Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: a systematic review and meta-analysis

Ross S D, Allen I E, Probst C A, Sercus B, Crean S M, Ranganathan G

CRD summary
This review concluded that erythropoiesis-stimulating proteins are effective and safe for the treatment of anaemia associated with myelodysplastic syndrome. In light of the methodological limitations of the review and a lack of study details, the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the efficacy and safety of erythropoiesis-stimulating proteins (ESPs) in anaemia of myelodysplastic syndrome (MDS).

Searching
MEDLINE was searched for papers published in English between 1980 and 2005; the search terms were reported. The reference lists of accepted papers, and of recent systematic reviews found using the Cochrane Library, were also checked. PubMed and Current Contents were searched for the past 6 months, in order to identify recently published papers not yet indexed in MEDLINE. The authors also searched abstracts from the 2003 to 2005 meetings of the American Society of Clinical Oncology, European Society for Medical Oncology and American Society of Hematology.

Study selection
Studies of adults with primary MDS and anaemia treated with an ESP were eligible for inclusion. Prospective interventional studies with at least 10 patients, or retrospective observational studies of at least 300 ESP-treated patients, were eligible. Any antineoplastic treatment except stem cell transplant was acceptable. In the included studies, 56% of the participants were men and the average age was 70 years (range: 57 to 88), with an average baseline haemoglobin (Hb) level of 8.4 g/dL and baseline erythropoietin level of 374 u/L. The average study duration (for 40 studies) was 18 weeks. Randomised controlled trials (RCTs), non-RCTs and uncontrolled case series (UCSs) were included. In 56 studies the ESP used was epoetin; 3 studies used darbepoetin. In 39 of the 56 epoetin studies, no concurrent chemotherapy was administered to the patients. Eligible studies had to report at least one of the following outcomes: Hb change, red blood cell transfusions, the number of patients with Hb response, and quality of life using validated instruments.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
RCTs were critically appraised using the Jadad scale; the trials were scored for method of randomisation, treatment blinding and accounting for all patients entered and withdrawn.

One investigator extracted the scores to data forms and another reviewed for agreement. Any discrepancies were resolved by consensus.

Data extraction
For RCTs, data on binary outcomes in the intervention and control groups were extracted and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, the results were expressed as mean differences with 95% CIs. For UCSs, the percentage of patients with each outcome was computed for each treatment group. Risks in ESP patients relative to control groups were computed as data permitted.

One reviewer extracted the data to data forms and another reviewed for agreement. Any discrepancies were resolved by consensus. Entered data were then verified back to the extraction forms.
**Methods of synthesis**

Meta-analyses examining pooled ORs were performed using both fixed-effect and random-effects models; it was unclear whether the studies had been weighted. Study heterogeneity was assessed using both Cochran's Q and $I^2$ statistics. Meta-regression analyses were run for predictors of Hb response: gender, baseline Hb, ESP type and ESP duration.

**Results of the review**

Fifty-nine studies (n=2,106) were included in the review: 4 RCTs (n=322), 1 non-RCT (n=32) and 54 UCSs (n=1,752).

In the 4 RCTs, treatment with epoetin resulted in a statistically significant increase in Hb (OR 5.2, 95% CI: 2.5, 10.8, p<0.01); the response rates were 27.3% in the epoetin group and 6.7% in the control group. There was no evidence of significant heterogeneity. When stratified by dosing frequency and duration, the ORs for Hb response did not differ much from the overall result. In the UCSs, the Hb response rate for epoetin (46 studies) was 32.1% (95% CI: 26.3, 37.9). Stratified analyses of the UCSs suggested that patients with a higher average baseline serum erythropoietin level (≥500 u/L) have a smaller Hb change (a 0.3 versus a 1.2 g/dL increase) and a lower rate of Hb response (27.3%) than groups with a lower baseline serum erythropoietin level (34.9%). For the 3 UCSs of darbepoetin, the average Hb response rate was 48.1% (95% CI: 25.2, 70.9). Further analyses were reported.

Meta-regression analyses for predictors of Hb response found none of the following covariates to be significant: baseline Hb, percentage male, size of study and ESP duration. The factor for treatment was significant for control compared with either epoetin or darbepoetin.

For the RCTs, none of the ORs reached statistical significance for incidence of adverse events.

**Authors' conclusions**

ESPs are efficacious and safe for the treatment of anaemia associated with MDS.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. However, only one database was searched for primary research, although other methods were used to identify additional published studies, and there were no attempts to minimise language bias (the search was restricted to English language studies). Publication bias was also not assessed. It is therefore possible that some relevant studies might have been missed during the search. The methods used to select the studies were not reported, so it is difficult to comment on the risk of bias and error being introduced into this process. The quality of the trials was assessed using the Jadad scale, which has limitations as it only scores the quality of reporting rather than the methodological quality, and it does not assess allocation concealment. In addition, details of the Jadad scores were not provided and were not used in interpreting the results of the review. However, the authors were careful to ensure that the UCSs were of large populations (at least 300 patients). Individual study details were not provided which makes interpretation of the results difficult, particularly the forest plot, since no details of possible study weightings were given. No numbers were provided for the meta-regression analyses. The results of heterogeneity tests did not include $I^2$ or p-values. It is not clear why seemingly the same data in the tables and figures did not tally. In summary, methodological limitations and a lack of study details mean the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that controlled trials of darbepoetin versus standard care or placebo controls are needed to establish efficacy and safety. Head-to-head trials of epoetin versus darbepoetin are also needed to compare Hb response, as well as quality of life and other efficacy measures.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.