Dose Efficiency of Aranesp® (Darbepoetin Alfa) Compared With Epoetin Alfa or Epoetin Beta in Dialysis Patients – A Meta Analysis

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BACKGROUND

- Anemia is a common complication of patients with chronic kidney disease who are undergoing dialysis.
- Erythropoeisis stimulating agents (ESAs) increase circulating hemoglobin levels and help reduce the need for blood transfusions and anemia-related hospitalisation. Darbepoetin alfa is a more potent, longer-acting ESA that can be administered to patients less frequently.
- The evaluation of comparative dose efficiencies among ESAs relies on an analysis of comparative, randomized, controlled trials.

OBJECTIVE

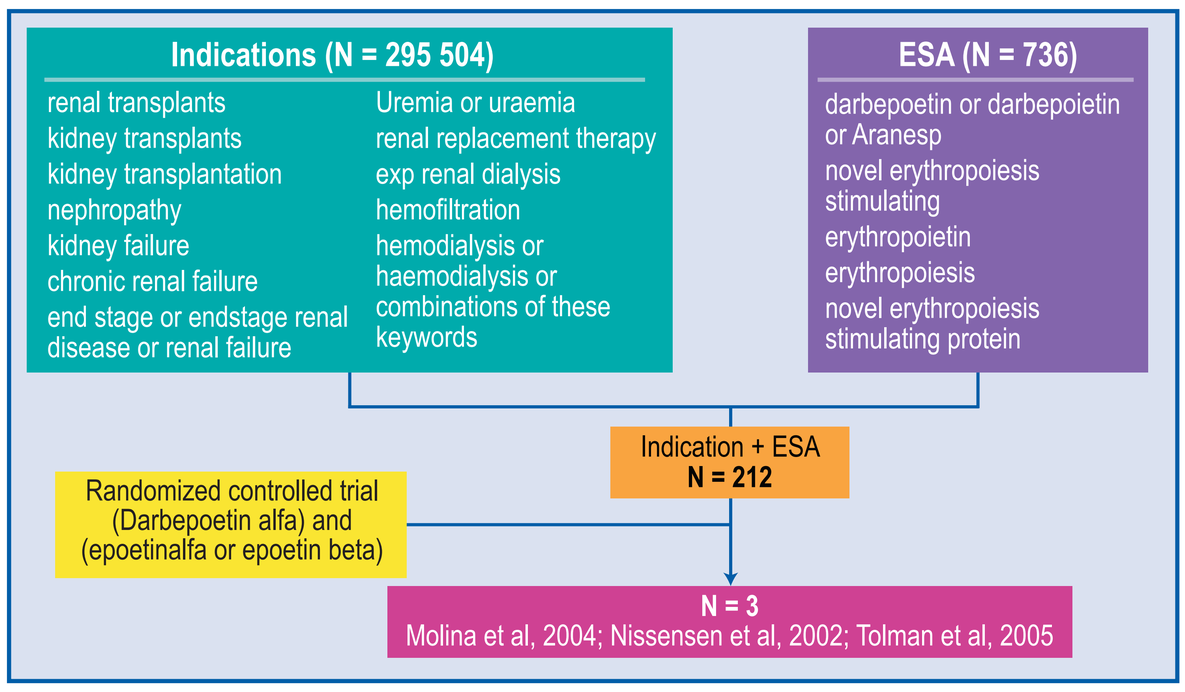
- The objective of this study was to perform a systematic review of the literature to estimate the relative doses of different ESAs that are required to obtain adequate hemoglobin control in patients receiving dialysis.

METHODS

- We performed a systematic review of the literature to identify studies in which dosing data were available. The following databases were searched: EMBASE, Ovid MEDLINE®, Ovid MEDLINE® In-Process, Other Non-indexed Citations, the Cochrane Database of Systematic Reviews (CDSR), the ACP Journal Club, the Database of Systematic reviews (DARE), and the controlled clinical trial registry (CCTR). Figure 1 shows the screening process applied to the literature review.

METHODS *(continued)*

Figure 1. Screening Process Applied to the Literature Review



- Studies were eligible for inclusion if they were randomized, well-controlled studies comparing darbepoetin alfa with recombinant human erythropoetin (rHu-Epo; epoetin alfa; epoetin beta). The conversion factor from epoetin alfa or epoetin beta to darbepoetin alfa was 200:1 as stated in the EU label for darbepoetin alfa. Both intravenous and subcutaneous routes of administration were included.
- The primary study outcome measure was the relative doses of epoetin alfa or epoetin beta compared with darbepoetin alfa that were required to achieve a target hemoglobin level (as defined in the study protocol) during the evaluation period.
- Data were pooled after testing for homogeneity of treatment effects across trials and dose efficiencies were summarized. Data were analysed according to standard meta-analytical methodology.[1]

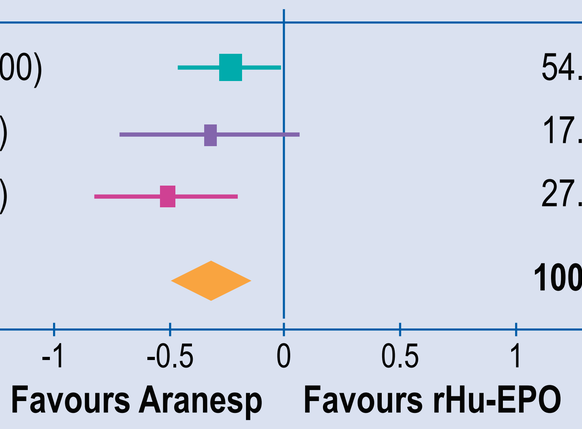
RESULTS

- Our search found 212 studies. Of these, we identified three published studies that met the inclusion criteria and could be included in the meta-analysis.[2-4]
- The three studies had no apparent signs of heterogeneity ($p = 0.46$) and consequently could be combined. After combining the three studies, we had data for 250 patients receiving darbepoetin alfa and 372 patients receiving epoetin alfa or epoetin beta.
- For comparable levels of hemoglobin, the dose savings achieved by administering darbepoetin alfa compared with epoetin alfa or epoetin beta ranged between 24% and 42% (Table 1).
- The mean effect size (i.e. the dose efficiency of darbepoetin alfa relative to epoetin alfa or epoetin beta) was found to be 32% ($p < 0.0001$). In other words, the combined analysis suggests that there is a 32% gain in efficiency for darbepoetin alfa compared with epoetin alfa or epoetin beta when using a starting conversion factor of 200 IU : 1µg.

Table 1. Reductions in Dose With Darbepoetin Alfa Compared With Epoetin Alfa or Epoetin Beta

Review: Aranesp Dose Efficiency vs rHu-EPO
Comparison: Dose Efficiency Aranesp vs rHu-EPO
Outcome: Dose at end of evaluation period

Study or sub-category	N	Aranesp Mean (SD)	N	rHu-EPO Mean (SD)	SMD (random) 95% CI	Weight %	SMD (range) 95% CI
Nissenson et al.	118	10836.00 (9512.00)	240	13639.00 (12805.00)		54.96	-0.24 (-0.46, -0.02)
Molina et al.	51	135.20 (126.00)	51	173.91 (109.20)		17.58	-0.33 (-0.72, 0.06)
Tolman et al.	81	75.00 (80.00)	81	133.00 (150.00)		27.49	-0.42 (-0.79, -0.17)
Total (95% CI)	**250**		**372**			**100.00**	**-0.32 (-0.48, -0.16)**



Test for heterogeneity: $Chi^2 = 1.56$. df = 2 ($P = 0.46$), $i^2 = 0\%$
Test for overall effect: $Z = 3.82$ ($P = 0.0001$)

DISCUSSION

- These results demonstrate that the administration of darbepoetin alfa to patients with chronic kidney disease undergoing dialysis can potentially provide up to 32% reduction in cost when using a starting dose conversion from 200 IU epoetin alfa or epoetin beta to 1µg of darbepoetin alfa as stated in the EU prescribing information. This finding is of particular importance due to the increasing budgetary concerns for hospitals in many countries
- The lack of well-controlled randomized studies investigating the dose efficiency question is a limitation in our study. A larger number of studies would allow improved precision in our estimate of dose efficiency.

CONCLUSIONS

- Using a starting dose conversion of 200:1 as stated in the EU label, in this meta-analysis, darbepoetin alfa is more dose efficient when compared with epoetin alfa or epoetin beta. The comparative dose savings observed in this meta-analysis of well-controlled trials suggest that relative ESA doses could be reduced by 32% for patients switching patients from epoetin alfa or epoetin beta to darbepoetin alfa.

REFERENCES

1. Montori V, Hatala R, Guyatt G. Summarizing the evidence. Evaluating differences in study results. In: *Users' Guides to the Medical Literature. A Manual for Evidence-based Clinical Practice.* Eds. Guyatt G, Rennie D. AMA Press 2002
2. Molina M, Garcia Hernandez, M A, Navarro M J, De Gracia, MC, Ortuno T. Change of EPO treatment from subcutaneous epoetin to intravenous epoetin or darbepoetin alpha. *Nefrologia* 2004; 24(6): 564-571.
3. Nissenson AR, Swan SK, Lindberg JS, Soroka SD, Beatey R, Wang C et al. Randomized, controlled trial of darbepoetin alfa for the treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002; 40(1): 110-118.
4. Tolman C, Richardson D, Bartlett C, Will E. 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(5); 1463-1470.

This study was supported by Amgen (Europe), Zug, Switzerland.