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Costs Associated With Intravenous Darbepoetin Versus Epoetin Therapy in Hemodialysis Patients: A Randomized Controlled Trial

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Abstract

Background: Anemia of chronic kidney disease is associated with adverse outcomes and a reduced quality of life. Erythropoiesis-stimulating agents (ESAs) have improved anemia management, and 2 agents are available in Canada, epoetin alfa (EPO) and darbepoetin alfa (DA). EPO and DA are considered equally effective in achieving target hemoglobin (Hb), but it is not clear whether there is a cost difference. There have been few head-to-head comparisons; most published studies are observational switch studies.

Objective: To compare the cost of DA and EPO and to determine the dose conversion ratio over a 12-month period.

Design: Randomized controlled trial.

Setting: Canadian outpatient hemodialysis center.

Patients: Eligible patients were adult hemodialysis patients requiring ESA therapy.

Measurements: The primary outcome was ESA cost (Can$) per patient over 12 months. Secondary outcomes included the dose conversion ratio, deviation from target ranges in anemia indices, iron dose and cost, and time and number of dose changes.

Methods: An open-label randomized controlled trial of intravenous (IV) DA versus EPO was conducted in 50 hemodialysis patients. Participants underwent a minimum 6-week run-in phase followed by a 12-month active study phase. ESA and iron were dosed using a study algorithm.

Results: The median cost was $4179 (interquartile range [IQR]: $2416-$5955) for EPO and $2303 (IQR: $1178-$4219) for DA with a difference of $1876 ($P$ = .02). The dose conversion ratio was 280:1 (95% confidence interval [CI]: 197-362:1) at the end of the run-in phase, 360:1 (95% CI: 262-457:1) at the 3-month point of the active phase, and 382:1 (95% CI: 235-529:1) at the 6-month point of the active phase. There were no significant differences between the 2 groups in weekly iron dose, Hb, serum ferritin, or transferrin saturation. The number of dose changes and the time to Hb stability were similar.

Limitations: Results may not be generalizable to hemodialysis units without algorithm-based anemia management, with subcutaneous ESA administration, or to the nondialysis chronic kidney disease population. The effective conversion ratio between EPO and DA is known to increase at higher doses; the Hb targets used in the study were slightly higher than those recommended today so it is possible that the doses used were also higher. Because of this, the cost savings estimated for DA could differ somewhat from the savings realizable in current practice.

Conclusions: In this study of hemodialysis patients with comparable anemia management, IV DA cost $1876 less per year per patient than IV EPO. The dose conversion ratio was greater than 350:1 by the 3-month point.

Trial registration: ClinicalTrials.gov (NCT02817555).

Abrégé

Contexte: L'anémie qui résulte de l'insuffisance rénale chronique est associée à des conséquences défavorables sur la santé du patient et par conséquent, à une diminution de sa qualité de vie. Le recours à des agents stimulants l'érythropoïèse (ASE) a permis d'améliorer considérablement le traitement de ce type d'anémie. Deux de ces agents sont disponibles au Canada: l'époétine alfa (EPO) et la darbépoétine alfa (DA). L'efficacité de ces deux molécules à cibler l'hémoglobine (Hb) est considérée comme équivalente, mais la différence de coût de leur utilisation reste à déterminer. Il existe très peu d'études de comparaison directe entre l'EPO et la DA, et la plupart des études publiées consistent en des études observationnelles de transition.

Objectifs de l'étude: Comparer les coûts d'utilisation de la DA et de l'EPO et déterminer le ratio de conversion de dose sur une période de 12 mois.

Type d'étude: Il s'agit d'un essai contrôlé randomisé.
Cadre de l'étude: Un centre d'hémodialyse ambulatoire canadien.
Patients: Les patients admissibles étaient des patients adultes sous hémodialyse et nécessitant un traitement par les ASE.
Mesures: Le principal critère évalué était le coût (en dollars canadiens) d'un traitement par les ASE pour chaque patient sur une période de 12 mois. Parmi les résultats secondaires figuraient le ratio de conversion de dose, l'écart de déviation par rapport à la cible pour les indicateurs de l'anémie, la dose de fer et son coût, de même que le temps de stabilisation de la dose et le nombre de changements de dose.
Méthodologie: Un essai ouvert, contrôlé et randomisé a été mené auprès de 50 patients en hémodialyse afin de comparer les traitements intraveineux (IV) par la DA et l'EPO. Les participants ont été suivis pour une phase préalable d'une durée minimale de six semaines avant la phase de l'étude active qui s'est étalée sur 12 mois. Les doses de l'ASE et du fer ont été établies à partir d'un algorithme.
Résultats: Le coût médian était de 4 179 $ (Écart interquartile: 2 416 à 5 955 $) pour l'EPO et de 2 303 $ (EI: 1 178 à 4 219 $) pour la DA, soit une différence de 1 876 $ (P = 0,02). Le ratio de conversion de dose était de 280:1 (IC95: 197:1-362:1) à la fin de la phase préalable, de 360:1 (IC à 95%: 262:1-457:1) après trois mois écoulés dans la phase active et de 382:1 (IC95: 235:1-529:1) après 6 mois de phase active. Aucune différence significative n'a été observée entre les deux groupes en ce qui concerne les doses hebdomadaires de fer, les taux d'hémoglobine et de ferritine sérique ou le coefficient de la saturation de la transferrine (TSAT). Enfin, le nombre de modifications de la dose et le temps de stabilisation de l'hémoglobine se sont avérés similaires.
Limites de l'étude: Il est possible que l'on ne puisse étendre ces résultats aux unités d'hémodialyse où la gestion de l'anémie ne repose pas sur un algorithme. Il est également hasardeux de généraliser ces résultats aux cas où les traitements par un ASE sont administrés par voie sous-cutanée, de même qu'au sein d'une population de patients non-dialysés. Il est connu que le ratio de conversion optimal entre l'EPO et la DA augmente pour les doses élevées. De plus, les cibles d'hémoglobine utilisées dans l'étude étaient légèrement supérieures à celles qui sont recommandées aujourd'hui, il est donc possible que les doses utilisées aient été elles aussi plus élevées. Par conséquent, les économies estimées pour l'administration de DA pourraient différer légèrement des économies réalisables dans la pratique courante.
Conclusions: Cette étude, réalisée auprès de patients hémodialysés dont les traitements de l'anémie par voie intraveineuse étaient comparables, conclut que l'utilisation de la DA permet une économie annuelle de 1 876 $ par rapport à l'utilisation de l'EPO. De plus, le ratio de conversion de dose s'est avéré supérieur à 350:1 après trois mois écoulés dans la phase active de l'étude.

Keywords
anemia, drugs and dialysis, erythropoiesis-stimulating agent, darbepoetin alfa, epoetin alfa

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What was known before

Epoetin alfa (EPO) and darbepoetin alfa (DA) are considered equally effective in achieving target hemoglobin (Hb) in dialysis patients with comparable adverse effect profiles, but the cost difference is unclear. Observational switch studies have provided evidence that the dose conversion ratio is greater than 200:1 but with significant variability.

What this adds

This research represents the first prospective, parallel-group randomized controlled trial of intravenous EPO and DA in hemodialysis patients with the primary outcome of cost. It provides evidence of a cost advantage with DA and a dose conversion ratio that exceeds 350:1.

Background

Anemia is one of the earliest, most characteristic, and morbid manifestations of chronic kidney disease (CKD) and is associated with left ventricular hypertrophy, adverse cardiovascular and clinical outcomes, and a reduction in quality of life.[1,2] Erythropoiesis-stimulating agents (ESAs) have dramatically improved the management of anemia in CKD.

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There are 2 agents currently used in Canada, epoetin alfa (EPO) and darbepoetin alfa (DA). DA differs from EPO in that it has a higher molecular weight, a longer half-life, and sustained biologic activity.[3] Based on relative peptide mass, it was initially recommended to dose DA using a fixed ratio of 200:1 (EPO:DA),[4,5] and drug cost was based on this conversion ratio. Although EPO and DA are considered to be equally effective in achieving target hemoglobin (Hb) with comparable adverse effect profiles,[3-6,7] it is not clear whether there is a cost difference.

The results of the 3 randomized controlled trials comparing EPO with DA indicate that the 200:1 ratio is likely not consistent and correct in the hemodialysis populations studied. Only 1 trial included just intravenous (IV) administration[8] but did not have dose or cost as the primary outcome. The other studies[9,10] evaluated dose but included subcutaneous administration. The route of administration is important as EPO was found to require higher doses when administered intravenously than subcutaneously in a meta-analysis of hemodialysis patients.[11] In our hemodialysis units, ESAs have almost exclusively been administered intravenously since the 1990s as is typical of many Canadian hemodialysis centers. The highest dose conversion ratio found in these studies was 260:1.[9]

The 2 ESAs have most often been compared in observational switch studies (comparisons pre and post conversion from one ESA to another in an entire population). Of 16 switch studies, 9 demonstrated a dose conversion ratio which was greater than 200:1,[12-21] 1 found the dose conversion ratio to be less than 200:1,[22] 5 found decreased doses and lower cost with DA compared with EPO,[23-27] and 1 found DA cost more than EPO but the result was not statistically significant.[28] Only 4 of the 16 studies demonstrated a dose conversion ratio >300:1.[13-15,18]

A 2009 meta-analysis concluded that an average 30% dose savings could be achieved by switching from EPO to DA.[29] In a systematic review and economic evaluation of ESAs in CKD conducted by Canadian Agency for Drugs and Technologies in Health, it was recommended that more head-to-head comparisons should be undertaken to fully evaluate cost differences between EPO and DA.[30] This research represents the first prospective, parallel-group randomized controlled trial of IV EPO and DA in hemodialysis patients with the primary outcome of cost.

Methods

This open-label, parallel-group, randomized controlled trial was conducted between September 2010 and May 2013. The study protocol was approved by the Health Research Ethics Authority (HREA) of Newfoundland and Labrador (Approval Number HIC10.104), and all procedures followed were in accordance with the standards of the HREA. Written, informed consent was obtained from each patient.

The primary outcome was the cost per patient of ESA required over 12 months to maintain Hb in the target range of 100 to 120 g/L as per the current Canadian guidelines at the time of the study.[2] Secondary outcomes included dose conversion ratio, time to dose stabilization, number of dose changes, iron dose and cost, and deviation from target ranges for Hb and iron indices. All EPO and DA doses were administered intravenously during dialysis through a hemodialysis machine port.

To establish the target sample size, the mean ESA cost per patient over a 12-month period before study initiation was determined to be $7000 with a standard deviation (SD) of $1500. It was decided that a cost difference of $800 annually per patient was reasonable and would have significant budgetary impact. The sample size required to detect a difference of $800 per patient per year for ESA with a 2-sided $\alpha = 0.05$ and power $(1 - \beta) = 0.80$ was 112 patients.

Inclusion and Exclusion Criteria

The eligible study population were incident and prevalent patients of the Waterford Hemodialysis Unit of Eastern Health (St. John's, Newfoundland and Labrador, Canada) who met the following inclusion criteria: (1) age ≥19 years; (2) in-center hemodialysis 2 or more times weekly; (3) anemia requiring ESA therapy or an Hb <100 g/L in the absence of other causes of anemia; (4) if female, must be using an approved method of contraception or judged unable to become pregnant; and (5) able to give informed consent. Patients who met any of the following exclusion criteria were not eligible: (1) acute kidney injury likely to resolve; (2) plans to change to peritoneal dialysis or home hemodialysis, or planned transplant from a living donor; (3) expected life span of less than 6 months due to a medical condition other than CKD; (4) current hematologic condition that may cause anemia; (5) use of medications known to cause anemia; (6) use of any investigational drug or androgen within 90 days of screening; (7) significant bleeding within 30 days of screening; (8) red blood cell transfusion(s) within 30 days of screening; (9) documented or suspected pure red cell aplasia; (10) current iron deficiency; (11) documented allergy or intolerance to IV sodium ferric gluconate; (12) known or probable ESA resistance; (13) uncontrolled hypertension; or (14) an intention to relocate to a different dialysis center in the near future.

Randomization

A variable, block randomization procedure was used with blocks of 4, 6 or 8. A random number sequence determined the order of the variable blocks and the sequence of assignment within each block. An investigator filled, numbered, and sealed opaque envelopes, and the sequence was sealed and filed. Once informed consent was obtained and before the start of the run-in period, an envelope was sequentially

Table 1. Standard ESA Study Doses.

Weekly EPO dose (units)	Prescribed	Weekly DA dose (μg)	Prescribed
1000	1000—1 × week	5	10—q2 weeks
2000	2000—1 × week	10	10—1 × week
3000	3000—1 × week	15	30—q2 weeks
4000	2000—2 × week	20	20—1 × week
5000	5000—1 × week	25	50—q2 weeks
6000	3000—2 × week	30	30—1 × week
8000	4000—2 × week	40	40—1 × week
10 000	5000—2 × week	50	50—1 × week
12 000	4000—3 × week	60	60—1 × week
16 000	8000—2 × week	80	80—1 × week
20 000	10 000—2 × week	100	100—1 × week
24 000	8000—3 × week	120	120—1 × week
30 000	10 000—3 × week	150	150—1 × week

Note. ESA = erythropoiesis-stimulating agent; EPO = epoetin alfa; DA = darbepoetin alfa.

opened for each patient to determine assignment to one of 2 groups: (1) continue EPO or (2) switch to DA.

Study Algorithm and Doses

A pharmacist-managed anemia protocol has been in place since 2005 in this hemodialysis unit with monthly data collection of ESA doses and anemia indices. The algorithm used in the study was established in 2009 based on the 2008 Canadian guidelines[2] and includes flow charts for ESA and iron dosing (Supplementary Material). This algorithm was used for more than a year prior to the randomization of the first patient in December 2010. From January to December 2010 using this algorithm, the mean Hb was 110 g/L and the mean proportion of Hb values in the target range (100-120 g/L) was 74%. The mean proportion of transferrin saturation (TSAT) values <20% was 16%, and the mean proportion of serum ferritin values <200 μg/L was 11%.

Standard ESA dosing was used in the study. When a dose change was required following the study algorithm, the calculated dose was rounded to the nearest standard weekly dose and was administered as per Table 1.

Run-in Period

Patients were enrolled over a minimum 6-week run-in period to ensure Hb stability and to allow ESA conversion in the DA group. Data from the run-in period were not included in the analysis of the primary outcome. Hb levels were measured at 2-week intervals. Those randomized to EPO remained on their current dose and frequency if the Hb was in the target range, and the study algorithm was used to determine subsequent EPO dosing. In those randomized to DA, EPO was discontinued at the end of the week preceding entry into the study and DA was started on the next day that EPO would have been given. Based on the current EPO dose, a 200:1 ratio was used to determine the initial DA dose, rounded up or down to the nearest available prefilled syringe. After the first Hb measurement, the study algorithm was used to determine DA dosing. The run-in period continued until the Hb was within the range of 100 to 120 g/L for 3 consecutive 2-weekly measurements at which point the patient was considered stable and entered the active phase.

Active Phase

During the 12-month active phase, Hb was measured and reviewed monthly. All changes in ESA dose were made in accordance with the study algorithm by the study investigators to maintain Hb in the target range. If a patient required a dose of EPO >30 000 units weekly or a dose of DA >150 μg weekly, the dose was not escalated any higher.

Iron

Patients received IV sodium ferric gluconate prescribed as per the study algorithm to maintain ferritin in the range of 200 to 800 ng/mL and TSAT between 20% and 50% as per current Canadian guidelines at the time of the study.[31] TSAT was measured monthly and ferritin every 3 months.

Analysis

Data were obtained at baseline, every 2 weeks during the run-in, and once monthly during the active phase and were entered directly into SPSS using unique patient identifiers. Intention-to-treat analysis was used including all data from patients who entered the active phase. In cases where 12 months of the active phase were not completed, the last available month's data were carried forward to the end.

The cost used in the analysis was the total dose of ESA over 12 months in each patient multiplied by the list cost which was $0.0142/unit for EPO and $2.68/μg for DA (Can$). The distribution of the cost was not normal, so medians and interquartile ranges (IQRs) were determined, and medians were compared using the Mann-Whitney *U* test.

For the secondary analyses, results were reported as means ± SD and the independent samples *t* test was used to compare means when the distribution of the data was normal. When the data were not normally distributed, results were reported as medians, and IQR and the Mann-Whitney *U* test was used to compare medians.

Results

Patient Characteristics

The patient flow is represented in Figure 1. Between September 2010 and February 2012, 208 hemodialysis patients were screened. Of these, 25 were not currently

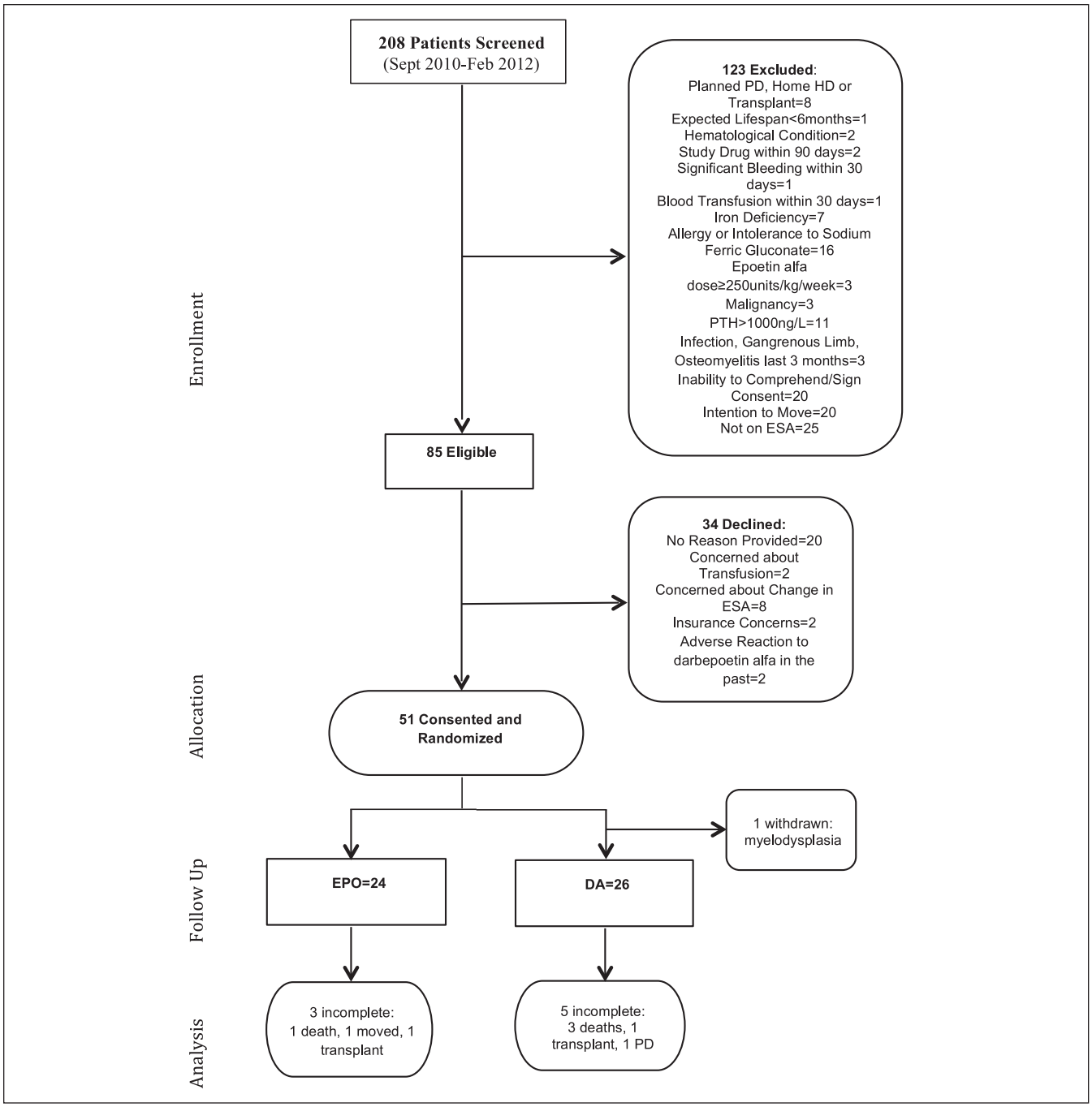

Figure 1. Patient flow.
Note. ESA = erythropoiesis-stimulating agent; EPO = epoetin alfa; DA = darbepoetin alfa; PD = peritoneal dialysis; HD = hemodialysis; PTH = parathyroid hormone.

treated with an ESA and 98 met one of the exclusion criteria. Of the remaining 85, 34 declined to participate and 51 patients consented.

Of the 51 patients enrolled, 24 were randomized to the EPO arm and 27 to the DA arm. Baseline characteristics are presented in Table 2. One patient in the DA arm was withdrawn before completion of the run-in phase due to a newly diagnosed hematological condition.

The final groups consisted of 24 patients in the EPO arm and 26 patients in the DA arm. Eight patients did not complete the full 12 months of follow-up in the active phase (5 in the DA group and 3 in the EPO group). Four died, 1 switched to peritoneal dialysis, 1 relocated, and 2 received kidney transplants.

The a priori sample size calculation which was set to detect a difference of $800 per patient required 112 patients.

Table 2. Demographics and Baseline Characteristics of Patients.

	Epoetin (n = 24)	Darbepoetin (n = 26)
Age, mean ± SD	59.8 ± 13.3	61.0 ± 15.1
Male	13	20
Female	11	6
Baseline epoetin dose (units weekly), median (IQR)	6000 (4000-8000)	6000 (3750-8000)
Diabetes mellitus	16 (67%)	17 (65%)
Coronary artery disease	8 (33%)	8 (31%)
Congestive heart failure	1 (4%)	5 (19%)
Myocardial infarction	3 (13%)	5 (19%)
Stroke or TIA	5 (21%)	1 (4%)
Peripheral artery disease	6 (25%)	4 (15%)

Note. IQR = interquartile range; TIA = transient ischemic attack.

The number of eligible and consenting patients was lower than anticipated, and it was decided to complete enrollment with 51 participants. With a sample size of 50 patients, using a 2-sided $\alpha = 0.05$ and a power $(1 - \beta) = 0.80$, a difference of $1215 per year per patient in ESA cost could be detected.

Total ESA Cost

Results for the primary outcome and anemia targets are summarized in Table 3. The median total cost for EPO over 12 months was $4178.70 ($2416.37-5955.12) and for DA was $2302.92 ($1177.86-4218.93). The median cost of DA was $1875.78 less per year than that of EPO, and the difference was statistically significant ($P = .02$).

ESA Dose

Table 4 provides a summary of the ESA doses in each study group. As per the study algorithm and standard dosing, EPO was administered once, twice, or 3 times weekly; DA was administered weekly or every 2 weeks. Weekly dose was determined and recorded for each patient.

Dose Conversion Ratio

The dose conversion ratio was determined by dividing the weekly EPO dose for each patient at the time of randomization by the weekly DA dose at the end of the run-in phase and at the 3- and 6-month points of the active phase. The mean dose conversion ratio at the end of run-in phase was 280:1 (95% confidence interval [CI]: 198-362:1). At 3 months, it was 360:1 (95% CI: 262-457:1), and at 6 months, it was 382:1 (95% CI: 235-529:1).

A similar calculation was performed for patients in the EPO arm to determine whether there was an overall trend in both groups to a decrease in dose over time. The ratio (EPO:EPO) was 1.1:1 (95% CI: 0.9-1.4:1) at the end of the run-in period, 1.2:1 (95% CI: 0.6-1.9) at 3 months, and 1.2:1 (95% CI: 0.8-1.5) at 6 months, indicating that the EPO doses were relatively stable.

Anemia Targets

Hb, serum ferritin, TSAT, iron dose, and iron cost were compared between the 2 groups, and there were no statistically significant differences. The median weekly iron doses were not different with the EPO group receiving 40.36 mg and the DA group 41.67 mg ($P = .99$). Median total annual iron cost was $726.56 in the EPO group and $750.0 in the DA group ($P = .99$) (Table 3).

To examine the Hb variability over the study period, the mean Hb in each arm was determined for each 2-week period of the run-in period and for each month of the active phase and is presented in Figures 2 and 3.

Dose Stabilization

During the run-in period, the median number of dose changes was 0 (IQR: 0-1.75) in the EPO group and 0 (IQR: 0-0.25) in the DA group ($P = .38$). The median number of weeks required to reach Hb stability was 4 in both groups ($P = .43$) with an IQR of 4 to 12 in the EPO group and 4 to 8.5 in the DA group. During the active phase, the median number of dose changes was 2 (IQR: 1-3) in the EPO group and 2 (IQR: 0-3.25) in the DA group (Table 5).

Sensitivity Analysis

Given that the dose conversion ratio is a major variable affecting the relative costs of EPO to DA, a sensitivity analysis was performed to estimate the effect of dose conversion ratios either higher or lower than those observed in this study on this outcome (Figure 4). Compared with the observed weekly cost of EPO at 3 months ($91.79, standard error: $9.79) and 6 months ($85.25, standard error: $10.37), a cost advantage for EPO is not expected unless the observed EPO:DA dose conversion ratio falls below 150:1. At dose conversion ratios greater than 275:1, DA has a definitive lower weekly cost.

The cost used in this study was list cost of $0.0142/unit for EPO and $2.68/μg for DA which provides cost parity at a dose conversion ratio of 200:1. ESA cost varies significantly from region to region due to pricing agreements and contracts. The dose conversion ratio results in this study could be used to determine price parity in any jurisdiction using local costs today or in the future.

Discussion

An open-label, parallel-group, randomized controlled trial of 50 hemodialysis patients with cost as an outcome was

Table 3. Comparison of Total ESA Cost and Anemia Indices During Active Study Phase.

	Epoetin (n = 24)	Darbepoetin (n = 26)	*P* value
Total ESA cost, $, median (IQR)	4178.70 (2416.37-5955.12)	2302.92 (1177.86-4218.93)	.02[a]
Hb, g/L, median (IQR)	108.0 (106.0-112.7)	109.8 (105.9-116.1)	.34[a]
Ferritin, µg/L, mean ± SD	847.58 ± 272.88	726.29 ± 377.13	.20[b]
TSAT, %, median (IQR)	26.71 (22.46-32.33)	28.58 (23.90-33.75)	.47[a]
Iron dose, mg (weekly), median (IQR)	40.36 (20.83-59.90)	41.67 (19.53-70.96)	.99[a]
Total iron cost, $, median (IQR)	726.56 (375.00-1078.13)	750.00 (351.56-1277.34)	.99[a]

Note. ESA = erythropoiesis-stimulating agent; IQR = interquartile range; Hb = hemoglobin; TSAT = transferrin saturation.
[a]Mann-Whitney *U* test.
[b]Independent samples *t* test.

Table 4. Weekly ESA Dose at Months 0, 3, 6, and 12 of Active Study Phase.

	Epoetin (units)	Darbepoetin (µg)
	n = 24	n = 26
Month 0		
Median (IQR)	6000 (4000-8000)	20 (15-30)
Mean ± SD	6292 ± 3701	30 ± 29.6
Month 3		
Median (IQR)	6000 (3750-8000)	18.3 (10-30)
Mean ± SD	6514 ± 3419	26.3 ± 26.8
Month 6		
Median (IQR)	6000 (3375-8000)	16.3 (9.6-30)
Mean ± SD	6368 ± 3374	24 ± 23.1
Month 12		
Median (IQR)	6125 (3542-8729)	17.9 (8.9-32.8)
Mean ± SD	6486 ± 3498	24.5 ± 23.6

Note. ESA = erythropoiesis-stimulating agent; IQR = interquartile range.

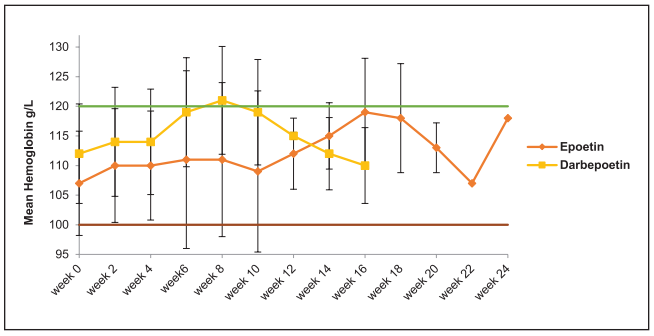

Figure 2. Mean hemoglobin (±SD) run-in phase.

conducted to compare IV EPO with DA. In this group of hemodialysis patients with comparable anemia management between arms, DA cost $1876 less per year per patient than EPO. The dose conversion ratio was 360:1 at 3 months and 382:1 at 6 months.

To date, most studies in this area have been preconversion and postconversion comparisons with limited applicability due to the lack of a control group and the inability to account

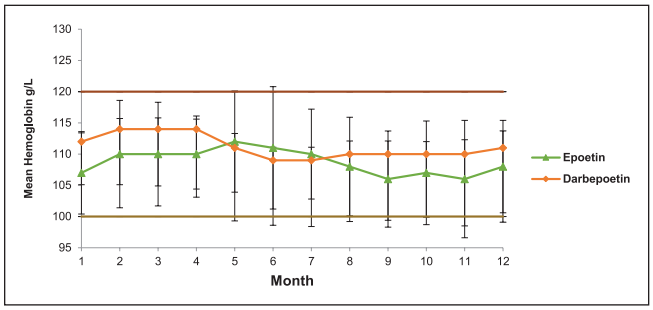

Figure 3. Mean hemoglobin (±SD) active phase.

Table 5. Median Number of Dose Changes and Weeks to Dose Stabilization.

	Epoetin	Darbepoetin	*P* value[a]
Number of dose changes run-in phase, median (IQR)	0 (0-1.75)	0 (0-0.25)	.38
Number of weeks to stable Hb, median (IQR)	4 (4-12)	4 (4-8.5)	.43
Number of dose changes active phase (median, IQR)	2 (1-3)	2 (0-3.25)	.84

Note. IQR = interquartile range; Hb = hemoglobin.
[a]Mann-Whitney *U* test.

for the tendency of ESA requirements to change in populations over time. This study was a randomized controlled trial with a number of strengths including a run-in period for dose stabilization, inclusion of only hemodialysis patients, IV ESA administration only, and the use of a standard validated algorithm for ESA and iron dosing. The study algorithm was developed using current Canadian guidelines at the time of the study[2,31] and had been in use in this dialysis center since 2009. The dose conversion ratio of epoetin:darbepoetin has been extensively studied, and while most often found to be higher than 200:1, there is much variability reported. It is generally agreed that predicting the dose conversion ratio is key to determining the relative cost of these agents. The 200:1 ratio was used to switch patients in this study from EPO to DA recognizing that it was likely a generous starting point and patients were closely monitored during the run-in

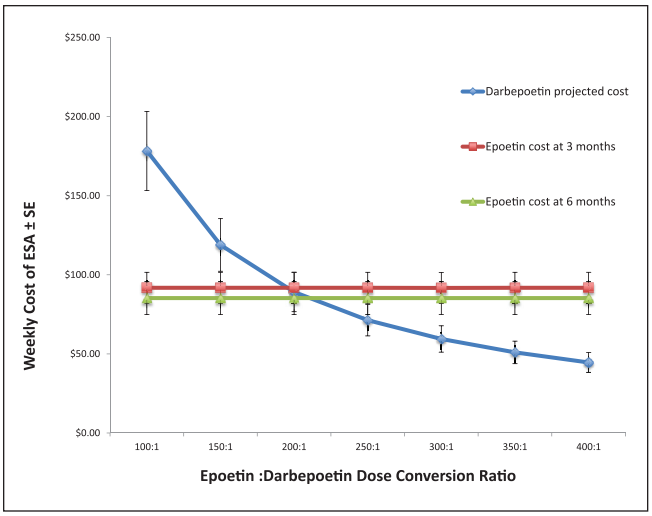

Figure 4. Sensitivity analysis of costs with varying dose conversion ratios.
Note. ESA = erythropoiesis-stimulating agent.

phase for required dose changes. The dose conversion ratio was calculated at the end of the run-in phase and at the 3- and 6-month points of the active phase. The rationale for the 6-month measure is based on previous studies and the half-life of red blood cells that suggest it requires 5 to 6 months for patients to achieve a stable dose with DA.[10,24] At all 3 points, the mean dose conversion ratio was greater than 200:1 and it increased beyond 350:1 as the study progressed supporting a cost advantage for DA over EPO. The finding also supports the ideas that DA dose requirements decrease over time when an initial 200:1 ratio is used to convert from IV EPO to IV DA and that dose stabilization after switching ESAs requires several months.

To validate the primary outcome data, it was important to determine whether achieved anemia targets and iron dosing were different between the 2 groups. There was no statistically significant difference in any of these measures. In addition, there was no difference found in the number of dose changes between the groups throughout both phases of the study.

The study had several limitations. The planned number of patients was not recruited. The most common reasons for exclusion were an inability to comprehend and sign the consent document, intention to move to another center, or intolerance to sodium ferric gluconate. The eligible population had a high proportion of elderly patients with multiple comorbidities who were unable to consent. This province has many rural satellite hemodialysis units, and while most initiate dialysis in the urban study center, they could not be enrolled as they intended to relocate to a satellite as soon as space permitted. The use of one iron product in all patients ensured a standard approach and eliminated a potential confounder, but excluded patients who could only tolerate alternate products. Thirty-four of the eligible patients declined to participate. Incomplete follow-up occurred in 8 patients, and the last available month's data were carried forward to the end and used in the analysis. This approach would likely create a bias favoring EPO as the doses of DA would be expected to decrease further as time went on considering the increasing dose conversion ratio throughout the study. The exclusion of patients with ESA resistance and iron intolerance as well as those who could not consent could impact the generalization of the results. Proponents of observational switch studies argue that the results are more applicable to the "real-world" scenario than a randomized trial with inclusion and exclusion criteria. In patients with ESA resistance and iron intolerance, DA could potentially offer a further cost advantage as there is evidence in the literature to support a higher dose conversion ratio at higher doses of EPO.[8,32,33] Specific measures of inflammation were not collected in this study; however, the exclusion criteria were designed to prevent the enrollment of patients with significant inflammatory processes and subsequent ESA resistance, and the randomization process would avoid significant differences between the 2 groups. As a predefined dosing algorithm with standard dosing was used in this trial, the results may not be generalizable to hemodialysis units without this approach to anemia management. This study was solely in hemodialysis patients receiving ESAs intravenously, and the results may not be the same in the nondialysis CKD population or in groups where ESAs are administered subcutaneously. The cost used in this trial was of drug acquisition only. A Canadian study of non-acquisition costs associated with ESA administration demonstrated a cost savings with the less frequent administration required by DA.[34] A comparison of nonacquisition costs coupled with the drug cost outcome in our study would provide a more accurate picture of total cost savings; however, there are no data to suggest that nonacquisition costs would negate the results of this study. Finally, the 200:1 ratio used to switch from EPO to DA was likely conservative based on previous literature, and subsequently, the dose requirements decreased progressively over time for the DA group. If a higher ratio such as 250:1 was used, there may have been less of a difference in the dose conversion ratio over the 12-month study period, but it would have resulted in an even larger difference in the primary outcome of cost.

This study took place between 2011 and 2013 with an anemia management algorithm based on the 2008 Canadian Society of Nephrology (CSN) guidelines.[2,31] These recommended that ESAs should be initiated when Hb is below 100 g/L with an acceptable target range of 100 to 120 g/L, and that iron should be administered to maintain serum ferritin >200 µg/L and TSAT >20%, considering the risk and benefit of continuing iron when serum ferritin is >800 µg/L. In 2012, KDIGO (Kidney Disease: Improving Global Outcomes) Anemia Work Group published clinical practice guidelines[35] for anemia management which recommend ESA initiation when Hb is between 90 and 100 g/L, to avoid falling below 90 g/L and not to maintain Hb above 115 g/L.

Iron is recommended if an increase in Hb is desired and the TSAT is ≤30% and ferritin is ≤500μg/L, but not to administer iron if ferritin is consistently >500μg/L. Subsequent CSN commentary on the KDIGO guidelines supported initiating ESA when Hb is 90 to 100 g/L but further defined an acceptable range of 95 to 115 g/L (target: 100-110 g/L) and stated that TSAT ≤20% and ferritin ≤200 μg/L are the strongest indicators for iron therapy.[36] Subsequently in following the CSN commentary, Hb targets are 5 g/L lower today than at the time of this study while the approach to iron management is essentially unchanged. A continued reduction in Hb targets over time has resulted in less aggressive ESA dosing. A US study demonstrated decreasing ESA doses between 2010 and 2013 with a change in weekly EPO dose from 9092 units to 7204 units and a decrease in monthly DA from 163 to 100 μg.[37] Similarly, in the study hemodialysis unit, there was a reduction in mean EPO dose as the 2008 CSN guidelines were fully implemented with a mean weekly EPO dose of 10 266 units, 8865 units, and 7714 units in 2008, 2009, and 2010, respectively. The ESA dose is an important consideration in this study as evidence has demonstrated that the dose conversion ratio between DA and EPO increases at higher doses. A combined analysis of 3 studies in dialysis patients found that the linear relationship between epoetin and darbepoetin doses becomes curvilinear at higher doses of epoetin, particularly above 7000 units weekly when less darbepoetin was required than a 200:1 ratio would predict. The ratio was found to continue to increase with higher epoetin doses.[8,32,33] In our study, the median EPO dose at baseline was 6000 units in both groups (Table 2). The median weekly doses throughout the study ranged from 6000 to 6125 units for EPO and from 16.3 to 20 μg for DA (Table 4). While an Hb target of 95 to 115 g/L would potentially result in lower doses overall for both EPO and DA, the study doses were sufficiently conservative (EPO <7000 units weekly) that the dose conversion ratio and the cost differential results would likely be similar today. In addition, the CSN commentary of 2012 resulted in iron protocols that are very similar to those based on the CSN 2008 guidelines with a continued focus on TSAT ≤20% and ferritin ≤200 μg/L, and it would be unlikely that ESA doses would be significantly different as a result of changes in iron management.

Conclusions

The vast majority of hemodialysis patients receive ESAs for anemia management, and it is a costly component of care. ESA drug cost is directly related to dosage, and even small differences in potency per unit cost of ESA can translate into large cost savings. In this study in a Canadian hemodialysis center, DA cost significantly less per patient per year than EPO and the dose conversion ratio was determined to be greater than 350:1 providing evidence for a cost advantage with IV DA compared with IV EPO. Although local costs may vary, the dose conversion ratio results can be applied to compare price parity in any region. This will be useful in the future consideration of the relative cost of emerging biosimilar ESA agents.

Ethics Approval and Consent to Participate

This study was approved by the Health Research Ethics Authority of Newfoundland and Labrador. Written, informed consent was obtained from each patient.

Consent for Publication

All authors provided consent for the publication of this work.

Availability of Data and Materials

Contact the corresponding author for further information on the data. Data is currently being used for secondary analyses.

Authors' Note

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Author Contributions

Research idea and study design: SWM, ALW; data acquisition: ALW; statistical analysis/interpretation: ALW, SWM; supervision/mentorship: SWM, BMC, BJB. Each author contributed important intellectual content during manuscript drafting and revision and accepts accountability for the overall work.

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Supplementary Material

Supplementary material is available for this article online.

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