Systematic review of the impact of erythropoiesis-stimulating agents on fatigue in dialysis patients

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CRD summary
The authors concluded that partial correction of anaemia, with erythropoiesis-stimulating agents, improved fatigue in patients with end-stage renal disease, who were on dialysis. The evidence indicated improved fatigue outcomes, but the authors' conclusions may not be sufficiently cautious, due to a lack of well-designed studies.

Authors' objectives
To evaluate erythropoiesis-stimulating agents, in the treatment of anaemia, to improve fatigue, in patients with end-stage renal disease, who were on dialysis.

Searching
MEDLINE and EMBASE were searched, for articles published in English, to June 2010. Search terms were reported. Reference lists of identified articles were screened.

Study selection
Studies evaluating treatment for fatigue, using any approved erythropoiesis-stimulating agent, in adults with end-stage renal disease, who were on dialysis, were eligible for inclusion. Randomised controlled trials (RCTs) and observational studies were eligible, if measures of fatigue before and after treatment were reported. Studies had to report at least one patient-assessed outcome, that included a fatigue, energy or vitality domain.

Included were one placebo-controlled trial, comparisons between patients with high and low haemoglobin levels, and comparisons of intravenous versus subcutaneous administration. Haemoglobin levels before treatment and target levels varied between studies. Outcome measures were described and the most common for fatigue were the Kidney Disease Questionnaire (KDQ) fatigue and the SF-36; other measures were the Nottingham Health Profile (NHP) energy, the Profile of Mood States (POMS) fatigue, and the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-fatigue) scales.

Two reviewers independently selected studies for inclusion. Disagreements were resolved through discussion with all the authors.

Assessment of study quality
The authors did not state that they assessed quality.

Data extraction
Data on relevant outcomes were extracted and reported as a percentage changes from before the intervention. The authors did not state how many reviewers extracted the data.

Methods of synthesis
The data were combined in a narrative synthesis, based on the fatigue instrument, and the mean change in haemoglobin – an increase of 1g per decilitre (dL) or more, from a mean baseline haemoglobin of less than 10g/dL; an increase of 1g/dL or more, from a mean baseline haemoglobin of 10g/dL or more; and no change (increase less than 1g/dL).

Results of the review
Fifteen articles, describing 10 studies and one extension study, were included. Five were RCTs, one of which was placebo controlled (1,359 participants; range 83 to 596), and six were cohort studies (1,337 participants; range 15 to 487). Follow-up ranged from four weeks to 24 months; most studies had less than one year of follow-up.

KDQ fatigue: After erythropoiesis-stimulating agents, one RCT reported a 22% improvement in the KDQ fatigue score for patients with a lower target haemoglobin, a 26% improvement in patients with a higher target, and 2.3% for patients...
on placebo, over six months. When this RCT was extended to an open-label design, starting or continuing patients on erythropoiesis-stimulating agents, for a further 12 months, patients formerly assigned to placebo experienced an 18% improvement in fatigue, and those already assigned to erythropoiesis-stimulating agents reported no further change in fatigue at 24 weeks. One RCT reported a greater improvement in fatigue scores with intravenous (18.6%) than with subcutaneous (11.1%) erythropoiesis-stimulating agents at 52 weeks. Two RCTs reported a non-significant deterioration (-0.2 to -6.6%) in low haemoglobin target groups, and a slight improvement in the high haemoglobin target group.

SF-36 vitality: One cohort study reported improvements in scores of 25% at 14 weeks and 23% at 16 weeks, after erythropoiesis-stimulating agents. One cohort study reported increased vitality at seven to 14 weeks of follow-up.

The results of the other scales were reported.

By baseline haemoglobin: One RCT, of patients who had received erythropoiesis-stimulating agents, found significant differences between high and low baseline haemoglobin groups, at 96 weeks, for SF-36 vitality scores. Studies of lower baseline haemoglobin, with partial correction to a minimum haemoglobin of 10g/dL or more, reported an average 34.6% improvement in fatigue. Studies with a higher baseline haemoglobin, with an increase of 1g/dL or more, reported an average improvement of 5.5%. Studies with no change in haemoglobin (less than 1g/dL; control or placebo groups) reported an average decline of 0.7% in fatigue outcomes.

Authors' conclusions
The findings demonstrated that partial correction of anaemia, with erythropoiesis-stimulating agents, improved fatigue in patients on dialysis. No considerable improvements were reported in studies that compared high versus low haemoglobin levels.

CRD commentary
The review question was clear, with defined inclusion criteria. Some relevant sources were searched, but inclusion was limited to studies published in English, meaning that some studies may have been missed. Appropriate methods were used to avoid reviewer error and bias in the selection of studies, but it is unclear whether similar methods were used in data extraction. Study quality was not assessed, making it difficult to determine the reliability of the evidence. A number of cohort studies were included, and these are prone to multiple biases. Only one placebo-controlled RCT was included. A narrative synthesis was appropriate given the differences in study design, participants, outcome measures, and duration of treatment.

The evidence indicated improved fatigue outcomes, but the authors' conclusions may not be sufficiently cautious, due to a lack of well-designed studies.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed to determine the best haemoglobin target, for erythropoiesis-stimulating agent therapy, to maximise the improvement in health-related quality of life outcomes, as well as fatigue, while minimising any potential harmful effects.

Funding
Funded by Amgen, a manufacturer of erythropoiesis-stimulating agents.

Bibliographic details

PubMedID
22187314
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.