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A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis

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Abstract

Background. Erythropoiesis-stimulating agents (ESAs) such as epoetin alfa and beta, and darbepoetin alfa have improved the management of anaemia secondary to chronic kidney disease. Numerous studies have reported a dose reduction when patients receiving dialysis were converted from epoetin to darbepoetin alfa using the starting dose conversion of 200:1 as indicated on the prescribing label by the European Medicines Agency. The objective of this meta-analysis was to summarize the existing body of scientific evidence to evaluate the potential dose savings when comparing epoetin alfa or beta to darbepoetin alfa.

Method. Medline and EmBase were searched to identify all published trials investigating ESA treatment in anaemic patients receiving dialysis and converted from epoetins to darbepoetin alfa. We selected prospective randomized controlled, non-randomized and observational studies involving patients on dialysis that compared epoetin and darbepoetin alfa dosing.

Results. Of 573 articles identified, 9 studies met the eligibility criteria and were included in our analysis. The overall percentage dose savings attained when dialysis patients were converted from epoetin to darbepoetin alfa was 30% (range: 4%–44%). Greater dose savings were noted with intravenous administration (33%) compared with subcutaneous (27%) and between switch-over studies (31%) and RCTs (27%). In all studies, target haemoglobin levels were maintained before and after conversion.

Conclusion. This meta-analysis demonstrates that when using an initial 200:1 conversion ratio, as indicated on the European label, from epoetin to darbepoetin, a subsequent reduction in dose was observed and an average 30% dose savings could be achieved.

Keywords: darbepoetin alfa; dialysis; dose savings; epoetin; meta-analysis

Introduction

Anaemia is a common consequence of chronic kidney disease (CKD) because of the inability of the kidney to produce enough erythropoietin to stimulate the production of red blood cells [1]. This deficiency results in lower haemoglobin (Hb) levels and oxygen availability [2]. Several studies have demonstrated that erythropoiesis (and subsequent increase in Hb levels) can be stimulated by administering recombinant erythropoiesis-stimulating agents (ESA) such as epoetin alfa, epoetin beta and darbepoetin alfa [3–5].

Frequency of dosing, route of administration and treatment phase have been identified as important factors for the optimal management of anaemia. The first studies of ESA treatment in patients with CKD focused on intravenous therapy given three times weekly [6]. Subsequent data, however, indicated that ESAs given subcutaneously can achieve the same therapeutic targets with lower epoetin dosages in patients undergoing haemodialysis (HD) [7]. Blood levels of darbepoetin alfa remain above the minimum erythropoeisis-stimulating concentration about three times longer compared with equivalent doses of epoetin alfa and epoetin beta resulting in the same biological response achieved with ESAs administered over a shorter time interval [4,8,9]. Clinical studies have shown that target haemoglobin levels can also be maintained through subcutaneous administration of epoetin once weekly (QW) or once every 2 weeks (Q2W) [10–13]. Currently, there is still much debate regarding the optimum route of administration and frequency of ESA dosing.

When switching patients receiving HD from epoetin alfa or beta to darbepoetin alfa, it has been reported in several studies that when using an initial conversion ratio of 200:1, target Hb values can be maintained and a dose saving can be achieved [14–17]. The initial conversation ratio (200:1) follows the indication on the European label for the treatment of renal anaemia and achieves satisfactory Hb target

ranges for patients converting from epoetin alfa or beta to darbepoetin alfa [18].

Extending the dosing schedule from QW to Q2W may save time for both healthcare professionals and patients and may reduce costs associated with anaemia treatment [19–22]. The objectives of this meta-analysis were to evaluate the relative dose savings in patients undergoing dialysis and switched from epoetin alfa or beta to darbepoetin alfa using the European-recommended initial conversion ratio of 200:1, and to assess the dose savings by administration route and frequency of dose.

Methods

Literature search

The search for this analysis was carried out by an experienced librarian and in accordance with the principles of evidence-based medicine. A search strategy was developed to identify all published trials investigating ESA treatment in anaemic patients receiving dialysis searching Medline and EmBase from the time of their initiation (i.e. 1950 and 1980, respectively) through December 2007. Only peer-reviewed articles in English, French, German, Spanish, Italian and Portuguese were searched. The following search items were included: erythropoietin, erythropoiesis, haematopoietin, epoetin, darbepoetin (including all brand names of drugs of interest), darbepoetin alfa, kidney failure, chronic renal disease, end-stage renal disease (ESRD), renal or haemodialysis or peritoneal dialysis, drug doses and year of publication. A second search was also performed, using the same search terms, by a research associate to verify and confirm the results of the first search.

Selection of studies

Studies selected for inclusion were required to have compared the efficacy of epoetin alfa or beta and darbepoetin in a direct comparison (i.e. head-to-head) or in a switch-over fashion, irrespective of duration of treatment. In addition, the studies were required to have only adult patient population ($\geq$18 years); anaemic patients with ESRD/chronic renal disease; patients who were undergoing dialysis (haemodialysis or peritoneal); information regarding average patient doses of epoetin and darbepoetin (i.e. endpoints for the different treatment arms or baseline for a switched arm if the endpoint prior to switch was not available). No minimum period of dialysis was required. All included articles had to describe prospective, randomized controlled, non-randomized or observational studies. The studies could be open-label or blinded, parallel-group, single-arm switch-over or cross-over.

Studies excluded from assessment were those that did not report treatment type or route of administration, did not report epoetin dose or mean dose, or evaluated diseases or treatments other than those targeted. Furthermore, we excluded studies that reported doses as median or geometric mean. The exclusion criterion for the geometric mean dose was statistical in nature in that the arithmetic mean has an associated standard deviation (SD) that could be used for standard meta-analytic methods (see quantitative data synthesis section), whereas the geometric mean does not have an SD reported. Case reports, retrospective studies, letters to the editor, comments, abstracts and review papers were also excluded from the analysis.

Validity assessment

After completion of the search, the articles were assessed for suitability. Article selection and data extraction were performed by two independent reviewers. Reviewers initially read article abstracts and reserved potential candidates based on the inclusion criteria.

The full text of each selected article was assessed, and the exclusion criteria were applied. Selected articles were then compared between reviewers, and any areas of disagreement were resolved by a third reviewer who verified all extracted data. Data extracted from selected articles included year of publication, type of study, treatment and patient characteristics, treatment efficacy, safety and dosing information. To ensure the accuracy of the data extraction, the information was entered into a spreadsheet by one assessor and cross-checked by a second independent assessor.

Quality assessment

First, the overall suitability of the included studies was assessed by using an adapted version of the MOOSE checklist for quality assessment of meta-analyses. In itself, the MOOSE approach provides a template for reporting meta-analyses of numerous types of studies, including but not limited to those following a randomized controlled trial design. The relevant components of the MOOSE approach were applied in order to draw up an overall impression of the quality of the included trials.

The quality of the selected studies was assessed using the Downs and Black approach, a previously published validated method for assessing the quality of randomized controlled trials and observational studies [23]. This method consists of 27 items grouped into different categories: reporting (10 items) whether the published information allows a clear understanding of the study results; external validity (3 items) whether the results can be generalized to a wider population of interest; internal validity/bias and confounding (13 items) whether necessary steps have been taken to minimize bias; and power (1 item) whether the power statement is sufficient. The scores were expressed as percentages with higher values indicating higher study quality.

In addition, the Jüni approach was applied to further identify biases related to the internal and external validity of selected randomized clinical trials.

Quantitative data synthesis

The primary outcome of interest was the dose difference observed between epoetin alfa or beta and darbepoetin alfa at study completion for all articles included in the meta-analysis. Secondary outcomes for clinical efficacy of the targeted treatments included haemoglobin levels at baseline and study end.

To determine relative dose savings, the observed dose ratios of the drugs of interest at the endpoint of each study (i.e. after achieving targeted haemoglobin levels) were compared to the initial dose-converting ratios following the switch from epoetin to darbepoetin alfa. We calculated dose savings by applying a formula that takes into account the recommended dose conversion rate of 200:1 approved for use by the European Medicines Agency (EMEA):

$$[100\% - \text{observed darbepoetin alfa dose}/(\text{rHuEPOdose}/200)].$$

The study results were then combined using standard meta-analysis techniques, with a weighting applied to each study based on the standard error of the treatment effect (a weighting that accounts for the variation in the treatment effect and the study size). Meta-analytic results of relative dose savings were also reported by type of study, route of administration and frequency of dose.

To calculate the mean dose saving for each study [with a respective 95% confidence interval (CI)], the variance of the ratio was obtained from Taylor's series expansion [24]. A 'pooled' mean ratio estimate (and 95% CI) was obtained using the standard meta-analytical approach for continuous data as noted above.

We also performed subgroup analysis according to baseline epoetin dose (darbepoetin alfa equivalent) and duration of treatment (darbepoetin alfa) using the same methodology as the overall analysis.

Results

Search results

Figure 1 shows the results of the search. Of the 573 items identified in the initial search, 141 articles were excluded due to duplicates and another 141 review articles were also removed from the selection. In total, 548 items were excluded based on the pre-defined exclusion criteria. Economic evaluations that did not meet eligibility criteria were excluded. Two additional articles were obtained separately through additional screening of bibliographies, as their indexing had not occurred in the databases at the time the initial search was performed. These articles were evaluated in addition to the list of 25 articles. Hence, a total of

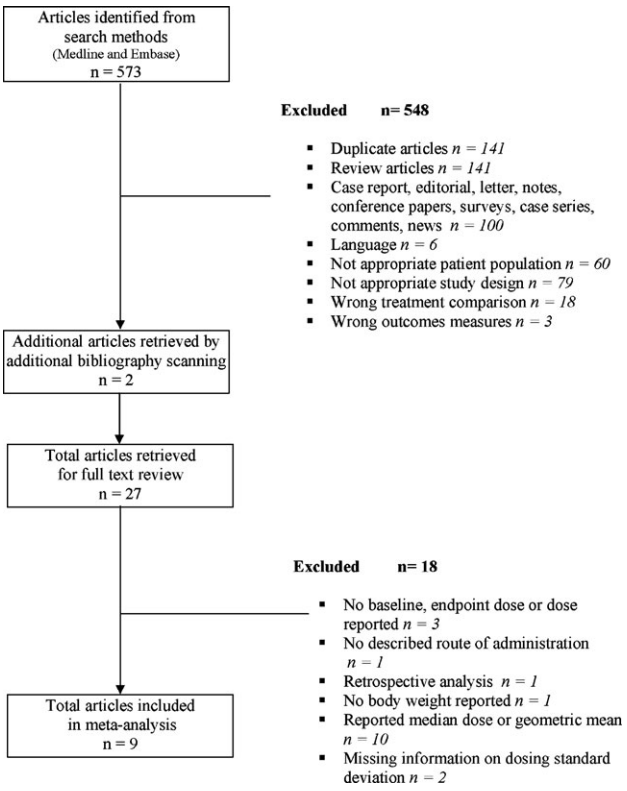

Fig. 1. Results of the literature search.

27 articles were retrieved for full-text review based on the first round of assessment for inclusion and exclusion criteria. Eighteen articles were excluded in the final assessment round; the rationale for exclusion is listed in Figure 1. Overall, nine studies were included for evaluation of primary and secondary outcomes [14–17,19,22,25–27].

Study characteristics

A total of 836 patients from eight countries were represented in the nine selected articles (Table 1). Eight of the nine selected articles were published in English; one article was published in Spanish and translated into English [26]. Of the nine studies, six were conducted in Europe, one was conducted in Australia, one in Saudi Arabia and one in North America. The majority of the selected studies ($n = 7$) used single-arm, switch-over study design (switching from epoetin to darbepoetin alfa), and two studies were randomized controlled trials.

There were a wide variety of study designs. The majority were characterized as open-label studies ($n = 7$) and single-centre studies ($n = 6$). The patients were stabilized on epoetin for various durations prior to receiving the study drug; none of the studies had a washout period before beginning darbepoetin treatment. The mean study duration was 28 weeks (range: 12–52 weeks). The route of administration was either intravenous or subcutaneous (sometimes varying in the same study). Target Hb level ranges varied from study to study (overall range: 90–130 g/L). Three studies compared the demographic characteristics of their study groups: the two randomized controlled trials found no significant demographic differences, whereas Molina *et al*. 2004 reported a heterogeneous study group population.

Six of the studies enrolled <100 patients (range: 25–51 patients) per study, and the remaining three studies contributed ~75% ($n = 623$) of the total number of patients evaluated in this analysis (Table 1). Both men and women were included in each study, and the mean age ranged from 50 to 69 years of age. Eight of the nine studies were conducted in the haemodialysis patient population and one study was conducted in the peritoneal dialysis patient population. Common aetiologies of chronic kidney disease were identified in the patient populations in seven of the nine studies: diabetes (range: 12%–33% of patients), glomerulonephritis (range: 6%–19%), and six of the nine studies reported hypertension (range: 12%–24%). One study did not report any disease states.

All studies compared epoetin alfa or beta with darbepoetin alfa. In eight of the nine studies, an initial 200:1 conversation ratio was used to convert the dose of epoetin alfa or beta to darbepoetin alfa. In the study that described the peritoneal dialysis patient population, the initial conversation ratio of 200:1 was not applied and conversion ratios varied according to the patient's haemoglobin level at the time of the switch from epoetin to darbepoetin alfa.

The mean overall study quality score was 75% when using the Downs and Black approach. The RCTs had the highest quality scores (93% and 82% for the double-blinded and non-blinded studies, respectively) although switch-over studies had a wide range of intermediate to high-quality scores (63–82%) (Table 1). In the additional Jüni assessment of the RCTs, only one bias of note was found when assessing the internal and external validity of the study by Nissensson *et al*., i.e. an attrition bias was identified since the exclusion of 82 patients from the study was not clearly explained. As for the study by Tolman *et al*., a selection bias was identified, as the generation of allocation sequences was not described and there was no concealment of allocation sequences given that it was an open-label study.

Quantitative data synthesis

When the patients were converted from treatment with epoetin to darbepoetin alfa, we noted considerable dose savings per study and a substantial overall dose savings of 30% (95% CI: 26, 33) (Figure 2). Substantial dose savings ranging from 20% to 44% were observed in eight of the nine studies (Figure 3). We also observed similar dose savings in the same eight studies regardless of the length of the study. The one study that did not demonstrate the same dose savings (4%) as the other eight studies also did not use the initial conversation factor of 200:1 [26].

Similar dose savings were observed in the RCTs (27%) compared with the switch-over studies (31%), although there were significantly fewer RCTs ($n = 2$) evaluated in this analysis (Table 2). Larger dose savings were observed with intravenous to intravenous administration (33%) relative to subcutaneous to subcutaneous administration (27%). Furthermore, Q2W dosing resulted in a smaller percentage of dose savings (17%) compared with QW (27%) (Table 2).

Hb values during the epoetin treatment period were reported in all nine studies, whereas the Hb values during the

Table 1. Characteristics of the nine articles included in the meta-analysis

Study	Country	Study design	Number of patients	Route of administration	Baseline epoetin dose[a]	Study duration (weeks)	% Dose savings by study duration duration (95% CI)	Quality Q score (%)
Ardevol *et al*. [22]	Spain	Switch	34	IV to IV	11 081	24	36.31 (22.45–50.16)	70.4%
Bock *et al*. [14]	Switzerland	Switch	100	IV or SC to IV	6 940	24	25.10 (15.99–34.22)	81.5%
Icardi *et al*. [25]	Italy	Switch	25	IV to IV	8 000	52	38.50 (31.45–45.55)	63.0%
Molina *et al*. [15]	Spain	Switch	51	IV/SC to IV/SC	11 998	24	23.18 (9.48–36.88)	70.4%
Nissenson *et al*. [16]	United States Canada	Randomized controlled trial	361	IV to IV	13 639	28	20.55 (10.02–31.09)	92.9%
Remón *et al*. [26]	Spain	Switch	35	SC to SC	5 892	36	4.24 (−15.18–23.67)	82.1%
Roger *et al*. [19]	Australia	Switch	37	SC to IV	10 700	12	20.93 (11.09–30.78)	70.4%
Shaheen *et al*. [27]	Saudi Arabia	Switch	31	SC to IV or SC	7 454	12	44.19 (32.30–56.08)	63.0%
Tolman *et al*. [17]	United Kingdom	Randomized controlled trial	162	SC to SC	9 017	36	32.87 (22.49–43.25)	82.1%

[a]Baseline EPO refers to the dose at the point of switch from epoetin to darbepoetin alfa or in the case of randomized controlled trials, steady-state dose value at the end of the study.

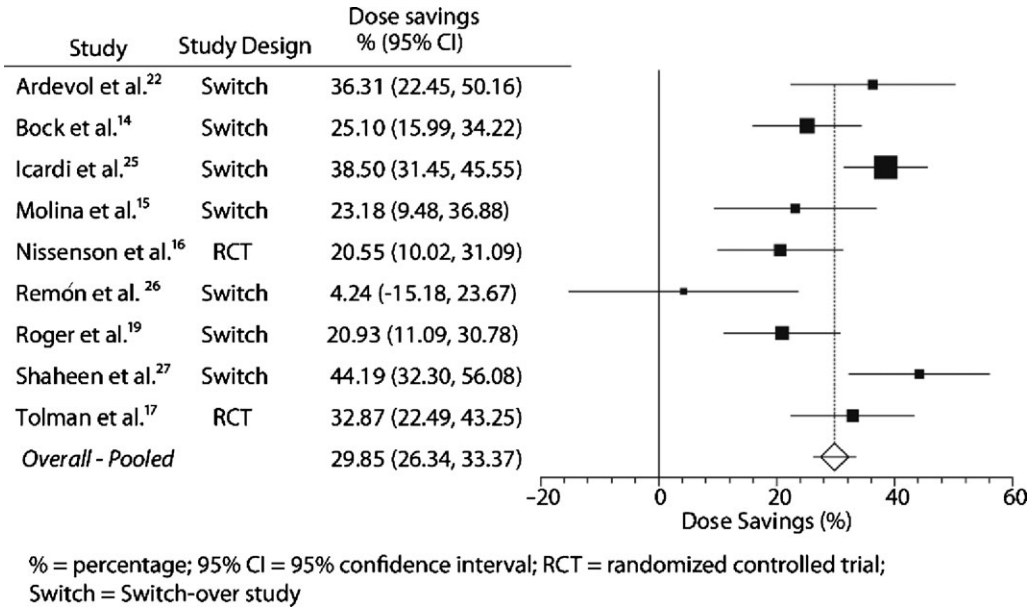

Fig. 2. Estimated dose savings for studies selected for analysis.

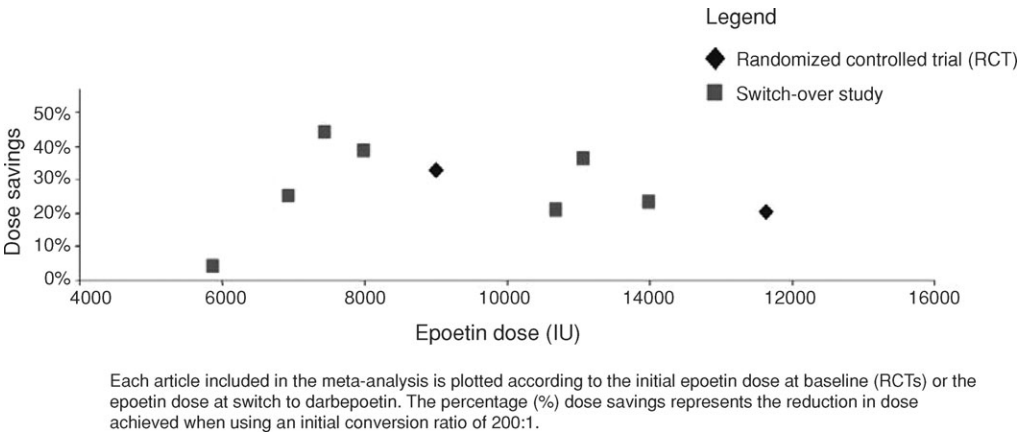

Fig. 3. Dose savings in the nine studies included in the meta-analysis.

Table 2. Overall outcomes according to study design, route of administration and frequency

Analysis type*	Subgroup	Number of studies	% Dose savings (95% CI)
Overall analysis	None	9	29.9% (26.3–33.4)
Analysis by design	RCT	2	26.8% (19.4–34.2)
	Switch	7	30.8% (26.8–34.8)
Analysis by route[a]	IV to IV[b]	3	33.5% (28.1–38.9)
	SC to SC[b]	2	26.5% (17.4–35.7)
Analysis by frequency	Q2W	1	17.1% (5.6–28.7)
	QW	5	27.1% (21.9–32.2)

*Analysis includes all studies ($n = 9$).
RCT = randomized controlled trial; Switch = Switch-over study; SC = subcutaneous; Q2W = biweekly.
[a]Analysis by route or frequency includes only selected studies with complete information and not mixed route of administration.
[b]The subgroup describes the studies reporting IV to IV or SC to SC.

Table 3. Mean haemoglobin values in epoetin (alfa or beta) and darbepoetin periods in all studies

Article	Hb value in the EPO period*	Hb value in the darbepoetin period*	Evaluation period of darbepoetin dose
Ardevol *et al*. [22]	12.1	12.0	At 24 weeks
Bock *et al*. [14]	11.8	11.9	Over weeks 21–24
Icardi *et al*. [25]	11.4	11.4	At 52 weeks
Molina *et al*. [15]	12.4	Not reported	At 24 weeks
Nissenson *et al*. [16]	11.2	11.4	Over weeks 21–28
Remón *et al*. [26]	12.0	12.0	At 36 weeks
Roger *et al*. [19]	12.2	12.4	At 12 weeks
Shaheen *et al*. [27]	11.6	Not reported	At 12 weeks
Tolman *et al*. [17]	11.5	11.9	At 36 weeks

Haemoglobin values are expressed in g/dL.
EPO = epoetin alfa or beta (depending on the study).
Haemoglobin = Hb.
*Values are reported as the arithmetic mean.

darbepoetin treatment period were only reported in seven studies (Table 3). Overall, Hb values were similar between the end of the epoetin phase and the end of the darbepoetin phase for each study. In addition, at the end of the darbepoetin evaluation period, Hb values were maintained within target range.

Discussion

This meta-analysis of nine clinical studies was the first to attempt to quantify dose savings when converting patients on dialysis (haemodialysis or peritoneal) from epoetin alfa or beta to darbepoetin alfa. Our findings show that when converting from epoetin to darbepoetin, dose savings are observed regardless of the type of study design, length of study time, route of administration or frequency of dose, in addition to the maintenance of target Hb levels over time after conversion.

The comparative dose savings observed in this meta-analysis of prospective studies suggest that the administration of darbepoetin alfa to patients with CKD undergoing dialysis can potentially provide on average a 30% reduction in dose when using a starting dose conversion from 200 IU epoetin alfa or epoetin beta to 1 μg of darbepoetin alfa as stated on the European label.

As we expected, RCTs had higher quality scores compared to the switch-over studies when using the Downs and Black approach. The Jüni quality assessment approach confirmed minimal biases in the internal and external validities of the RCTs. Although there were only two RCTs selected for this meta-analysis, comparable dose savings were observed overall. The longest study duration (52 weeks) had 38% dose savings, and two studies with a 12-week study duration showed 21% and 44% dose savings, respectively, demonstrating that over a wide range of times, dose savings can be achieved relatively quickly and sustained over time.

The frequency of dosing is a critical aspect to determine dose savings, and in our study we found that the dose savings for QW was higher than those for Q2W (27% versus 17%, respectively); however, this result may be due to the limited number of qualifying studies in this analysis with a Q2W dosing scheme ($n = 1$) compared to the number of QW ($n = 5$). The finding of a 17% reduction in dose should not be discounted because this reduction may contribute to an overall cost savings.

Eight articles were in the haemodialysis patient population and used the initial conversion rule of 200:1; however, one article included a peritoneal dialysis patient population and the resulting dose savings were considerably lower than those observed in the other studies. This may be a result of the dialysis patient population studied where in clinical practice lower doses of epoetin were typically used for peritoneal dialysis compared to haemodialysis. Additionally, this study used a variety of conversion ratios at the time of switching the patients from epoetin to darbepoetin; hence, not all patients were converted at an initial 200:1 ratio.

One striking finding from this meta-analysis was that there appears to be no association between baseline epoetin dose and dose savings. This finding is contrary to other results found in the literature [14,16] where high-dose savings could be observed when a high baseline epoetin dose was used before converting to darbepoetin alfa. Our results may have been due to the lack of granularity of the data (i.e. means from studies compared with individual patient level data) or the relative homogeneity of the mean doses of epoetin observed in the studies that were included in the meta-analysis.

We also found that dose savings were associated with the route of administration of epoetin. This analysis showed that although dose savings were achieved through subcutaneous administration, larger dose savings were observed in patients who received epoetin and darbepoetin via the intravenous route when compared with the subcutaneous route of administration. This could be due to the relatively larger doses of epoetin required with intravenous administration compared to subcutaneous, as reported by Kaufman *et al*. [28]. Although in this meta-analysis, dose savings were higher in haemodialysis patients when epoetin or darbepoetin alfa was administered intravenously, dose savings could also be expected when considering other published literature where there was no dose penalty observed for patients who were switched from subcutaneous to

intravenous, intravenous to subcutaneous with darbepoetin alfa, or from epoetin alfa to darbepoetin alfa while maintaining haemoglobin levels [29,30]. High-dose savings with intravenous administration coupled with no dose penalty may be one of the most significant benefits for patients, in addition to other potential cost savings.

Furthermore, these results confirm that target Hb levels are maintained when converting from epoetin alfa or beta to darbepoetin in patients receiving either peritoneal or haemodialysis. This observation suggests that if over time (the longest study evaluated in this meta-analysis was 52 weeks) target Hb levels can be achieved at lower doses of darbepoetin, then savings on drug costs are possible. Several European studies have demonstrated cost savings following the switch from epoetin alfa to darbepoetin alfa treatment [20,22]. Our study confirms that a large part of the savings results from reduced drug expenditure.

Informed by the adapted MOOSE checklist, several limitations were identified in our review of the literature. Firstly, we combined studies that utilized different designs, follow-up times, patient populations, routes and frequency of administrations of the study drugs, target Hb level ranges and sample sizes. Secondly, none of the studies had epoetin washout periods prior to administrating darbepoetin. This limitation can be explained by the fact that the study population contained seriously ill patients for whom cessation of epoetin treatment would be contrary to the Declaration of Helsinki. Thirdly, we could not control for some residual confounding factors because many of the studies that were included in our meta-analysis were non-randomized studies.

In conclusion, our analysis has shown a consistent result in the reviewed studies underlining a significant dose savings using the initial conversion ratio of 200:1, as stated on the European label, when patients are switched from epoetin alfa or beta to darbepoetin. The dose savings occurs irrespective of the route of administration, dose and time of observation, and the implications of these findings are clinically relevant to healthcare providers and payers.

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References

1. Kazmi WH, Kausz AT, Khan S *et al*. Anemia: an early complication of chronic renal insufficiency. *Am J Kidney Dis* 2001; 38: 803–812
2. Anand S, Nissenson AR. Renal anemia management in the chronic kidney disease population. *Ann Long Term Care* 2002; 10: 43–52
3. Macdougall IC, Gray SJ, Elston O *et al*. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999; 10: 2392–2395
4. Macdougall IC. Novel erythropoiesis-stimulating agents: a new era in anemia management. *Clin J Am Soc Nephrol* 2008; 3: 200–207
5. Locatelli F, Olivares J, Walker R *et al*. Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency. *Kidney Int* 2001; 60: 741–747
6. Eschbach JW, Kelly MR, Haley NR *et al*. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989; 321: 158–163
7. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; 40: 439–446
8. Carrera F, Disney A, Molina M. Extended dosing intervals with erythropoiesis-stimulating agents in chronic kidney disease: a review of clinical data. *Nephrol Dial Transplant* 2007; 22(Suppl 4): iv19–iv30
9. Brunkhorst R, Bommer J, Braun J *et al*. Darbepoetin alfa effectively maintains haemoglobin concentrations at extended dose intervals relative to intravenous or subcutaneous recombinant human erythropoietin in dialysis patients. *Nephrol Dial Transplant* 2004; 19: 1224–1230
10. Hertel J, Locay H, Scarlata D *et al*. Darbepoetin alfa administered every other week maintains hemoglobin levels over 52 weeks in patients with chronic kidney disease converting from once-weekly recombinant human erythropoietin: results from simplify the treatment of anemia with Aranesp (STAAR). *Am J Nephrol* 2006; 26: 149–156
11. Hertel JE, Locay HR, Scarlata DS *et al*. Darbepoetin alfa administration to achieve and maintain target hemoglobin levels for 1 year in patients with chronic kidney disease. *Mayo Clin Proc* 2006; 81: 1188–1194
12. Locatelli F. Once weekly treatment with epoetin-beta. *Nephrol Dial Transplant* 2005; 20(Suppl 6): vi26–vi30
13. Suranyi MG, Lindberg JS, Navarro J *et al*. Treatment of anemia with darbepoetin alfa administered de novo once every other week in chronic kidney disease. *Am J Nephrol* 2003; 23: 106–111
14. Bock HA, Hirt-Minkowski P, Brunisholz M *et al*. Darbepoetin alpha in lower-than-equimolar doses maintains haemoglobin levels in stable haemodialysis patients converting from epoetin alpha/beta. *Nephrol Dial Transplant* 2008; 23: 301–308
15. Molina M, García Hernández MA, Navarro MJ *et al*. Change of EPO treatment from subcutaneous epoetin to intravenous epoetin or darbepoetin alpha. *Nefrologia* 2004; 24: 564–571
16. Nissenson AR, Swan SK, Lindberg JS *et al*. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; 40: 110–118
17. Tolman C, Richardson D, Bartlett C *et al*. Structured conversion from thrice weekly to weekly erythropoietic regimens using a computerized decision-support system: a randomized clinical study. *J Am Soc Nephrol* 2005; 16: 1463–1470
18. European Medicines Agency. *European Public Assessment Report*—Aranesp (22 June) 2008
19. Roger SD, Cooper B. What is the practical conversion dose when changing from epoetin alfa to darbepoetin outside of clinical trials? *Nephrology (Carlton)* 2004; 9: 223–228
20. Summers S, Winnott G, Matijevic A. An audit comparing subcutaneous epoetin alfa to intravenous darbepoetin alfa in chronic hemodialysis patients. *Dial Transplant* 2005; 34: 358–362
21. Shalansky K, Jastrzebski J. Complete switch to darbepoetin in a hemodialysis unit. *Clin Nephrol* 2005; 64: 55–63
22. Ardèvol M, Fontseré N, Casals M *et al*. A feasibility cost-analysis study of recombinant human erythropoietin and darbepoetin alfa in ambulatory haemodialysis patients during current clinical practice. *Eur J Hosp Pharm Sci* 2006; 12: 47–51
23. Downs S, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; 52: 377–384
24. Mood AM, Graybill FA, Boes D. *Introduction to the Theory of Statistics*. New York: McGraw-Hill, 1974

25. Icardi A, Sacco P, Salvatore F *et al*. Long-term intravenous epoetin-alpha/darbepoetin-alpha ratio in iron-replete hemodialysis patients. *J Nephrol* 2007; 20: 73–79
26. Remón C, Quiros P, Fernández Marchena D *et al*. Darbepoetin in the treatment of the renal anaemia in the patient undergoing peritoneal dialysis previously treated with epoetin alfa. *Nefrologia* 2005; 25: 170–177
27. Shaheen FA, Akeel N, Alfi A *et al*. Darbepoetin use for the treatment of anemia in hemodialysis patients in Saudi Arabia. *Saudi J Kidney Dis Transpl* 2006; 17: 365–372
28. Kaufman JS, Reda DJ, Fye CL *et al*. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. *N Engl J Med* 1998; 339: 578–583
29. Aarup M, Bryndum J, Dieperink H *et al*. Clinical implications of converting stable haemodialysis patients from subcutaneous to intravenous administration of darbepoetin alfa. *Nephrol Dial Transplant* 2006; 21: 1312–1316
30. Cervelli MJ, Gray N, McDonald S *et al*. Randomized cross-over comparison of intravenous and subcutaneous darbepoetin dosing efficiency in haemodialysis patients. *Nephrology (Carlton)* 2005; 10: 129–135

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