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Use of darbepoetin alfa in the treatment of anaemia of chronic kidney disease: clinical and pharmacoeconomic considerations

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Abstract

The introduction of erythropoiesis-stimulating agents (ESAs) into everyday clinical practice has greatly improved the care of patients with chronic kidney disease. ESAs have reduced the need for blood transfusions, improved survival, decreased cardiovascular complications and enhanced patient quality of life. The longer acting ESA, darbepoetin alfa (Aranesp®), which can be administered less frequently than traditional ESAs, provides further benefits to both patients and healthcare professionals relative to the epoetins. Clinical studies have shown that darbepoetin alfa administered once every 2 weeks or once every month allows enhanced convenience and cost savings with no compromise in efficacy, while maintaining patients within target haemoglobin ranges.

Keywords: anaemia correction; chronic kidney disease; erythropoiesis-stimulating agents; pharmacoeconomics

Introduction

Anaemia in patients with chronic kidney disease (CKD) is a common complication that has been associated with poor outcomes such as cardiovascular complications and mortality [1,2]. Erythropoiesis-stimulating agents (ESAs) have been available for almost two decades and remain the central strategy for the treatment of anaemia in patients with CKD. The use of ESAs in the management of renal anaemia has been shown to improve survival, reduce cardiovascular morbidity and enhance quality of life [3–7]. In the last 2 years however, new studies have called into question the safety of treating patients to higher haemoglobin (Hb) levels after patients treated to Hb targets >13 dL had a greater risk of cardiovascular events (CREATE [8], CHOIR [9] and an accompanying meta-analysis [10]). Subsequently prescribing information for ESAs has been updated to recommend a target Hb range of 10–12 g/dL for all patients [11–14]. A recently published secondary analysis of the CHOIR study [15] suggests that high doses of epoetin alfa, rather than high Hb targets, were the culprit for the increased risk of poor outcomes. The ongoing randomized Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT) is anticipated to add further clarity to this issue [16,17].

Thus, anaemia management is rapidly evolving, as new trial designs and an increasing number of treatment options continue to advance the understanding of Hb control in patients with CKD. Clearly, maintaining patients within target Hb ranges is more important than ever, and the ability of ESAs to contribute to Hb control will be under new scrutiny. Darbepoetin alfa, the first ESA to offer extended dosing intervals over the erythropoietin molecules, epoetins alfa and beta, has played an important role in enhancing anaemia management. In this review, we will explore the clinical and economic considerations for the use of darbepoetin alfa in the treatment of anaemia in CKD patients.

Dosing frequency

Currently approved dosing intervals for ESAs in the treatment of renal anaemia are shown in Table 1 [11–14,18–20]. Darbepoetin alfa is indicated for less frequent administration than the epoetins/epoetin biosimilars. Table 2a summarizes the evidence from clinical studies supporting the efficacy and safety of darbepoetin alfa administered once every 2 weeks (Q2W) and once every month (QM) in patients with CKD not on dialysis [21–28]. In Table 2b, studies supporting darbepoetin alfa once weekly (QW) and Q2W regimens in patients on dialysis are summarized [29–33]. Patients receiving epoetin twice weekly (BIW) or three times weekly (TIW) can be converted to darbepoetin alfa administered QW, while those receiving epoetin QW can be converted to darbepoetin alfa administered Q2W [12]. A darbepoetin alfa QM dosing interval is recommended in patients not on dialysis who are already stable on darbepoetin alfa Q2W [12].

Less frequent dosing intervals, Q2W and QM, have also been approved for pegylated epoetin beta based on recently reported studies in patients not on dialysis and on dialysis [34–37].

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Table 1. Approved European Union dosing intervals with ESAs for CKD patients

	3×/2× weekly	Once weekly	Every 2 weeks	Once monthly
Epoetin alfa (Eprex®) [11]	✓	–	–	–
Epoetin alfa biosimilars (Abseamed®, Binocrit® or Epoetin alfa HEXAL®) [18–20]	i.v. only	i.v. only[a]	–	–
Epoetin beta (NeoRecormon®) [13]	✓	s.c. only	s.c. only	–
Pegylated epoetin beta (MIRCERA®) [14]	–	–	✓[b]	✓[c]
Darbepoetin alfa (Aranesp®) [12]	–	✓	✓[d]	s.c. only[e]

[a]For maintenance only.
[b]For correction only.
[c]In pretreated patients only.
[d]For maintenance in haemodialysis patients and correction in patients not on dialysis (s.c.).
[e]For maintenance in patients not on dialysis (s.c.).
i.v., intravenous; s.c., subcutaneous.

Route of administration

The preferred route of administration for ESAs to CKD patients who are not on dialysis is via the subcutaneous (s.c.) route because of a lack of readily available intravenous (i.v.) access [6]. However, it is worth noting that there have been fewer reported incidences of pure red cell aplasia following administration of epoetin alfa via the i.v. route than via the s.c. route. For patients undergoing haemodialysis, the European Best Practice Guidelines (EBPG) for the management of anaemia in patients with CKD recommend that the i.v. route may be preferable for comfort and convenience, but acknowledge that this route can increase the dose requirement for epoetin alfa [6]. As shown by Kaufmann *et al.* [38] in 208 haemodialysis patients, the mean weekly epoetin alfa dose was 32% lower when administered by the s.c. route compared to the i.v. route [95.1 (±75.0) versus 140.3 (±88.5) IU/kg/week; $P < 0.001$].

In contrast to epoetin, darbepoetin alfa has similar dose requirements for both the s.c. and i.v. routes [31,39]. In a study by Vanrenterghem *et al.* [31], 522 dialysis patients who were stable on either s.c. or i.v. recombinant human erythropoietin (rHuEPO) therapy were randomized to either continue their existing treatment ($n = 175$) or receive an equivalent dose of darbepoetin alfa administered via the same route, but at a reduced dose frequency ($n = 347$). While darbepoetin alfa dose requirements were similar for the s.c. and i.v. routes, rHuEPO dose requirements were 22% lower for the s.c. versus the i.v. route. The equivalence of s.c and i.v. dose requirements for darbepoetin alfa offers greater simplicity of anaemia management for physicians relative to the epoetins since a change in administration route is less likely to necessitate dose adjustment.

Haemoglobin control

As noted above, the ability to maintain patients within target Hb ranges is of increasing interest due to concerns over a possible negative impact of high Hb levels and the well-documented negative effects of low Hb levels. As shown in Table 2a, studies of extended dosing regimens with darbepoetin alfa in CKD patients not on dialysis have shown maintenance of Hb within target range in a high proportion of patients (79–96%). High proportions of patients on dialysis also maintained Hb within the target range while receiving darbepoetin alfa at extended dosing intervals. As shown in Table 2b, in a study by Mann *et al*., 85% of patients treated with darbepoetin Q2W ($n = 1101$) maintained Hb in the target range [33]; similar proportions were observed in recent smaller studies as detailed below.

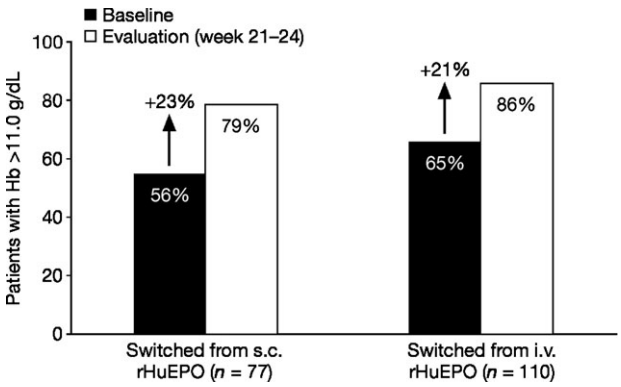

Fig. 1. Patients achieving Hb >11 g/dL after switching from recombinant human erythropoietin BIW or TIW weekly to once weekly dosing with darbepoetin alfa [40].

In a study by Carrera *et al*. [32], 105 haemodialysis patients stable on darbepoetin alfa QW were switched to darbepoetin alfa Q2W. The dose was titrated to maintain patient Hb levels between 11 and 13 g/dL. During QW dosing, 65% of patients maintained Hb levels between these values and during Q2W dosing, 81% of patients maintained Hb levels within the target range (Table 2b).

In a study by Rutkowski *et al.* [40], haemodialysis patients stable on BIW or TIW epoetin, administered s.c. or i.v., were switched to i.v. darbepoetin alfa administered QW for 24 weeks. The dose of darbepoetin alfa was adjusted to maintain patient Hb in the range 11–13 g/dL. Overall mean Hb concentrations (measured during weeks 20–24) increased following the switch to darbepoetin alfa by 0.7 g/dL and up to 23% more patients achieved a Hb concentration >11 g/dL (Figure 1).

Conversely, in a study by Biggar *et al.* [41], 90 haemodialysis patients were switched from darbepoetin alfa to epoetin beta treatment. Prior to the switch, the mean Hb concentration was 11.4 (±1.0) g/dL and the mean weekly

Table 2. Studies of darbepoetin alfa administered at extended dosing intervals in CKD patients (a) not on dialysis and (b) receiving dialysis

Panel a

Studies of CKD patients not on dialysis	Number of patients	Study design	Treatment + evaluation period	Hb target (g/dL)	Outcome
Hertel *et al.* [21]	524	rHuEPO QW → DA Q2W Multicentre	Up to 52 weeks (evaluation weeks 20–32)	≤12	Mean (SD) baseline Hb (g/dL) = 11.2 (1.27) Mean (SD) evaluation Hb (g/dL) = 11.4 (0.04)
Hertel *et al*. [22]	911	No previous ESA → DA Q2W Multicentre	Up to 52 weeks (evaluation weeks 20–32)	≤12	Mean (SD) baseline Hb (g/dL) = 9.9 (1.0) LSM evaluation Hb (g/dL) = 11.54 [95% CI, 11.47–11.61]
Toto *et al.* [23]	608	No previous ESA → DA Q2W Multicentre, open label	Up to 24 weeks	11–13	Patients in Hb target range: 96% [95% CI, 94–98]
Ling *et al.* [24]	97	DA Q2W → DA QM Multicentre, open label	29 weeks (evaluation weeks 21–29)	10–12	Patients in Hb target range: 79% [95% CI, 71–87]
Agarwal *et al.* [25]	98	DA Q2W → DA QM Multicentre, open label	29 weeks (evaluation weeks 21–29)	10–12	Patients in Hb target range, by age: <65 years: 80% [95% CI, 68–92] ≥65 years: 79% [95% CI, 68–90] ≥75 years: 80% [95% CI, 64–96]
Agarwal *et al.* [26]	152	DA Q2W → DA QM Multicentre, open-label	28 weeks (evaluation weeks 25–33)	11–13	Mean Hb ≥11.0 g/dL in 76% [95% CI, 68–83] of patients receiving at least one dose of DA Mean Hb>11.0 g/dL in 85% [95% CI, 78–91] of patients completing the study
Hoggard *et al.* [27]	442	EA Q1W/Q2W → DA QM (then preference at week 21) Multicentre, open-label	28 weeks (assessed week 21 for preference)	10–12	86% [95% CI, 79–91] of patients previously receiving EA Q1W preferred DA QM at week 21 Overall (regardless of previous EA dosing frequency), 88% [95% CI, 84–91] of patients preferred DA QM at week 21
Disney *et al.* [28]	66	Q2W → DA QM Multicentre, open-label	28 weeks (evaluation weeks 21–33)	10–13	83% [95% CI, 74–92] of patients had a mean Hb ≥10 g/dL)

(*Continued*)

Table 2. Continued

Panel b

Studies of CKD patients receiving dialysis	Number of patients	Study design	Treatment + evaluation period	Hb target (g/dL)	Outcome
Martinez Castelao *et al.* [29]	826	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre	24 weeks (evaluation weeks 21–24)	10–13	Mean change in Hb: −0.09 g/dL [95% CI, −0.2 to 0.0]
Del Vecchio *et al.* [30]	950	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively	24 weeks (evaluation weeks 21–24)	10–13	Mean change in Hb: −0.10 g/dL [95% CI, −0.18 to −0.02]
Vanrenterghem *et al.* [31]	522	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively versus continued rHuEPO Open label	52 weeks (evaluation weeks 25–32)	9–13 (and within −1.0 and +1.5 of baseline)	Mean (SE) change in Hb: DA group: −0.03 (0.11) g/dL rHuEPO group: −0.06 (0.13) g/dL
Carrera *et al*. [32]	105	DA QW → DA Q2W Single centre, open label	12 months (switch after 6 months)	11–13	Mean (SD) Hb (g/dL): Baseline: 11.75 (1.66) 6 months: 11.46 (1.6) 12 months: 11.54 (1.6) During QW dosing: 65% of patients maintained Hb levels within the target range During Q2W dosing: 81% of patients maintained Hb levels within the target range
Mann *et al.* [33]	1101	rHuEPO QW → DA Q2W Multicentre pooled analysis of eight randomized trials	24 weeks (evaluation weeks 21–24)	10–13	Mean (SD) Hb 11.53 (0.77) g/dL at baseline and 11.35 (1.04) g/dL at evaluation [mean change of −0.27 g/dL (95% CI, −0.2 to 0.34)] 85% of patients maintained Hb levels within the target range

BIW, twice per week; CI, confidence interval; CKD, chronic kidney disease; DA, darbepoetin alfa; EA, epoetin alfa; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; LSM, least squares mean; QM, every month; Q2W, every 2 weeks; QW, every week; rHuEPO, recombinant human erythropoietin (epoetin alfa or epoetin beta); SD, standard deviation; SE, standard error; TIW, three times per week.

darbepoetin alfa dose was 4335 (±3217) IU/week (using the recommended European initial equimolar dose conversion factor, 1 μg darbepoetin alfa converted to 200 IU epoetin beta) [12]. After the switch to epoetin beta, the mean Hb concentration was 11.1 (±0.9) g/dL and the mean weekly dose of epoetin beta had been increased by 13% to 4885 (±3077) IU/week. Furthermore, while 71% of the patients had a mean Hb concentration ≥11 g/dL during darbepoetin alfa treatment, following the switch to epoetin beta this figure decreased to 50%. Thus, darbepoetin alfa therapy demonstrated enhanced efficacy and a reduced dosing requirement.

As shown in these two studies, and also noted in the EBPG [6], an increased proportion of patients achieve target Hb levels after switching to darbepoetin alfa from epoetin.

Dosing efficiency

One of the principal benefits to be derived from the switch from older ESAs (epoetin alfa or epoetin beta) to darbepoetin alfa is the reduction in dose. Dose savings have been demonstrated in a number of clinical trials on switching to darbepoetin alfa QW or Q2W (Table 3) [29,39,42–48].

Tolman and colleagues studied the effects of converting an unselected, iron-replete population of dialysis patients, stable on s.c. epoetin beta TIW therapy, to s.c. epoetin beta QW or darbepoetin alfa QW, with the aid of a computerized decision-support system for anaemia management [42] (Table 3). Dose conversions were made using the 200:1 rule, as recommended by the Aranesp® European label, which states that the initial weekly dose of darbepoetin alfa (μg/week) can be determined by dividing the total weekly dose of rHuEPO (IU/week) by 200 [12]. While QW dosing with either epoetin beta or darbepoetin alfa provided adequate control of patient Hb, switching to darbepoetin alfa QW allowed a 20% dose reduction compared with a 24% increase in dose among the patients switched to epoetin beta QW (Figure 2). Following the switch, the anaemia management system continued to analyse Hb data each month, acting as a Hb 'clamp', fixing population Hb outcomes to a predictable distribution and advising on dose adjustments required to maintain mean Hb in the range 11–12 g/dL. A per-protocol analysis of patients completing the study showed similar Hb outcomes in patients switching to QW epoetin beta or QW darbepoetin alfa, both at randomization and at study end (Figure 2). However, in patients switching to darbepoetin alfa QW therapy, a significant reduction in mean dose was recorded during the course of the study (from 0.59 μg/kg/week to 0.46 μg/kg/week; $P = 0.002$), compared to a significant increase in mean dose (from 107.5 to 133.2 IU/kg/week; $P = 0.002$) in patients switching to QW epoetin beta (Figure 2). Strikingly, the mean dose of epoetin beta (133 IU/kg/week) at 9 months was 44% higher than the mean darbepoetin alfa dose (92 IU/kg/week).

Other studies have also demonstrated varying degrees of dose saving after switching from rHuEPO to darbepoetin alfa QW [43–45] (Table 3). Results from a recent meta-analysis, including the studies by Molina *et al.* [43], Nissensen *et al.* [45] and Tolman *et al.* [42], showed darbepoetin alfa to be more dose efficient when compared to rHuEPO (epoetin alfa or epoetin beta) [49]. The analysis included 250 patients on darbepoetin alfa and 372 patients receiving rHuEPO. Dose efficiency of darbepoetin alfa relative to rHuEPO was calculated to be 32% ($P < 0.0001$) for the combined studies.

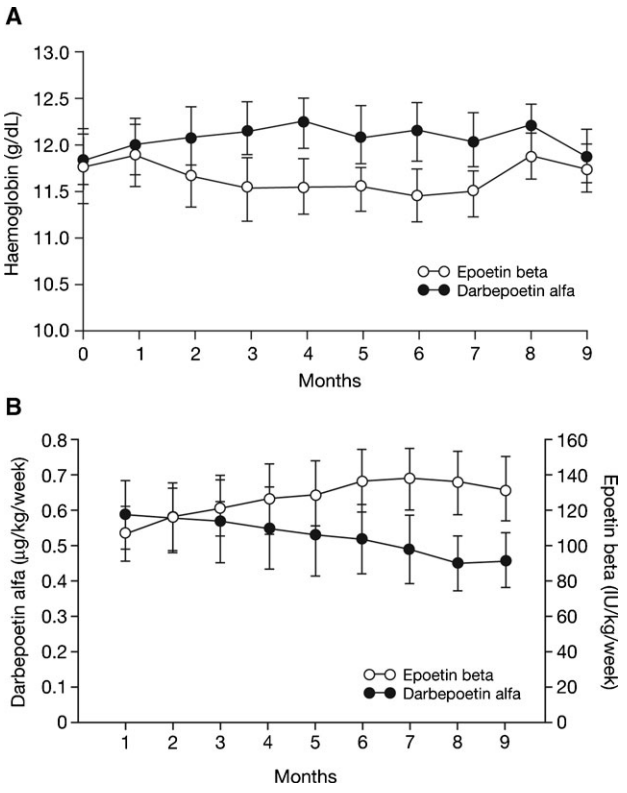

Fig. 2. Mean haemoglobin [95% confidence interval (CI)] (**A**) and mean dose (95% CI) levels (**B**) after switching from epoetin beta three times weekly to once weekly dosing with either darbepoetin alfa or epoetin beta [42].

The EFIXNES study similarly demonstrated increased dose efficiency following a switch from rHuEPO to darbepoetin alfa at extended dosing intervals [46] (Table 3). Haemodialysis patients who were stable on s.c. or i.v. rHuEPO, with mean Hb concentrations in the range 10.8–13.0 g/dL, were switched to i.v. darbepoetin alfa (those on rHuEPO TIW or BIW were switched to darbepoetin QW, while those on rHuEPO QW were switched to darbepoetin alfa Q2W). The primary endpoint, the dose of darbepoetin alfa required to maintain Hb levels within ±1 g/dL of the baseline value, was assessed over a 4-week evaluation period. Hb remained stable following the switch from rHuEPO QW to darbepoetin alfa Q2W, and there was a 25% overall dose reduction, with the greatest dose savings occurring in patients on higher initial doses. For example, while patients whose baseline rHuEPO dose was <3000 IU/week had an 8% decrease in dose upon switching to darbepoetin alfa therapy, those with a baseline dose of 7000–10 000 IU/week had a 37% dose reduction.

Other studies have also demonstrated varying degrees of dose saving after switching from rHuEPO to darbepoetin alfa QW or Q2W [29,39,47,48] (Table 3).

Table 3. Dose savings on switching from epoetin alfa or epeotin beta BIW or TIW to darbepoetin alfa QW or Q2W

Study	Number of patients	Study design	Treatment + evaluation period	Hb target range (g/dL)	Outcome
Tolman *et al.* [42]	217	EB TIW → DA QW versus EB TIW → EB QW Single centre, open label	9 months	11–12	Change in mean dose on conversion to DA: −20% (0.59 to 0.46 μg/kg/week) Change in mean dose on conversion to EB QW: +24% (107 to 133 IU/kg/week)
Molina *et al.* [43]	112	rHuEPO s.c. → rHuEPO i.v. versus rHuEPO s.c. → DA QW s.c. or i.v.	24 weeks (evaluation at weeks 8, 16 and 24)	11–13	DA group: 25% decrease in REI by week 24 rHuEPO group: 39% increase in REI by week 24
Hörl *et al.* [44]	250	rHuEPO BIW/TIW → DA QW	24 weeks (evaluation weeks 21–24)	10–13	Change in mean dose on conversion to DA: −13.3% [36.7 (95% CI 33.9–39.7) to 31.8 μg/week (95% CI 28.7–35.2)]
Nissenson *et al.* [45]	507	rHuEPO TIW → DA QW versus continued rHuEPO TIW Multicentre, double-blind	28 weeks (evaluation weeks 21–28)	9–13	Change in mean (SD) dose on conversion to DA: Decrease from 63.18 (49.27) to 54.18 (47.56) μg/week Change in mean (SD) dose with continued rHuEPO: increase from 12 706 (10 349) to 13 639 (12 805) U/week
Bock *et al.* [46]	132	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre, open-label	24 weeks (evaluation weeks 21–24)	Within ± 1 of baseline levels (10.8–13)	Change in mean DA dose: −25% (34.7 ± 2.1 to 26.0 ± 1.8 μg; $P < 0.0001$)
Locatelli *et al.* [39]	343	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre, open label	24 weeks (evaluation weeks 21–24)	10–13	Change in mean DA dose: i.v. group: 25.2 to 21.5 μg/ week; $P = 0.004$ s.c. group: 20.8 to 22.7 μg/ week; $P = 0.014$
Brunkhorst *et al.* [47]	1502	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre, open label	24 weeks (evaluation weeks 21–24)	10–13	Change in mean dose on conversion to DA: i.v. group: decrease from 23.23 [95% CI 22.34–24.17] to 19.92 μg/ week [95% CI 19.02–20.87] s.c. group: decrease from 22.95 [95% CI 21.90–24.06] to 21.61 μg/ week [95% CI 20.36–22.94]
Kessler *et al.* [48]	1008	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre	24 weeks (evaluation weeks 21–24)	10–13	Change in median dose on conversion to DA: i.v. group: decrease from 27.3 to 22.3 μg/week s.c. group: increase from 22.9 to 23.3 μg/week
Martinez Castelao *et al.* [29]	826	rHuEPO BIW/TIW or QW → DA QW or Q2W, respectively Multicentre	24 weeks (evaluation weeks 21–24)	10–13	Change in mean dose on conversion to DA: i.v. group: −19.7% [95% CI −24.9 to −14.2] s.c. group: −4.7% [95% CI −8.5 to −0.7]

CI, confidence interval; DA, darbepoetin alfa; EB, epoetin beta; i.v., intravenous; QW, once weekly; Q2W, every 2 weeks; REI, resistance index (weekly dose per kg/haemoglobin level); rHuEPO, recombinant human erythropoietin (epoetin alfa or epoetin beta); s.c., subcutaneous; SD, standard deviation; TIW, three times per week.

In agreement with these data, results from a study by Biggar and colleagues (discussed in the previous section [41]) demonstrated that conversion of dialysis patients from darbepoetin alfa to epoetin beta resulted in poorer control of Hb levels at equimolar doses. Following the switch, the mean Hb level decreased from 11.4 to 11.1 g/dL ($P = 0.0016$) and a 13% increase in the mean dose of epoetin beta was necessary in order to maintain Hb $\geq$11 g/dL. These findings are supported by further studies by Carrera *et al.* [50] and Orazi *et al.* [51], which showed that converting from darbepoetin alfa to epoetin alfa (Orazi *et al.*) or epoetin beta (Carrera *et al.*) led to a decrease in the Hb level, with an increase in epoetin dose.

Cost efficiency

In addition to the greater convenience that extended dosing intervals bring to both patients and healthcare staff, the use of longer acting agents such as darbepoetin alfa may also yield significant increases in cost efficiency, based on European clinical practice patterns. Studies in various countries within Europe have demonstrated improvements in cost and operational efficiency following a switch from epoetin alfa to darbepoetin alfa therapy [52–55]. In addition, the MERCURIUS project, which is ongoing in 13 European countries, is expected to yield information on how improvements could be made in ESA delivery and utilization in hospitals throughout Europe [56].

In a UK study [52], 82 haemodialysis patients, stable on s.c. epoetin alfa (administered BIW or TIW), for $\geq$6 months prior to the study, were converted to i.v. darbepoetin alfa QW or Q2W using the 200:1 initial dose conversion rule. Following the switch, there was an increase in the mean Hb concentration and an increase in the proportion of patients meeting the EBPG Hb target range. There was also a significant decrease in the cost of ESA therapy (calculated from costs published in the British National Formulary), which more than offset a modest increase in the use of iron (from £4.82/patient/week with epoetin alfa to £5.55/patient/week with darbepoetin alfa). While the average cost of epoetin alfa therapy was £62/patient/week, the cost for darbepoetin alfa therapy was £48/patient/week—a 23% reduction per patient resulting in a £75 000 yearly saving for the dialysis unit. Furthermore, this figure does not take into account further potential savings in drug preparation and administration costs resulting from less frequent dosing with darbepoetin alfa compared with epoetin alfa.

Similarly, in a Spanish study, 34 haemodialysis patients, stable on i.v. rHuEPO QW, BIW or TIW, were switched to i.v. darbepoetin alfa therapy (using the 200:1 dose conversion factor) and dose adjustments were made to maintain Hb concentrations close to 12 g/dL [53]. Treatment cost was calculated from both the ESA drug acquisition cost and the nursing cost related to drug administration. As shown in Table 4, the mean ESA dose fell from 11 081 IU/week with rHuEPO (equivalent to 55.4 μg/week darbepoetin alfa) to 35 μg/week after 6 months ($P < 0.001$), with a saving of €146.22 per patient/month (cost reduction of 36.5%).

A third study conducted in Italy found that, for 61 evaluable patients switched from i.v. epoetin beta to i.v. darbepoetin alfa QW, there were cost reductions of €570–710 per patient per semester [54].

Table 4. Increased cost efficiency on switching from epoetin alfa or epoetin beta treatment to darbepoetin alfa therapy in Spanish haemodialysis patients ($n = 34$)

	rHuEPO	Darbepoetin alfa		
	Baseline	1 month	3 months	6 months
Mean weekly dose	11 081 IU	50 μg*	39 μg*	35 μg*
Mean dose/ patient/month	44 324 IU	202 μg	157 μg	141 μg
Mean drug cost/ patient/month	€398.92	€360*	€282.89*	€254.12*
Mean nursing cost/ patient/month	€1.98	€0.70	€0.49	€0.56
Mean total cost/ patient/month[a]	€400.90	€360.7*	€283.38*	€254.68*

Data from Ardevol *et al.* [53], reprinted with permission from Pharma Publishing and Media Europe. Copyright 2006. All rights reserved.
rHuEPO, recombinant human erythropoietin.
[a]Drug plus nursing time costs.
*$P < 0.05$ versus rHuEPO.

In view of these highly promising data, further studies in large patient cohorts will be required to more clearly determine the potential cost reductions associated with the switch from older ESAs to darbepoetin alfa therapy in individual countries.

In addition to economic savings, the switch from epoetins to longer acting agents should also result in valuable time savings for healthcare staff. A time and motion study conducted at five dialysis centres in Sweden has provided a useful indication of likely gains [55]. The time taken by healthcare personnel to carry out various activities associated with the administration of epoetin alfa, epoetin beta and darbepoetin alfa was recorded. Activities included review of medical records to obtain the correct dose, retrieval of drugs from the refrigerator and preparation for injection, injection of the drug, drug ordering from the pharmacy, receipt and unpacking of drugs from the pharmacy and waste management. A total of 342 patients receiving ESA treatment at various dosing intervals (44% QW, 23% BIW, 24% TIW and 9% at other dosing intervals) were included in the study. The average time taken for ESA management per dialysis session was 3 min (range 93–226 s). The average time spent per patient per year was 4.7 h, and the average time taken per centre per year was 319 h (range 55–586 h). Time savings with Q2W dosing were estimated compared to other dosing intervals. With Q2W dosing the estimated average time spent on ESA management per patient per year was 1.3 h—a saving of 3.4 h per year compared with the current dosing intervals. However, large variations in time spent were observed, depending on the size of the dialysis centre. In addition, the estimated average time per centre per year was 89 h (range 23–133 h)—a saving of 230 h compared with the current dosing intervals. While further large-scale international studies are required to more fully assess the impact of extended ESA dosing intervals on healthcare resource utilization in the management of anaemic CKD patients, these data suggest that the more

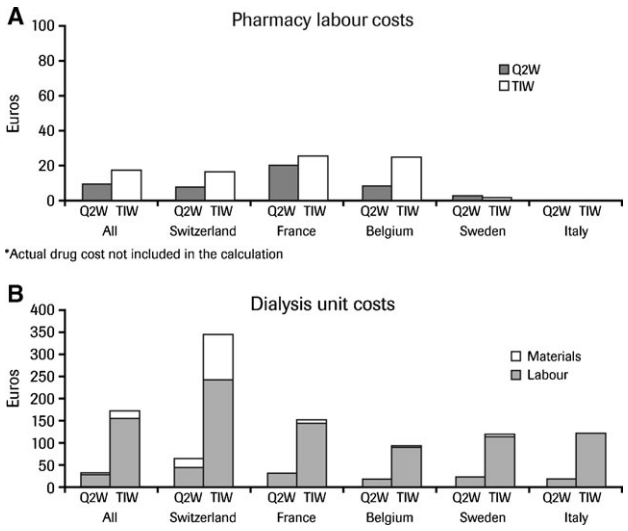

Fig. 3. The MERCURIUS study: overall and by country cost per patient per year* after switching from rHuEPO TIW to darbepoetin alfa Q2W. (**A**) Pharmacy labour costs; (**B**) dialysis unit materials and labour costs [56].

widespread use of longer acting agents in certain situations could provide economic benefits.

The MERCURIUS project, now underway in 13 European countries, should provide a clearer picture of the benefits of extended ESA dosing intervals in CKD patients undergoing haemodialysis. This study, taking a much broader view than the Swedish time analysis, aims to characterize the whole process of ESA delivery at each study centre, from initial drug ordering to the disposal of waste product. MERCURIUS will also evaluate the impact of changing from current ESA dosing frequencies to Q2W dosing with darbepoetin alfa. When available, its findings should yield useful recommendations on how hospitals can improve operational efficiency, including improved ESA utilization. Preliminary data collected by Burnier *et al.* [56] from eight centres in five European countries have estimated mean costs for various activities associated with ESA administration. By using a fixed Q2W dosing schedule, Burnier *et al.* estimated a mean reduction in cost of 25% in pharmacy labour and 64% in dialysis unit labour. Figure 3 shows the cost per patient per year overall and individually in five countries; pharmacy labour costs, as well as dialysis unit materials and labour costs, were reduced after switching to darbepoetin alfa Q2W from epoetin TIW. Other potential benefits of less frequent dosing include less waste from packaging and cooling elements for transport, reduced risk of needle stick injuries for medical staff and reduced potential for incorrect dosing. It is hoped that the results of MERCURIUS will allow the setting of benchmarks and the sharing of best practice between European dialysis centres.

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