Prevalence and prognosis of paroxysmal nocturnal haemoglobinuria and the clinical and cost-effectiveness of eculizumab

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CRD summary
This review concluded that for haemolytic patients with a history of transfusions, eculizumab was effective in reducing haemolysis and transfusion requirements, reducing anaemia and rate of thrombosis, and improving quality of life. The authors’ conclusions appear to follow from the available data, however, it should be noted that this judgement of effectiveness was based on one small RCT and two uncontrolled studies of unclear quality.

Authors’ objectives
To review the clinical effectiveness and cost effectiveness of eculizumab for paroxysmal nocturnal haemoglobinuria (PNH), and to review the natural history and prevalence of the disease. The latter objective is outwith the scope of DARE and is not considered further here.

Searching
Cochrane Library, EMBASE and MEDLINE were searched from inception to November 2007 (search terms reported). References of retrieved papers were checked, relevant industry internet sites were searched and the authors made contact with experts and industry. Searches were not limited by language of publication.

Study selection
Eligible study designs included randomised controlled trials (RCTs), controlled trials and before/after studies provided there were at least 10 participants. The included studies were either RCTs or before/after studies. The intervention was eculizumab. Included studies all used the same dosage regimen of 600 mg eculizumab weekly for four weeks followed by 900 mg every 14 days. The comparators and population of interest was not specified (included patients all had some history of transfusions) and any outcomes were considered to be eligible (most studies reported on measures of haemolysis and anaemia among others).

Study selection was carried out by two independent reviewers and any disagreements were resolved by discussion.

Assessment of study quality
Validity assessment for the RCTs was carried out according to guidance from CRD Report 4 and included items on randomisation, allocation concealment, blinding, comparability of groups, follow-up, missing data and power calculations. Validity was assessed by one reviewer and checked by a second reviewer. Disagreements were resolved through discussion.

Data extraction
Data were extracted by one reviewer and checked by a second reviewer. Some data were reported as having been extracted from graphs in the original papers.

Methods of synthesis
A narrative synthesis was carried out due to the small number of studies and their varied designs.

Results of the review
A total of four studies were included in this review (data taken from multiple publications) with a combined total n of 195. One study was an RCT of good quality, two studies were uncontrolled prospective open label before/after comparisons and the final study was a mixture of retrospective and prospective data that included patients from the three previous studies.

Overall eculizumab reduced transfusion requirements and anaemia, and reduced haemolysis according to an RCT (n=87; p<0.001) and an uncontrolled study (n=97). The RCT also reported mean haemoglobin levels as significantly
decreasing in the placebo group during the trial despite receiving more units of transfused red blood cells (p<0.001). Quality of life was improved following treatment with eculizumab, particularly with regard to fatigue according to a comparison of the results from the RCT and uncontrolled studies with results from an open-label study of cancer patients. The authors of the primary studies reported the findings from a pooled analysis of three published studies and suggested the rate of thromboembolism decreases up to seven-fold in patients treated with eculizumab.

The most common adverse events were headache, upper respiratory tract infection and viral infection; no patients withdrew due to side effects.

Cost information
A preliminary cost-effectiveness analysis was carried out (no economic studies were identified and little information was available on relevant parameters). Assuming that between 16 per cent and 33 per cent of PNH patients are treated with eculizumab, the annual savings from standard care would range between £1,000 to £10,000 per patient. The incremental cost-effectiveness ratio for PNH patients varied from £1.2M per life year gained (LYG) to £1.4M per LYG, depending on the time horizon (10 to 15 years).

Authors' conclusions
For haemolytic patients with a history of transfusions, eculizumab was effective in reducing haemolysis and transfusion requirements, reducing anaemia and rate of thrombosis, and improving quality of life. But, good estimates of effect size await further research.

CRD commentary
This review addressed a clear question with partially specified inclusion criteria. The searches did not access unpublished literature, but the scarcity of research on this drug and the fact that it has been licensed only since 2007 make the review unlikely to have missed any relevant studies. The methodological processes were reported clearly and conform to systematic review guidelines. The quality assessment was not fully reported for the non-RCT studies were assessed. The narrative synthesis was appropriate given the limited data. The authors' conclusions appear to follow from the available data, however, it should be noted that this judgement of effectiveness was based on one small RCT and two uncontrolled studies of unclear quality.

Implications of the review for practice and research
Practice: the nature of the review precluded any explicit recommendations being made for practice and it was intended to inform commissioning decisions.

Research: the authors stated that future research should include investigation of quality of life in terms of utility values.

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Record Status
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.