The cost-effectiveness of weekly epoetin alfa relative to weekly darbepoetin alfa in patients with chemotherapy-induced anemia

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of epoetin alpha (EPO) and darbepoetin alpha (DARB) for the treatment of chemotherapy-induced anaemia (CIA). Dosing regimens approved by the Food and Drug Administration (FDA) were used (EPO 40,000 U once weekly and DARB 2.25 microg/kg once weekly).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised anaemic cancer patients receiving chemotherapy.

Setting
The setting was secondary care. The economic study was conducted in the USA.

Dates to which data relate

Source of effectiveness data
The effectiveness data were derived from a comparison of two studies.

Modelling
A decision analytic model was constructed to estimate the cost-effectiveness of the two treatment strategies. The model was constructed using data from two similar studies. The follow-up period was 16 weeks.

Outcomes assessed in the review
Effectiveness was measured by estimating erythropoietic treatment success, which was defined as the proportion of patients successfully treated (i.e. not requiring red blood cell transfusions). Two time periods for treatment success were considered: throughout the study (weeks 0 to 16), and from week 5 to week 16 (allowing adequate time for treatment response to erythropoietic agents before assessing erythropoietic treatment success).
Study designs and other criteria for inclusion in the review
The authors chose to compare published results of two double-blind, randomised, Phase III trials using FDA-approved dosage of the treatments (Kotasek et al. 2004, a scientific poster, and Witzig et al. 2005, a published article). The authors believed these to be the only reported trials employing FDA-approved dosages that had similar patient characteristics (age, gender, tumour types and baseline haemoglobin level), study duration (16 weeks) and measurements for blood transfusions. No systematic review of the literature was reported.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Two primary studies were included in the review. The EPO population was derived from a placebo-controlled study (n=166), which included anaemic cancer patients over 18 years of age who were receiving myelosuppressive chemotherapy (Witzig et al. 2005). The exclusion criteria were red blood cell transfusion within 2 weeks of study entry, previous treatment with EPO within 1 year of the study, or adjuvant therapy or high-dose chemotherapy with stem-cell rescue. DARB patients were derived from a non-inferiority dosing trial (n=367) (Kotasek et al. 2004). The individuals included in the study had non-myeloid malignancies and planned chemotherapy. Patients were excluded from the study if they had received red blood cell transfusions (more than two within 4 weeks or any within 2 weeks) or erythropoietic therapy within 3 months of enrolment.

Methods of combining primary studies
Each trial provided effectiveness evidence for one treatment group and they were compared directly.

Investigation of differences between primary studies
Data permitting, statistical tests (i.e. t-tests and chi-squared tests) were conducted to compare baseline and demographic characteristics of the two populations. EPO and DARB patients had similar mean age, gender distributions and baseline haemoglobin levels. Both populations also included patients with multiple tumour types, although the distribution of the tumour types differed between the two treatment groups, (p<0.001). Although the EPO and DARB groups were acknowledged to be from different source populations and the studies were conducted in different countries, the authors did not investigate how these differences affected the estimate of the relative effectiveness of the technologies.

Results of the review
The proportion of patients successfully treated was higher in the EPO treatment group than in the DARB treatment group during the two study periods considered (75% versus 63% for weeks 0 to 16 and 85% versus 73% for weeks 5 to 16).

Measure of benefits used in the economic analysis
The measure of benefit used was the increase in patients successfully treated during weeks 0 to 16 and during weeks 5 to 16.
**Direct costs**
The cost estimates were based on 16-week drug costs in the two clinical studies. These were calculated using May 2005 wholesale acquisition costs and the average drug use over the course of treatment. Discounting was not carried out as it was not relevant to the short timescale. The mean cumulative DARB dose was calculated using the mean weekly dose for DARB and the mean patients' weight in the study sample. The mean cumulative dose for EPO was calculated as a weighted average of the weekly dose in the study sample using initial dosage, escalated dosage and proportion of patients escalated. The quantities and the costs were reported separately. No other direct costs were included in the analysis.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
No indirect costs were included.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was performed using the average sales price plus 6% as an alternative source of the drug costs. This was relevant because from January 2005, reimbursement for Medicare Part B covered drugs (e.g. EPO and DARB) and was set at 106% of the average sales prices or wholesale acquisition cost.

**Estimated benefits used in the economic analysis**
The estimated benefits were reported in the "Results of the Review-" section.

**Cost results**
The mean drug cost per patient during weeks 0 to 16 was $9,039 in the EPO group and $13,555 in the DARB group.

**Synthesis of costs and benefits**
The authors provided average and incremental cost-effectiveness ratios. EPO dominated DARB because it was less costly and more effective. The incremental cost-effectiveness of EPO relative to DARB was -$376 per 1% increase in patients successfully treated during weeks 0 to 16 or weeks 5 to 16.

A threshold analysis was conducted to determine the percentage decrease in wholesale acquisition cost required to equate the drug costs between the two treatments. The wholesale acquisition cost of DARB would need to be reduced by 33% for equalisation.

A sensitivity analysis on the prices did not alter the relative cost-effectiveness of EPO and DARB. EPO remained more effective and less costly hence, dominant.

**Authors' conclusions**
Epoetin-alpha (EPO) was more effective and less costly than darbepoetin alpha (DARB) at Food and Drug Administration (FDA)-approved dosages. Hence, EPO is a dominant alternative to DARB for the treatment of chemotherapy-induced anaemia (CIA).
CRD COMMENTARY - Selection of comparators
The comparators used appear to have been chosen because they represented current practice in the authors’ setting and because their acquisition costs were relatively high and among top drug expenditures of hospitals and clinics. You should decide if the comparators represent current practice for the treatment of CIA in your own setting.

Validity of estimate of measure of effectiveness
The authors used data from the available studies selectively and compared the effectiveness results from the two trials directly. They did not state that a systematic review of the literature had been undertaken, but argued that the two chosen studies were the closest match available. This statement was not justified with descriptions of other studies or any other type of evidence. The patients’ baseline and demographic characteristics were presented and examined statistically. The authors acknowledged differences in setting (country), sample size and source populations between the studies used to estimate effectiveness for each treatment group, but did not explore the impact of differences when estimating effectiveness or include any sensitivity analysis of these parameters.

Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis. It considered the proportion of patients successfully treated and not requiring blood transfusions. This measure could be useful in this case, but it limits the ability to compare the results with those from other economic evaluations in other health fields.

Validity of estimate of costs
Although the authors reported that the costs were estimated from a payer’s perspective, only the direct drug costs were included. The authors suggested that other costs, such as office visits, laboratory costs, transfusion costs and patient opportunity costs, would be similar between the two treatment groups. If, as previous research apparently indicated, drug cost was the single, largest cost component, then these omissions might not affect the authors’ conclusions. However, the impact of different treatment settings was not considered in the estimation of the costs. The costs and the quantities were reported separately, allowing greater generalisability of the analysis. No statistical analysis of the quantities was performed, although they were not derived from patient-level data but from summary data. A sensitivity analysis of the prices was conducted using a second published source, and this did not change the cost-effectiveness results. The results of a threshold analysis indicated the extent of the change required to impact on the relative cost-effectiveness of EPO. The sources and dates of the prices were adequately reported, easing reproduction. Discounting was appropriately not performed since the study had a very short-term time horizon.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability was not discussed. Average cost-effectiveness ratios, which are meaningless and possibly misleading measures in health economics, were presented.

The authors reported several limitations to their study. First, the efficacy data came from two populations in two countries. Second, only drug costs were incorporated. Third, the results were based on reported data at an aggregate level. Fourth, one study had been presented as a conference poster only and not a peer-reviewed article. The authors argued that none of these would influence the results of their analysis, although this claim seems unlikely. They also failed to acknowledge the prevailing wisdom that combining trial data in this way has little or no scientific basis. The authors noted that a head-to-head trial had been completed, but did not satisfactorily explain why they chose to perform their analysis using non head-to-head data rather than the higher quality and more reliable data from a head-to-head trial. It was also unclear why the authors chose to focus on FDA-approved dosages while, at the same time, implying that these are not what are used in clinical practice.

Implications of the study
The authors noted that a randomised head-to-head study designed to compare outcomes and resource use between EPO and DARAB has recently been completed and will provide additional data for the question at hand. They also
recommended that additional research should be conducted to document the cost-effectiveness of the treatments using the most commonly prescribed dosages in clinical practice.

**Source of funding**
Funded by Ortho Biotech Clinical Affairs, LLC.

**Bibliographic details**

**PubMedID**
16238908

**DOI**
10.1185/030079905X65501

**Other publications of related interest**
Kotasek D, Canon JL, San Miguel J, et al. Correction/maintenance dosing (front loading) of darbepoetin alfa: final results from a randomized phase 3 active controlled trial (poster presentation). American Society of Hematology; 2004 Dec 4-7; San Diego, USA.


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anemia /chemically induced /drug therapy; Antineoplastic Agents; Clinical Trials, Phase III as Topic; Darbepoetin alfa; Double-Blind Method; Epoetin Alfa; Erythropoietin /administration & dosage /analogs & derivatives /economics; Female; Hematinics /administration & dosage /economics; Humans; Male; Middle Aged; Neoplasms /drug therapy; Randomized Controlled Trials as Topic; Recombinant Proteins

**AccessionNumber**
22005001710

**Date bibliographic record published**
30/06/2006

**Date abstract record published**
30/06/2006