the Hb change curve using patient-level Hb readings collected at weekly intervals:

\[
\text{Hb AUC}_{16} = \sum_{i=4}^{16} \Delta Hb_i + \frac{\Delta Hb_{16}}{2},
\]

where \(\Delta Hb_i = Hb_i - Hb_{i-1}\).

In a further sensitivity analysis, Hb AUC\textsubscript{16} was calculated according to monthly Hb measurements. We selected this range for sensitivity testing, because many published clinical studies indicated that the Hb readings were determined or reported only monthly.

The cumulative dose and weekly Hb AUC\textsubscript{16} were chosen as the base case scenario. The cumulative dose corresponded to the overall drug utilization and was more relevant to payers, who are concerned with cost and effectiveness throughout a treatment episode. We chose weekly Hb AUC\textsubscript{16} because weekly Hb change data were more precise than monthly Hb change data.

In calculating Hb AUC\textsubscript{16}, we considered all Hb measurements recorded within 28 days of a RBC transfusion to be missing in order to avoid the confounding effect of transfusions. We used the last-value-carried-forward principle to impute missing Hb values.

The DCR is a more comprehensive metric than the dose ratio, which does not take treatment effectiveness into account. Furthermore, both the numerator (cumulative dose) and the denominator (Hb AUC) used for the DCR calculation were comprehensive measures that reflect patients’ dose and Hb outcomes over the whole treatment course instead of at discrete time points.

**Calculating Variability in the Dose–Conversion Ratio**

To evaluate sensitivity, we used two different statistical approaches to determine the 95% CI around the DCR point estimate.

Initially proposed by O’Brien et al.,\textsuperscript{32} the Delta method was developed to estimate the standard error around a ratio of two random variables. We used this approach to calculate the standard error around the DCR. Confidence limits were then obtained as the DCR value ± 1.96 times the estimated standard errors.

We also used a nonparametric bootstrapping procedure to resample patients from the study population and to calculate the DCRs in each of the multiple samples.\textsuperscript{32,33} Thus, we estimated the empirical distribution of the data without imposing any probability density function. The following algorithm was used:

- A sample of \(n\) patients is drawn, with replacement from the study population; the DCR is then calculated on the basis of this sample. In our case, we drew a total of 172 EPO patients and 174 DARB patients (i.e., sample sizes from the efficacy populations).
- The sampling (the first step) is repeated, and the DCR is calculated \(N\) times. In our case, we used 500 replications

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to determine the 95% CI around the point estimate.
• The DCRs are ordered from the lowest to the highest observed values.
• The 95% CI is identified according to the 2.5 and 97.5 percentiles of the ranked values.

RESULTS
Study Population
Of the 358 subjects enrolled in the trial, 352 received at least one dose of study drug and had at least one post-baseline Hb reading or transfusion; these patients formed the modified intent-to-treat (mITT) population. For our analysis, six subjects (three receiving EPO and three receiving DAR) were further excluded because they lacked any post-baseline Hb readings independent of RBC transfusions in the previous 28 days.

Figure 2 presents the patient disposition flow chart. A total of 346 patients, 172 assigned to receive EPO and 174 assigned to receive DAR, formed our study population.

Baseline Characteristics
The baseline characteristics of patients in both treatment groups are summarized in Table 1. There were no significant differences between the EPO and DAR patients with respect to sex, age, or baseline Hb level.

Dose–Conversion Ratio and 95% Confidence Intervals
Doses and Hb AUC16 values that were used to calculate the DCR between EPO and DAR are presented in Table 2. The average cumulative doses over 16 weeks of treatment were 427,497 ± 235,670 units of EPO and 1,193 ± 593 mcg of DAR. Average weekly doses were 38,213 units of EPO and 103 mcg of DAR.

Hb AUC16 calculations, based on weekly and monthly Hb change values, yielded similar values. Hb AUC16 was statistically significantly higher with EPO patients than with DAR patients:
• weekly Hb AUC16: EPO, 14.2 g/dl; DAR: 7.9 g/dl (P = .001)
• monthly Hb AUC16: EPO, 14.4 g/dl; DAR, 7.7 g/dl (P < .001)

Table 3 shows the DCRs of EPO to DAR using the doses and Hb AUC16 values as calculated in different scenarios. The DCRs were similar (range, 190:1–207:1). The base case scenario corresponded to a DCR of 199:1. The estimated 95% CI around the DCR calculated with the Delta and bootstrap methods are also presented in Table 3. The 95% CIs derived from these two methods were comparable, with the upper boundary of the DCR confidence limits systematically lower than 300:1.

DISCUSSION
This secondary analysis of patients is from the first randomized head-to-head clinical trial that was designed and powered to evaluate the efficacy of EPO 40,000 units once weekly versus DAR 200 mcg every two weeks. The DCR point estimate was 199:1 in the base case scenario, with a tight range of 190:1 to 207:1, depending on the dosages and Hb AUC16 values used to conduct the analysis.

The 95% CI revealed that the upper boundary of the confidence limits was systematically lower than or about 300:1. These results suggest a lower DCR estimate than the 330:1 ratio adopted by the CMS in 2004 and 2005.

The DCR of 199:1 obtained in this study, based on cumulative doses and weekly Hb AUC16, was similar to that obtained by Rosenberg et al.23 and was substantially lower than that reported by Scott.22 This difference could have been a result of the use of a

<table>
<thead>
<tr>
<th>Enrolled patients (N = 358)</th>
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<tr>
<td>Epoetin alfa (N = 178)</td>
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<tr>
<td>Darbepoetin alfa (N = 180)</td>
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| Had at least one dose of study drug and at least one post-baseline Hb reading or transfusion (mITT population) (N = 175) |
| Had at least one dose of study drug and at least one post-baseline Hb reading or transfusion (mITT population) (N = 177) |

| Had at least one post-baseline Hb reading independent of transfusion (N = 172) |
| Had at least one post-baseline Hb reading independent of transfusion (N = 174) |

FIGURE 2 Patient disposition. Hb = hemoglobin; mITT = modified intent-to-treat.

Table 2 Epoetin alfa and Darbepoetin alfa Doses and Area-under-the-Hemoglobin-Change Curve over 16 Weeks (Hb AUC16)

<table>
<thead>
<tr>
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<th>EPO (N = 172)</th>
<th>DAR (N = 174)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Average cumulative dose, mean ± SD</td>
<td>427,497 ± 235,670 units</td>
<td>1,193 ± 593 mcg</td>
<td>N/A</td>
</tr>
<tr>
<td>Average weekly dose, mean ± SD</td>
<td>38,213 ± 11,006 units</td>
<td>103 ± 18 mcg</td>
<td>N/A</td>
</tr>
<tr>
<td>Weekly Hb AUC16 g/dl (SD)</td>
<td>14.2 (16.4)</td>
<td>7.9 (18.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Monthly Hb AUC16 g/dl (SD)</td>
<td>14.4 (16.2)</td>
<td>7.7 (18.0)</td>
<td>&lt; .001</td>
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DARB = darbepoetin alfa; EPO = epoetin alfa; SD = standard deviation.
**Dose–Conversion Ratio for Epoetin alfa and Darbepoetin**

<table>
<thead>
<tr>
<th>Table 3 Dose–Conversion Ratio (DCR) and 95% Confidence Interval</th>
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<tr>
<td><strong>Method</strong> Method</td>
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<tr>
<td>Avg. cumulative dose, weekly Hb AUC&lt;sub&gt;16&lt;/sub&gt;</td>
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<tr>
<td>Avg. cumulative dose, monthly Hb AUC&lt;sub&gt;16&lt;/sub&gt;</td>
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<td>Avg. weekly dose, weekly Hb AUC&lt;sub&gt;16&lt;/sub&gt;</td>
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<td>Avg. weekly dose, monthly Hb AUC&lt;sub&gt;16&lt;/sub&gt;</td>
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Avg. = average; Hb AUC<sub>16</sub> = area-under-the-hemoglobin-change curve over 16 weeks of treatment.

common effectiveness measure (Hb AUC) used in the Rosberg study and in this research. The choice of the effectiveness measure appeared to be a determinant in calculating the DCR.

In our analysis, we chose Hb AUC to represent the efficacy measure because it provides a more comprehensive illustration of the hematological profile, compared with existing Hb measures that assess Hb effects at discrete time points, such as the hematopoietic response rate and the Hb change at week 16.

Duh et al. considered Hb AUC to be statistically superior to the hematopoietic response rate. Hence, it was appropriate that Hb AUC was used to normalize the DCR between EPO and DARB.

Our sensitivity analyses demonstrated that the use of an alternative monthly measure of Hb AUC did not have a strong impact on the resulting DCRs. This finding was consistent with Duh’s results, which demonstrated the reliability of Hb AUC by comparing its values derived from primary patient data versus aggregate data and by assessing the impact of the frequency of Hb readings on Hb AUC values.

Our study supported the 199:1 DCR (the ratio of EPO units to DARB micrograms) between EPO and DARB. This ratio was more favorable for EPO in terms of cost-effectiveness than the assumption of 330:1 by the CMS in 2004. This finding of a 199:1 DCR conformed to the preclinical evidence based on the protein mass of the two molecules as well as a phase 3, randomized study by Vansteenkiste et al. Moreover, the 200:1 DCR continues to be used to switch patients from EPO to DARB and to evaluate the effectiveness of DARB in correcting anemia in other countries. This ratio has also been used to establish government reimbursement levels in Europe, Canada, and Australia.

In the U.S., the CMS adopted a higher conversion ratio, possibly resulting from a lack of published, comparative clinical trial data at the time of policy development. An evidence-based evaluation of the DCR is critical to the appropriate allocation of health care resources.

**STUDY LIMITATIONS**

Our assessment had potential limitations; it was a post hoc analysis of a randomized head-to-head study in which the doses and frequency of EPO and DARB administrations that were stipulated in the clinical trial protocol might not reflect actual drug utilization in clinical practice.

In addition, the DCR equation assumes a linear relationship between the cumulative dose and Hb AUC. Although this statistical assumption has not been tested in the literature, we believe that linearity is the most commonly assumed distributional form when data dispersion is unknown. Furthermore, the DCR metric requires both dose and effectiveness measures, and it can be sensitive to the measures chosen. It is therefore crucial to employ adequate measures for calculating the ratio. We based the DCR calculation on comprehensive cumulative doses and Hb AUC over the 16-week clinical trial, and this approach reflects the entire course of the erythropoietic therapy.

Calculating the DCR metric can also be affected by the study design. For example, the dosage can be driven by Hb levels, and the timing of dosage adjustments can also influence the cumulative dose and hence the DCR. Given that the present clinical trial included comparative treatment groups, we would expect that the study design might have similar effects on both EPO and DARB. In fact, one main advantage of using a DCR instead of a dose ratio is that a DCR limits the impact of the study design on the DCR by controlling for the treatment effectiveness in addition to the quantity of drug administered.

The timing of dose adjustments in this study (week four for EPO, week six for DARB) was based on the NCCN and the ASCO/ASH treatment guidelines. This dosing-adjustment schedule enhances the relevance of the study results, because it reflects recognized therapeutic guidelines.

As a consequence of the regression to the mean phenomenon, a lower baseline Hb tends to be associated with a steeper rise in Hb, which is in turn associated with a higher Hb AUC. However, given that baseline Hb levels (EPO, 10.2 g/dl; DARB, 10.1 g/dl; P = .26) and the proportion of patients with a baseline Hb below 10 g/dl (EPO, 35%; DARB, 38%; P = .56) are similar between these two treatment groups, we do not think that this phenomenon affects these groups differentially.

This point underscores an important feature of Hb AUC, which captured Hb changes throughout the study period. In a study published in 2005, Campos et al. found that early Hb response (a rise of Hb 1 g/dl or more within the first four weeks) was associated with improved quality-of-life scores and a reduced need for transfusions. The results highlight the importance of early Hb response in the treatment of CIA. In this context, it is important to use an effectiveness measure, such as Hb AUC, that incorporates information about early and overall responses in comparisons of erythropoietic agents.

In addition to our study, another head-to-head randomized trial, by Glaspy et al., compared the effectiveness of EPO 40,000 units given once weekly versus DARB 200 mcg given every two weeks. However, the Glaspy study did not report the needed Hb measures and cumulative doses to apply the methodology that we described here to establish the DCR between these two agents. Further research is warranted to determine whether our findings can be validated in other trials.

**CONCLUSION**

Our analysis indicated a DCR of 199:1 between epoetin alfa and darbepoetin alfa based on data from an open-label, prospective, randomized, head-to-head clinical trial. From this finding, we
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inhaled that 199 units of EPO achieved an equivalent level of hematological effectiveness as 1 mcg of DAR, as measured by Hb AUC_{tc}. The 95% CI around the DCR point estimate, revealed in our analysis, ranged from 113:1 to 303:1, which is lower than the 330:1 DCR adopted by the CMS in 2004 and 2005; however, it is in line with the DCR of 200:1 used by payers around the world.

REFERENCES


