Dose conversion and cost effectiveness of erythropoietic therapies in chemotherapy-related anemia: a Canadian application

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Objective. To determine the dose-conversion ratio (DCR) between epoetin alfa and darbepoetin alfa in cancer patients and compare the treatment costs of both agents at the estimated DCRs.

Methods. A comprehensive search of the literature was carried out on clinical trials evaluating patients with chemotherapy-related anemia treated with epoetin alfa or darbepoetin alfa. A multivariate meta-analysis regression was conducted to determine the relative doses of these two agents at which they were equally effective. The effectiveness measure used was the area under the hemoglobin change curve. Using the estimated DCR for each dosing regimen, the relative cost of epoetin alfa and darbepoetin alfa treatments in Canada was evaluated.

Results. Twenty-nine study arms, evaluating 12 923 patients (10 582 treated with epoetin alfa and 2341 treated with darbepoetin alfa), were eligible for this study. Results comparing specific dosing regimens indicated that the DCRs were systematically lower than 200:1. The cost premium associated with darbepoetin alfa weekly drug cost was between 37 and 44% above epoetin alfa for the same level of effectiveness.

Conclusion. Based on the evidence from this meta-analysis, epoetin alfa appeared to be more cost-effective compared to darbepoetin alfa in Canada for cancer patients. ***J Oncol Pharm Practice (2006) 12: 165–178.***

Key words: chemotherapy related anemia; epoetin alfa; darbepoetin alfa; cost effectiveness; dose conversion ratio

INTRODUCTION

Cancer patients treated with myelotoxic chemotherapy often experience multiple side effects, including cancer-related anemia (CRA), which results in fatigue, lower quality of life (QOL), and a reduced ability to work.[1–3] Anemia may also reduce cancer patients' compliance and response to chemotherapy.[2,3]

Epoetin alfa,[4,5] and darbepoetin alfa,[6] have been shown to be effective treatments for CRA in patients with non-myeloid malignancies, by increasing red blood cells and, thereby, ameliorating anemia-related symptoms.[7–12]

Studies evaluating the dose conversion ratio (DCR; ie, the ratio of doses at which the two agents are equally effective) between these two agents have just started to emerge from the medical literature.[13,14] A DCR of 200 U of epoetin alfa:1 mcg of darbepoetin alfa, was suggested based on the ratio of the two molecules' protein mass, as well as in a Phase III

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double-blind, placebo-controlled, randomized registration trial of darbepoetin alfa, conducted by Vansteenkiste *et al*.[9] Nissenson,[15] also suggested that the initial protein mass formula was appropriate to identify a therapeutic starting dose for chronic kidney disease patients switched from epoetin alfa to darbepoetin alfa. More recently, Rosberg *et al*.[14] performed a meta-analysis of published prospective clinical trials of epoetin alfa and darbepoetin alfa for the treatment of CRA, and found that the estimated DCRs ranged from 126:1 to 191:1, depending on the dosing regimen for each erythropoietic agent. This analysis used a standard area under the hemoglobin (Hb) change curve (Hb AUC) to normalize treatment effectiveness.

Since the definition of treatment effectiveness has a direct impact on the DCR calculation, it is crucial that the most informative measure be used. Hb AUC has recently been shown to be an objective, clinically meaningful, and comprehensive summary statistic to quantify the clinical benefits of erythropoietic agents.[16] Hb AUC has the important advantage of accounting for the complete hematologic profile over the entire course of treatment rather than at an arbitrary discrete time point, as in the hematological response measure.

Determining a DCR is relevant to physicians, payers, and the health care system, since it ensures that the agents are optimally dosed and that health care resources are efficiently utilized. Specifically, payers want to assess which of the two alternative treatments is likely to be the cheapest for a given level of effectiveness. This relative cost effectiveness, which focuses on the average cost of a unit of the drug given prevailing dosages, is best suited as a tool to anticipate alternative levels of funding needed.

The purpose of the current research is to conduct a cost effectiveness analysis of epoetin alfa versus darbepoetin alfa using prices of erythropoietic agents in Canada. To do so, we updated the meta-analysis initially proposed by Rosberg *et al*.,[14] using available data published in 2003–2005. We drew from the approach and methodology used in the analysis of Rosberg *et al*.,[14] to assess drug effectiveness. Namely, the treatment efficacy between the two agents was normalized using Hb AUC.

METHODS

As described below, our approach draws heavily from the methodology proposed by Rosberg *et al*.[14]

Literature search

The MEDLINE and Cancerlit databases were searched for all papers, abstracts, book chapters and other research communications, from June 2003 to July 2005, that included one of the following key words: 'epoetin alfa', 'darbepoetin alfa', 'recombinant human erythropoietin AND Cancer', 'Epogen', 'Eprex AND Cancer', 'Procrit', and 'Aranesp'. The reference sections of all papers reporting on clinical trials of epoetin alfa or darbepoetin alfa use in CRA were checked for additional papers. In addition, the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) online databases were searched for relevant abstracts from the 2003–2005 meetings.

Study eligibility criteria

In addition to the study arms identified by Rosberg *et al*.,[14] reports of prospective trials of epoetin alfa and/or darbepoetin alfa for the treatment of CRA published between 2003 and 2005 were included.

Studies were included if:

- They enrolled adult ($\geq$18 years) patients
- They had at least 10 patients enrolled
- The patient population was anemic (mean baseline Hb $\leq$11 g/dL)
- The dosing protocol during the study was clinically relevant (starting dose $\geq$1.5 and $\leq$4.5 mcg/kg per week for darbepoetin alfa or $\geq$25 000 and $<$60 000 U/week for epoetin alfa)
- Patients were followed for at least 8 weeks (the minimum time frame to provide sufficient information regarding the relationship between dosing and response).

Studies were excluded if:

- They used a front-loading regimen (because these regimens' doses are significantly higher than any doses used in clinical practice; eg, $>$300 mcg QW).
- They did not report mean changes in Hb or sufficient information to estimate a mean dose (eg, did not report the proportion of patients requiring dose escalation).

Data abstraction

The relevant information was abstracted from eligible studies and inserted into an Excel data collection form with prepared fields. Data collected included the number of patients, initial and escalated doses, treatment period, Hb values at baseline and subse-

quent weeks, method of Hb measurement (with or without excluding Hb readings preceded by a transfusion in the past 28 days), proportion of patients with dose escalation, proportion of patients with an increase of 1 g/dL or more at week 4, and an indicator for study arms that enrolled only patients with hematological malignancies. In instances where relevant data were only reported graphically, values were estimated by physically measuring the charts with a ruler.

Weekly dose estimation

In cases where mean weekly dose was not reported, the following algorithms were used to calculate epoetin alfa or darbepoetin alfa weekly dose:

a) For studies with no dose escalation: the number of weeks of treatment was multiplied by the weekly dose. If the weekly dose was expressed in units or mcg per kilogram, 70 kg was assumed to be the weight of a typical patient unless otherwise indicated.[17–19] In one case, the information available did not allow us to distinguish patients who received a weight-based dose from those who received a fixed dose. The estimated dose was then computed using 50% of weight-based dose and 50% of fixed dose.[20]

b) For studies with dose escalation: a weighted average of the weekly dose in the study sample was calculated. For example, if the dose was escalated for 20% of the patients at week 4 during a 12-week treatment period, the mean dose was calculated as: {[0.8∗prescribed starting dose] + [0.2∗(4/12∗prescribed starting dose + 8/12∗prescribed escalated dose)]}.[8,21–24]

If the proportion of patients receiving an escalated dose was not reported, it was assumed equal to the proportion of patients whose change in Hb would trigger a dose escalation per protocol.[9]

In one instance, no numerical information was provided regarding either the proportion of patients receiving an escalated dose or the proportion of patients experiencing a change in Hb that would trigger a dose escalation. In this case, graphical data was available that was used to estimate the proportion of patients receiving an escalated dose.[25]

Estimation of Hb AUC

For each study, a Hb AUC from baseline through week 13 was estimated by calculating the area under the curve of Hb change from baseline observed at specific time points. For studies with observations at weeks 4 and 13, the Hb AUC was calculated as follows (Hb_0 is baseline Hb level, Hb_4 is the level at week 4, and Hb_{13} is the level at week 13).[26,27]

$$\text{Hb AUC} = 4*(Hb_4 - Hb_0)*0.5 + 9*(Hb_4 - Hb_0) + 9*(Hb_{13} - Hb_4)*0.5$$

Figure 1 illustrates the Hb AUC calculation. In three arms, the first Hb change was reported at 5 weeks rather than 4 weeks.[20,28] The area A in Figure 1 below corresponds to the first term in the equation above, the area C to the second term and the area B to the third term. In this case, the Hb AUC was estimated based on week 5 and 13 Hb values. In four other arms (two epoetin alfa and two darbepoetin alfa), Hb values were only reported for week 9 and week 17. For these study arms, we imputed the Hb values at weeks 4 and 13 using the values observed at weeks 9 and 17, respectively, for the purpose of the Hb AUC calculation.[29,30] In addition, in several studies, the final Hb value was reported at 12 weeks.[8–11,17,20–25,31–33] In these cases, the week 12 values were carried forward to week 13 and the Hb AUC was calculated as follows:

$$\text{Hb AUC} = 4*(Hb_4 - Hb_0)*0.5 + 8*(Hb_4 - Hb_0) + 8*(Hb_{12} - Hb_4)*0.5 + (Hb_{12} - Hb_0)$$

In general, due to data constraints, the Hb AUC was estimated only for those individuals who were on active study drug at the time of the Hb reading. In some epoetin alfa three times weekly (TIW) studies, however, changes were reported only on the basis of all individuals enrolled.[17,22] Also, in some studies, change in Hb was calculated only for those patients who did not have a transfusion during the 28 days prior to the Hb assessment. In order to account for different calculation methods, a dummy variable was included in the regression analysis, as described in the next section.

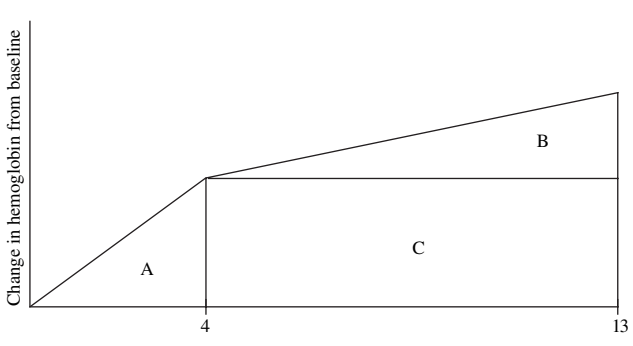

Figure 1. Calculation of Hb AUC.

Regression analysis

Data were analysed using linear regression. The dependent variable, Hb AUC, was regressed on epoetin alfa TIW dose, epoetin alfa once weekly (QW) dose, darbepoetin alfa QW dose, darbepoetin alfa once every two weeks (Q2W) dose, baseline Hb level, baseline Hb level square, an indicator for study arms with hematological malignancies, and whether transfusion within 28 days of an assessment was considered when recording Hb. The four epoetin alfa and darbepoetin alfa dose variables were set to the average weekly dose value or 0, based on the drug and regimen used in the study arm. The regression equation was as follows:

$$\begin{aligned}\text{Hb AUC} = {} & a + b(\text{epoetin alfa TIW dose}) \\ & + c(\text{epoetin alfa QW dose}) \\ & + d(\text{darbepoetin alfa QW dose}) \\ & + e(\text{darbepoetin alfa Q2W dose}) \\ & + f(\text{baseline Hb}) + g(\text{baseline Hb})^2 \\ & + h(\text{indicator for hematological malignancies}) \\ & + i(\text{indicator for transfusion restriction}) + \varepsilon\end{aligned}$$

The regression was frequency-weighted using the number of individuals in each study arm, and the variance-covariance matrix of the coefficients was normalized so that they added up to the actual sample size. Robust standard errors were calculated.[34,35]

As platinum-based chemotherapy is more likely to induce anemia, a variable capturing the proportion of patients who received platinum-based chemotherapy may be relevant to the model. However, the information regarding the proportion of patients treated with platinum-based chemotherapy was available only for 15 study arms (12 for epoetin alfa and three for darbepoetin alfa) out of the 29 study arms identified for this analysis. Therefore, such a variable could not be included in the model without losing a significant portion of the sample. A sensitivity analysis was conducted including the proportion of patients receiving platinum-based chemotherapy when available, and the sample mean for the arms where the information was not available.

Regimen-specific DCRs

In the regression equation above, the coefficient *b* captures the increase in Hb AUC for an additional epoetin alfa Unit administered TIW, while *c* captures the increase in Hb AUC for an additional epoetin alfa Unit administered QW. Similarly, *d* and *e* capture the increase in Hb AUC for an additional darbepoetin alfa Unit administered QW and Q2W, respectively. As far as the coefficient for darbepoetin alfa and epoetin alfa doses represent the marginal impact on Hb AUC for an additional mcg or Unit, their ratio would indicate the DCR between the two agents for the corresponding dosing regimens. However, the epoetin alfa:darbepoetin alfa DCR might not equal the ratio of the two coefficients, since the mean of a ratio of random variables is generally not equal to the ratio of the means of those two random variables. Instead, the DCR must be estimated using a bootstrapping simulation commonly used for modeling the median of a ratio of random variables.[36] Therefore, 10 000 draws from a multivariate normal distribution were simulated using the empirical distribution of the regression coefficients *b*, *c*, *d*, and *e* (ie, estimates and the variance-covariance matrix). Since the distribution of a ratio of random variables follows a Cauchy distribution, ie, with infinite tails, the medians of the simulated coefficients were used to calculate the DCRs between epoetin alfa and darbepoetin alfa treatments.[37] For the same reason, the 2.5 and 97.5% percentiles of the distribution were used as the upper and lower limits of the 95% confidence interval.

Cost implications of the DCR in Canada

One of the objectives of this analysis was to determine the relative cost of epoetin alfa and darbepoetin alfa treatments in Canada. Weekly drug costs for epoetin alfa were estimated assuming 30 000 U in the case of epoetin alfa TIW dosing regimen, and 40 000 U in the case of epoetin alfa QW. The equally effective darbepoetin alfa dose for these two regimens was determined using the estimated DCRs. Average weekly drug costs for epoetin alfa and darbepoetin alfa treatments were obtained by multiplying the weekly doses by the 2005 drug acquisition costs in Canada. Drug costs used for the analysis were $CDN 2.68/mcg for darbepoetin alfa and $0.01425/U for epoetin alfa, except for 40 000 U, where the cost was $0.01005/U. The relative cost-effectiveness (RCE) of epoetin alfa to darbepoetin alfa was calculated by multiplying the DCR by the ratio of Unit drug prices as follows: RCE = (1/DCR)* [($CDN/mcg darbepoetin alfa)/($CDN/U epoetin alfa)].

RESULTS

Selection of studies

The literature search identified 59 new papers and abstracts since the Rosberg analysis.[14] Sixteen were

reporting prospective darbepoetin alfa clinical trials, 38 were epoetin alfa clinical trials, and five were comparative studies of epoetin alfa versus darbepoetin alfa. Fifty-three studies (16 darbepoetin alfa, 35 epoetin alfa, and two comparative; see Appendix A) were rejected for the following reasons: pediatric population,[38,39] baseline anemia level not moderate,[12,40–44] incomplete dosing information,[45–48] missing Hb information,[44,46–59] not chemotherapy-related anemia,[60,61] duplicate studies,[62–76] dosage not clinically relevant or/and front-loading dosing regimen.[77–89] Three epoetin alfa studies and three comparative studies of epoetin alfa and darbepoetin alfa, representing seven epoetin alfa and three darbepoetin alfa new study arms, met the study eligibility criteria.[11,20,29,30,32,33] These study arms were combined with the initial sample identified by Rosberg *et al*.[7,8,10,17,18,21,22,24–26,31,90] The current sample, thus, includes a total of 29 arms (15 epoetin alfa and 14 darbepoetin alfa) and 12 923 patients. The number of patients in the epoetin alfa arms and darbepoetin alfa arms add up to 10 582 and 2341, respectively. For epoetin alfa patients, TIW and QW dosing regimens were observed in 6255 and 4327 patients, respectively. For darbepoetin alfa patients, 182 subjects received their treatment at QW interval, while 2159 were treated Q2W.

The study arm characteristics presented in Table 1 confirm the Rosberg *et al*.[14] findings demonstrating that patients receiving epoetin alfa responded faster to treatment than patients receiving darbepoetin alfa. Indeed, weighted average Hb change at week 4 was 1.2 g/dL for epoetin alfa study arms versus 0.8 g/dL for darbepoetin alfa. Baseline Hb results also revealed a trend towards earlier treatment with erythropoietic agents, as judged by the increase in baseline Hb over time.

Regression analysis

Table 2 shows the results of the regression analysis. All coefficients for the different dosing regimens of epoetin alfa and darbepoetin alfa, as well as the coefficients on the indicator of hematological cancer and transfusion restriction, were significant at the 1% level. The results indicate that the average weekly dose had a significant positive impact on Hb AUC, even after controlling for other covariates. Probably because of limited variation in the data, baseline Hb level was not a significant determinant of Hb AUC.

Regimen-specific analyses

Results comparing specific dosing frequencies are shown in Figure 2. In all scenarios, the DCR between epoetin alfa and darbepoetin alfa is <200:1. More specifically, the DCRs are 137:1 (95% CI: 104:1–166:1) for epoetin alfa TIW:darbepoetin alfa QW; 133:1 (95% CI: 82:1–167:1) for epoetin alfa TIW:darbepoetin alfa Q2W; 191:1 (95% CI: 154:1–229:1) for epoetin alfa QW:darbepoetin alfa QW; and 185:1 (95% CI: 121:1–230:1) for epoetin alfa QW:darbepoetin alfa Q2W. These results are consistent with the estimated DCRs for the corresponding dosing regimens reported by Rosberg *et al*.[14]

Cost-effectiveness analysis

Results comparing epoetin alfa and darbepoetin alfa weekly drug costs at the estimated DCRs are shown in Figure 3. The weekly acquisition cost for 30 000 U of epoetin alfa is \$428 (ie, 30 000∗\$0.01425). Based on the DCR for epoetin alfa TIW and darbepoetin alfa QW (the labelled regimens in Canada) estimated in this study (137:1), the equivalent dose of darbepoetin alfa for 30 000 U of epoetin alfa is 219 mcg (30 000 U epoetin alfa/[137 U of epoetin alfa:1 mcg of darbepoetin alfa] = 219 mcg). Therefore, darbepoetin alfa weekly drug cost, for the same level of effectiveness, is estimated to be \$587, resulting in a RCE of 1.37 for epoetin alfa TIW versus darbepoetin alfa QW. The corresponding RCEs were 1.42 for epoetin alfa TIW:darbepoetin alfa Q2W, 1.39 for epoetin alfa QW:darbepoetin alfa QW, and 1.44 for epoetin alfa QW:darbepoetin alfa Q2W.

Sensitivity analyses

Two studies reported Hb level only at baseline, week 9, and week 17.[29,30] Since the Hb AUC values for these studies might be overestimated compared to the other study arms, we conducted a sensitivity analysis by removing these arms from the regression model. Results from this analysis revealed slightly lower DCRs, but not statistically different from the estimated DCRs using the full sample. Likewise, the regression model was robust to the addition of an indicator for the proportion of patients who received platinum-based chemotherapy, resulting in DCRs not statistically different from the estimated DCRs using the base case specification.

DISCUSSION

This updated meta-analysis, based on the available studies, synthesizes results from disparate trials and controls for differences resulting from multiple investigators and clinical trial settings. The regimen-specific analyses show that the lowest DCRs (below

Table 1. Study arms used in analysis

Short cite	No. of patients	Hematological malignant patients only	Treatment period (weeks)	Initial dose	Escalated dose	Baseline Hb level (g/dL)	Hb change Week 4	Hb change Week 13[a]	Area under the curve	Estimated dose	Proportion of platinum chemotherapy
Epoetin alfa TIW											
Dammacco *et al.*[22]	69	Yes	12	150 U/kg	300 U/kg	9.3	0.7	1.8	13.2	39 018	N/A
Demetri *et al.*[7]	2237	No	16	10 000 U	20 000 U	9.3	1.45	1.8	17.7	34 588	0.46
Glaspy[31]	2019	No	16	150 U/kg	300 U/kg	9.2	1.1	1.9	16.1	30 943	0.39
Littlewood *et al.*[21]	251	No	28	150 U/kg	300 U/kg	9.9	0.85	2.5	17.6	42 803	0.01
Pawlicki *et al.*[17]	215	No	16	150 U/kg		9.1	1.5	2.8	23.0	31 500	0.54
Quirt *et al.*[24]	218	No	16	150 U/kg	300 U/kg	9.0	1.1	2.8	20.6	39 690	0.17
Granetto *et al.*[32]	255	No	12	10 000 U	20 000 U	9.61	0.89	2.13	15.99	32 680	1.00
Granetto *et al.*[32]	255	No	12	150 U/kg	300 U/kg	9.65	1.15	2.11	17.45	34 440	1.00
Harousseau *et al.*[20]	736	No	28	10 000 U or 150 U/kg	20 000 U or 300 U/kg	9.6	1.35	2.46	19.17	37 638[b]	N/A
Epoetin alfa QW											
Gabrilove *et al.*[8]	2869	No	16	40 000 U	60 000 U	9.5	1.0	2.1	16.5	44 453.3	0.36
Shasha *et al.*[21]	442	No	16	40 000 U	60 000 U	9.9	1.1	2.0	16.6	44 646	N/A
Witzig *et al.*[11]	166	No	16	40 000 U	60 000 U	9.5	1.2	2.9	21.7	46 420	0.15
Schwartzberg *et al.*[29,d]	69	No	16	40 000 U	60 000 U	10.6	1.1[c]	1.7[c]	14.8	38 863	0.12
Glaspy *et al.*[30]	603	No	12–16	40 000 U	60 000 U	10.2	1.6[c]	1.7[c]	18.05	42 714	0.42
Waltzman *et al.*[33]	178	No	12–16	40 000 U	60 000 U	10.2	0.7	1.3	10.7	38 179	0.39
Darbepoetin alfa QW											
Hedenus *et al.*[28]	22	Yes	12	2.25 mcg/kg		9.4	0.4	1.64	9.2	157.5	N/A
Hedenus *et al.*[28]	22	Yes	12	4.5 mcg/kg		9.7	0.83	2.46	15.0	315	N/A
Glaspy *et al.*[90]	35	No	12	1.5 mcg/kg		9.91	0.6	1.6	11.1	105	N/A
Glaspy *et al.*[90]	59	No	12	2.25 mcg/kg		9.91	0.7	1.5	11.3	157.5	N/A
Glaspy *et al.*[90]	29	No	12	4.5 mcg/kg		9.91	1.0	2.8	19.1	315	N/A

Heatherington *et al.*[18]	15	No	12	2.25 mcg/kg	4.5 mcg/kg	9.6	1.2	2.3	18.2	152.6	N/A
Darbepoetin alfa Q2W											
Glaspy *et al.*[90]	33	No	12	3 mcg/kg		9.82	0.61	1.6	11.2	105	N/A
Glaspy *et al.*[90]	31	No	12	5 mcg/kg		9.82	0.58	2.4	14.6	175	N/A
Glaspy *et al.*[90]	32	No	12	7 mcg/kg		9.82	0.61	2.4	14.8	245	N/A
Glaspy *et al.*[90]	32	No	12	9 mcg/kg		9.82	1.23	2.4	18.8	315	N/A
Vadhan-Raj *et al.*[10]	1173	No	16	3 mcg/kg	5 mcg/kg	10.4	0.6	1.6	12.6	125.7	N/A
Glaspy *et al.*[31]	606	No	12–16	200 mcg	300 mcg	10.2	1.2[c]	1.6[c]	15.0	114.5	0.42
Schwartzberg *et al.*[29,d]	72	No	16	200 mcg	300 mcg	10.5	1.0[c]	1.9[c]	15.05	105.5	0.13
Waltzman *et al.*[33]	180	No	12–16	200 mcg	300 mcg	10.1	0.2	0.7	5.3	102.6	0.42

[a]If Hb level was observed at week 12, then Hb value was carried forward to week 13 using the last value carried forward (LVCF) method.
*[b]In this case, the available information does not allow us to distinguish patients who receive weight-based dose from those who receive fixed dose. The estimated dose is then calculated using 50% of weight-base dose (U/kg*70 kg) and 50% of fixed dose.*
[c]In this case, Hb level was observed at weeks 9 and 17. The AUC was then calculated by carrying the Hb level at week 9 and 17 back to weeks 4 and 13, respectively.
[d]Only patients with breast cancer.
U, units; mcg, microgram; kg, kilogram; TIW, three times weekly; QW, once weekly; Q2W, once every two weeks; Hb, hemoglobin.

Table 2. Summary results for the regression analysis

Dependent variable: Hb AUC Independent variables	Coefficient	Robust *t*-statistics
Weekly darbepoetin dose	0.0438[a]	3.56
Weekly epoetin dose	0.0002[a]	3.72
Thrice weekly epoetin dose	0.0003[a]	4.00
Bi-weekly darbepoetin dose	0.0424[a]	3.05
Baseline Hb	−3.3770	−0.06
Baseline Hb^2	0.0129	0.00
Hematological cancer	−7.3764[a]	−5.70
Transfusion restriction[b]	4.0874[a]	2.28
Constant	37.5570	0.13
Patients	12 923	
No. of studies	17	
No. of study arms	29	
R^2	0.7026	

[a]Significant at 1%.
[b]This dummy variable takes the value of 1 if Hb readings preceded by a transfusion in the past 28 days are excluded from the calculation of Hb change.
Hb, hemoglobin.

150:1) were obtained when comparing epoetin alfa TIW to darbepoetin alfa QW or epoetin alfa TIW to darbepoetin alfa Q2W. DCRs were slightly higher (approximately 190:1) when comparing epoetin alfa QW to darbepoetin alfa QW and epoetin alfa QW to darbepoetin alfa Q2W. Results from this analysis are based on 12 923 patients that originated from 29 study arms of erythropoietic agents use and are, therefore, highly generalizable.

The inclusion in the regression model of a variable controlling for the proportion of patients receiving platinum-based chemotherapy in each study did not affect the DCR estimations in any significant way. Likewise, the regression model was robust to the exclusion of two studies that reported Hb level only at baseline, week 9, and week 17.

The DCRs calculated in this study based Hb AUC to normalize treatment effectiveness, are similar to those obtained by Rosberg *et al*.,[14] but are substantially lower than those reported by Scott.[13] This may be due to the use of a common effectiveness measure (Hb AUC) in Rosberg's study and this research. As epoetin alfa produces a quicker response, the DCRs estimated on the basis of cumulative change in Hb, such as Hb AUC, tend to be lower than those estimated based on response only at the end of treatment. The choice of the effectiveness measure appears to be a determinant in the calculation of the DCR. We used Hb AUC as the effectiveness measure because it has the important advantage of being a more comprehensive measure of the hematological profile compared to single time point-based or

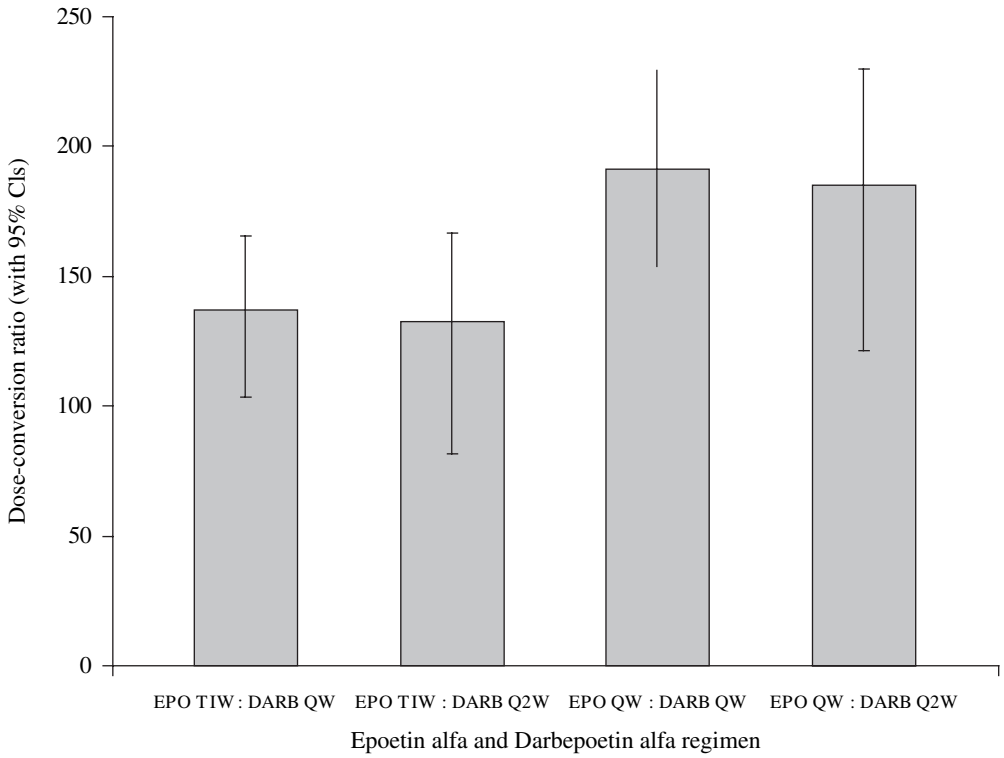

Figure 2. Estimated regimen-specific dose conversion ratios.

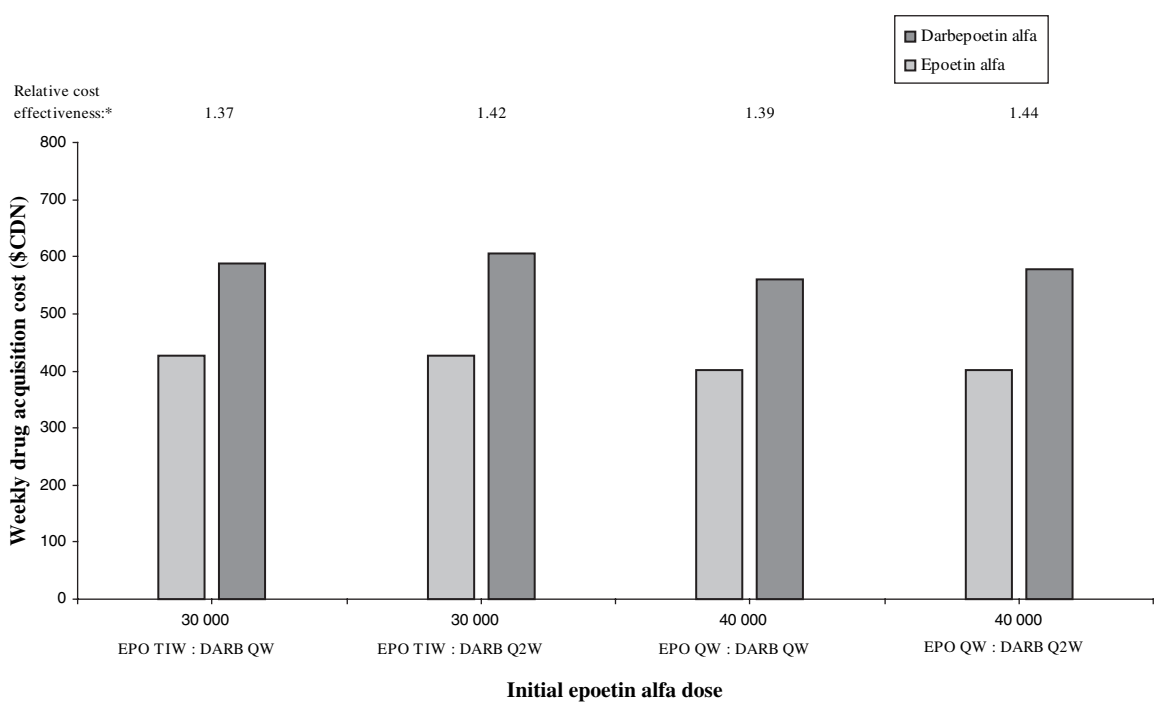

Figure 3. Weekly drug costs at estimated dose conversion ratios. Prices used for the analysis were expressed in 2005 Canadian dollars: $2.68/mcg for darbepoetin alfa and $0.01425/unit for epoetin alfa, except for 40 000 units where cost was $0.01005/unit. *Darbepoietin alfa drug cost/Epoetin alfa drug cost at estimated DCRs.

threshold-based measures (eg, hematopoietic response rate and week 16 Hb change). Indeed, Hb AUC has recently been shown to be a statistically superior measurement compared to the traditional hematopoietic response rate. Furthermore, greater Hb AUC values have been demonstrated to be associated with reduced transfusion requirements, decreased drug utilization, and improved patient quality of life.[16] Hence, Hb AUC is the preferred outcome measure to normalize the treatment effectiveness in determining the DCR between epoetin alfa and darbepoetin alfa.

Although generalizable, this analysis has several limitations. Due to limited data, the algorithms used to compute weekly doses do not consider the common dosing protocol requirement that the study drug be withheld if an abnormally high Hb level is reached and then resumed at a lower dosage when the patient reaches a normal Hb concentration, typically 12.0 g/dL. In addition, Hb targets may differ across individual trials.[7,8,10,31] Furthermore, because we did not have access to the underlying patient-level data, it was impossible to determine the DCR for different types of cancer (eg, breast, lung, etc.) or control for uneven distributions across studies. However, we controlled for hematological versus solid malignancies in calculating the DCRs by inserting a binary variable for study arms that enrolled only patients with hematological malignancies.

Based on the 2005 Canadian drug prices, the cost-effectiveness analysis demonstrated that the weekly drug acquisition cost of epoetin alfa was less than that of the equivalent dose of darbepoetin alfa for all of the DCRs calculated in this study. To achieve the same patient outcome, darbepoetin alpha would cost $158–178 per week than an equivalent epoetin dose depending on the dosing regimens of each agent.

CONCLUSION

This analysis demonstrated that, when compared on the basis of cumulative change in Hb (Hb AUC), the DCR between epoetin alfa and darbepoetin alfa for treatment of CRA range from 133:1 for the epoetin alfa TIW:darbepoetin alfa Q2W regimen to 191:1 for the epoetin alfa QW:darbepoetin alfa QW regimen. These results indicate that, for all regimens, the weekly acquisition cost for epoetin alfa is less than for an equivalently effective dose of darbepoetin alfa in Canada.

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APPENDIX A

Study arms not eligible

Reason for exclusion	Reference	Drug type
1. Pediatric study	38	Epoetin
	39	Epoetin
2. Dosage not clinically relevant		
3. Baseline anemia level not moderate	40	Darbepoetin
	41	Epoetin
	42	Epoetin
	43	Darbepoetin
4. Incomplete dosing information	45	Darbepoetin
5. Missing Hb information	49	Epoetin
	50	Epoetin
	51	Darbepoetin
	52	Darbepoetin
	53	Darbepoetin
	54	Darbepoetin
	55	Darbepoetin
	56	Epoetin
	57	Epoetin
	58	Epoetin
	59	Epoetin
6. Not chemotherapy-related anemia	60	Epoetin
	61	Epoetin
7. Front-loading dosing regimen		
8. Duplicate studies	62	Epoetin
	63	Darbepoetin
	64	Epoetin
	65	Epoetin
	66	Epoetin
	67	Epoetin
	68	Epoetin
	69	Epoetin
	69	Darbepoetin
	70	Epoetin
	71	Epoetin
	72	Darbepoetin
	73	Darbepoetin
	74	Darbepoetin
	75	Epoetin
	76	Darbepoetin
	76	Epoetin
Multiple problems		
2, 7	77	Epoetin
2, 7	78	Epoetin
2, 7	79	Epoetin
2, 7	80	Epoetin
2, 7	81	Darbepoetin
2, 7	82	Darbepoetin
2, 7	83	Darbepoetin
2, 7	84	Epoetin
2, 7	85	Epoetin
2, 7	86	Epoetin
2, 7	87	Epoetin
2, 7	88	Epoetin
2, 7	89	Epoetin
3, 5	44	Darbepoetin
4, 5	46	Epoetin
4, 5	47	Epoetin
4, 5	48	Epoetin