NEPHROLOGY

Nephrology **20** (2015) 663–665

COCHRANE COMMENTARY

Edited by Angela Webster (angela.webster@sydney.edu.au)
Written by Deirdre Hahn (deirdre.hahn@health.nsw.gov.au) and Elisabeth Hodson (Elisabeth.hodson@health.nsw.gov.au)

FREQUENCY OF ADMINISTRATION OF ERYTHROPOIESIS-STIMULATING AGENTS FOR THE ANAEMIA OF END-STAGE KIDNEY DISEASE IN DIALYSIS

What is this review about?

This review investigated the use of different frequencies of erythropoiesis-stimulating agents (ESAs) in dialysis patients. The review considered darbepoetin alfa, continuous erythropoietin receptor agonists (CERA) and recombinant human erythropoietin (rHuEPO) preparations. This was an update to include new evidence of a review initially published in 2002 and last updated in 2005.

What are the findings?

Haemoglobin levels did not differ between groups whether CERA was administered every 2 weeks (4 studies, 1126 participants; mean difference (MD) 0.08 g/dL, 95% confidence interval (CI) −0.04 to 0.21; $I^2 = 0\%$) or every 4 weeks (2 studies, 672 participants; MD −0.03 g/dL, 95% CI −0.17 to 0.12; $I^2 = 0\%$) *versus* rHuEPO given two to three times/week (Fig. 1). There were no significant differences in all-cause mortality (Fig. 2), adverse events due to hypertension, numbers requiring transfusions or haemodialysis access thrombosis. Only one study directly compared CERA given at two weekly intervals with weekly darbepoetin. Haemoglobin was statistically higher among participants who received CERA compared with those on darbepoetin, although this difference was unlikely to be of clinical significance (1 study, 249 participants; MD 0.30 g/dL, 95% CI 0.05 to 0.55). There were no significant differences in all-cause mortality, adverse events due to hypertension, number of patients requiring transfusions or haemodialysis access thrombosis.

In studies that compared darbepoetin given weekly *versus* rHuEPO administered two to three times/week, there was no significant difference between final or change in haemoglobin (6 studies, 1245 participants; MD 0.02 g/dL, 95% CI −0.09 to 0.12; $I^2 = 0\%$). There were also no significant differences in all-cause mortality (five studies), hypertension (four studies), total treatment-related adverse events (three studies) or vascular access complications (four studies). There was a small but statistically significant increase in transfusion requirements among rHuEPO-treated patients

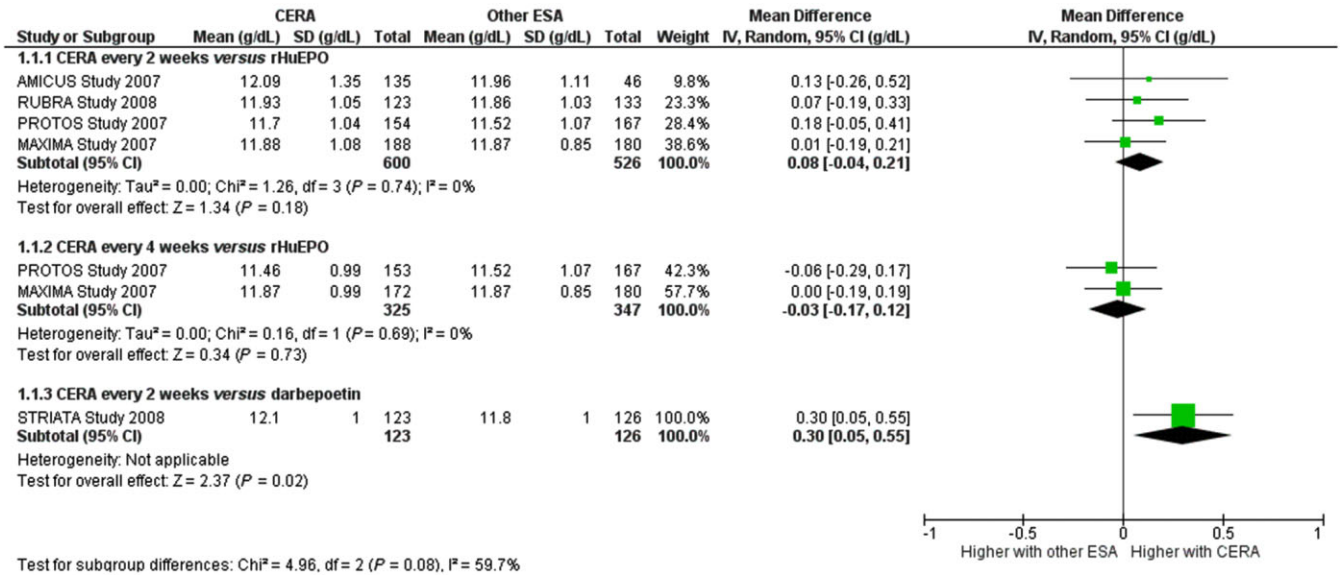

Fig. 1 Final haemoglobin levels in studies comparing CERA given every 2 or 4 weeks and rHuEPO given two to three times per week or darbepoetin given every week (mean difference and 95% confidence interval (CI)). CERA, continuous erythropoietin receptor agonist; df, degrees of freedom; ESA, erythropoiesis-stimulating agent; IV, Inverse variance statistical method; rHuEPO, recombinant human erythropoietin; SD, standard deviation.

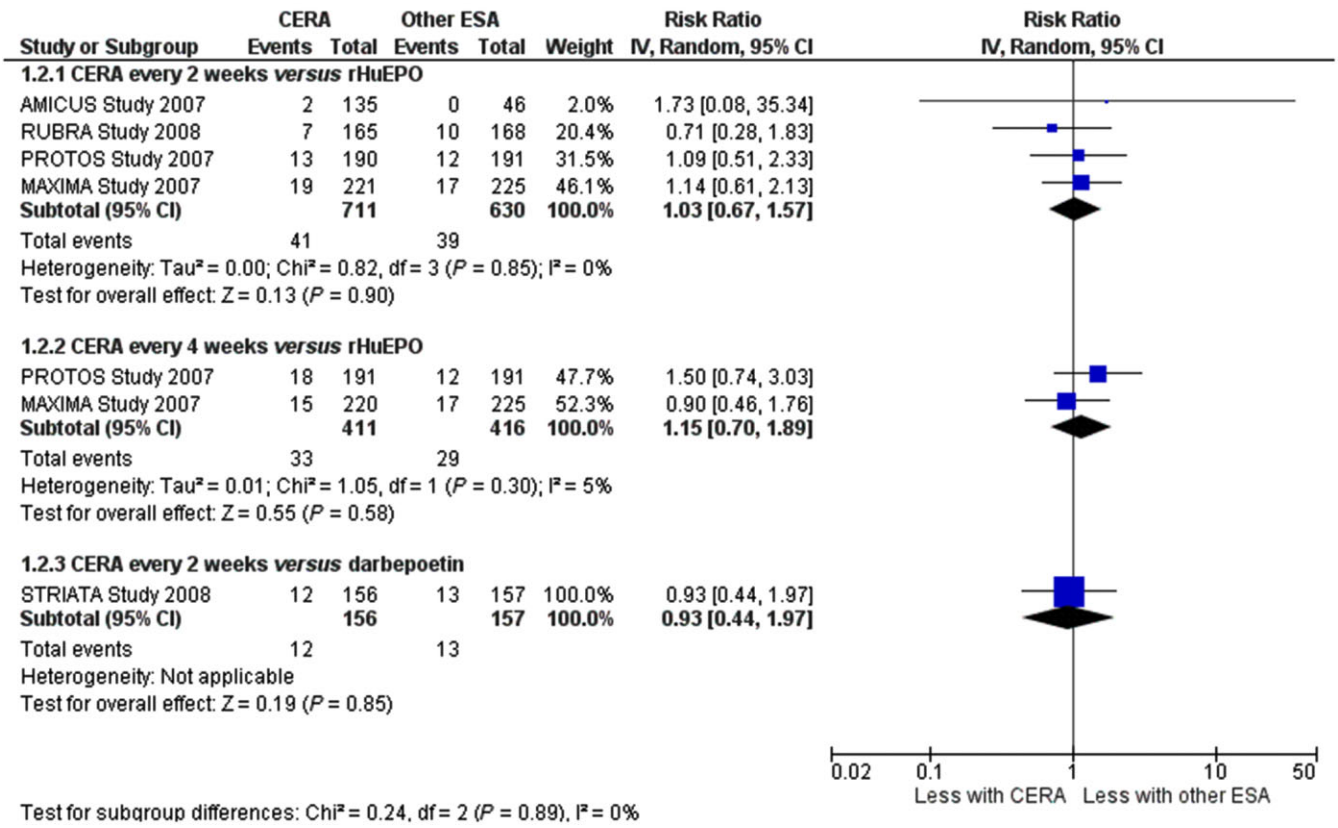

Fig. 2 Risk of all-cause mortality in studies comparing CERA given every 2 or 4 weeks and rHuEPO given two to three times per week or darbepoetin given every week (risk ratio and 95% confidence interval (CI)). CERA, continuous erythropoietin receptor agonist; df, degrees of freedom; ESA, erythropoiesis-stimulating agent; IV, Inverse variance statistical method; rHuEPO, recombinant human erythropoietin.

(3 studies, 1069 participants; risk difference −0.02, 95% CI −0.05 to −0.00; $I^2 = 0\%$).

For rHuEPO given weekly *versus* rHuEPO given two to three times, there were no significant differences between final haemoglobin or haematocrit (7 studies, 363 participants; standard mean difference −0.17, 95% CI −0.39 to 0.05; $I^2 = 0\%$), hypertension (4 studies), transfusion requirements (1 study) or access thrombosis (1 study). All-cause mortality was not reported.

What are the findings based on?

A total of 33 studies (5526 participants) were included in this review, with 16 multicentre and 17 single-centre studies. Nine studies were non-inferiority trials and three studies were equivalence trials. There was marked diversity in comparisons of interventions, duration of treatment and follow-up, though the primary outcome of final haemoglobin or change in haemoglobin was consistent among the studies. Sample sizes ranged from 15 to 572 participants, with many of the earlier rHuEPO studies having small numbers and newer multicentred trials recruiting larger numbers. Quality of study methodology was variable with older studies more likely to be at a higher risk of bias. Only 9 and 14 studies were assessed at low risk of bias for sequence generation and allocation concealment respectively. Four studies were placebo controlled, though all studies were considered to be at low risk of performance or detection bias because the primary outcome of haemoglobin level was a laboratory-derived assessment and unlikely to be influenced by lack of blinding. In earlier studies, important outcomes such as mortality were not reported, and overall patient-centred outcomes were generally poorly reported. Thirteen of 33 studies recorded all-cause mortality; only 4 reported cardiovascular mortality data and none reported on cardiovascular morbidity. Although hypertension and vascular access complications are known to be associated with ESA administration, these were reported in only 14 and 11 studies respectively. It is widely accepted that ESA therapy reduces transfusion requirements; however, 22 studies failed to report on transfusion events.

Implications for practice

- Darbepoetin and CERA are non-inferior to rHuEPO in achieving haemoglobin targets without significant differences in adverse events.

- Greater convenience offered by extended dosing intervals of longer acting ESA, for both patients and healthcare providers, may result in improved cost-efficiency. Audits have demonstrated that administration of ESA at two weekly intervals resulted in significant reductions in pharmacy, dialysis unit staff and equipment costs.
- In many countries, the use of newer longer acting but more costly ESA would have to be balanced against the costs associated with more frequent administration of cheaper rHuEPO preparations.

Clinical perspective

This review has demonstrated that newer ESAs administered at less frequent intervals are non-inferior to rHuEPO. However, this review included only studies that evaluated ESAs for people on dialysis and the majority of participants received haemodialysis. Only one study included only patients receiving peritoneal dialysis, and this study evaluated different frequencies of rHuEPO. We did not identify any studies in children on dialysis. Only one study with 249 evaluated participants compared darbepoetin and CERA. Ideally, further large, well-designed, randomized controlled trials comparing darbepoetin and CERA are required as well as studies in peritoneal dialysis patients and children on dialysis. Because additional large multicentre comparative studies of longer acting ESA may not be performed, collaborative meta-analyses of studies on anaemia management with ESAs may provide additional information on the benefit and harms of managing anaemia in dialysis patients.

Hahn D, Cody JD, Hodson EM. Frequency of administration of erythropoiesis-stimulating agents for the anaemia of end-stage kidney disease in dialysis patients. *Cochrane Database of Systematic Reviews* 2014; Issue 5. Art. No.: CD003895. DOI:10.1002/14651858.CD003895.pub3.