Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients

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
Optimisation of epoetin therapy with intravenous iron therapy in hemodialysis patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised patients receiving chronic hemodialysis. Eligibility criteria included:

- age older than 18 years;
- haematologic parameters of mean cell volume >80 fl, TSAT between 19 and 30%, serum ferritin between 150 and 600 ng/ml, haemoglobin >9.5 g/dl;
- stable rhEPO dose for anaemia management over the previous 3 months, but this baseline dose had to exceed 700 U intravenously three times per week;
- no prior adverse reactions to parenteral iron.

Exclusion criteria were haemolytic anaemia, known aluminium toxicity, the presence of acute infection or inflammation, haematologic malignancies, active known acute or chronic gastrointestinal bleeding, or moderate hyperparathyroidism.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The dates of the effectiveness data, resource use data, cost data and the price year were not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same patient sample as that used in the effectiveness analysis.
**Study sample**

Forty-two patients receiving chronic hemodialysis completed a 16 to 20 week run-in period, during which maintenance ivID and recombinant erythropoietin (rhEPO) therapy were administered in amounts to achieve average TSAT of 20 to 30% and baseline levels of haemoglobin of 9.5 to 12.0 g/dl. Nineteen patients were randomised to the control group and 23 patients to the study group. The sample size was based on a 40% difference in Epoetin dose at a p value of 0.05 and a power of 80%; the required number of patients was 14 in each group.

**Study design**

The study took the form of a prospective, open-label, randomised controlled trial carried out at a single centre. Seventeen patients in the control group and 20 patients in the study group completed six weeks of treatment and 15 patients in the control group and 17 patients in the study group completed the six months of the study. Patients were followed-up for six months. Randomisation to the two groups was performed after enrolment, at which time all oral iron was discontinued. The investigator and staff were blinded to the zinc protoporphyrin (ZPP) and reticulocyte haemoglobin content (CHr) measurement results.

**Analysis of effectiveness**

A modified intention to treat analysis was used, with the last observation being carried forward only for those subjects who finished at least six weeks of the experimental phase of the study. Primary health outcomes were the rhEPO dose needed to maintain prestudy haemoglobin levels, serum iron and total iron binding capacity (TIBC), serum ferritin, TSAT, serum parathyroid hormone levels, ZPP, CHr, and incidence of hospitalisation, infections, and deaths. The two groups were similar in terms of age, gender, haemoglobin levels, Epoetin dose, iron indices of TIBC, TSAT, and ferritin, iron requirements, hyperparathyroidism, alkaline phosphatase levels, and baseline serum albumin.

**Effectiveness results**

ZPP did not change in either group.

Average haemoglobin during the six months was 10.3 in the control group and 10.6 in the study group.

In the control group there was no change from baseline in CHr during months 4 to 6 of the study: 0.23 compared with an increase of 1.41 in the study group, (p<0.05). CHr increased in 15 of the 20 study group patients.

Doses of Epoetin in the control group were constant during the six months, whereas they progressively decreased in the study group. The study group had more subjects with decreases in Epoetin dose (12 versus 4) during the last three months compared with the amount received during their four months stabilisation period and fewer patients with increases (2 versus 5) or no change in dose (6 versus 9), (p=0.0038).

During the four-month run-in period, the amount of iron administered to the two groups was similar. The iron dextran administered to patients to maintain a TSAT of 20 to 30% remained unchanged.

Maintenance ivID requirements in the study group increased from 176 to 501 mg/month and were associated with a progressive increase in serum ferritin to 658 ng/ml.

The monthly dose of iron and the presence/absence of an inflammatory state in the last three months were statistically significant factors influencing a change in ferritin level between month 6 and month 0.

Alkaline phosphatase and parathyroid hormone were unchanged and similar for both groups.

Two patients in the control group and one patient in the study group died.

There were no differences in hospitalisations or infection rate.

**Clinical conclusions**
Maintenance of TSAT between 30 and 50% reduces rhEPO requirement significantly over a six-month period.

Measure of benefits used in the economic analysis
The authors did not develop a summary benefit measure in the economic analysis. The study therefore used a cost-consequences design and the benefits are associated with the effectiveness results reported above.

Direct costs
Direct costs were not discounted (time horizon less than 1 year). Quantities and costs were not reported separately. Direct costs reflected treatment costs and related to the costs of syringes, saline diluent, iv administration sets and drugs. The quantity/cost boundary adopted was that of the hospital. The estimation of drug costs was based on wholesale prices. The price year was not reported.

Statistical analysis of costs
The authors reported cost savings per patient with maintenance of the TSAT between 30 and 50%.

Indirect Costs
Indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were reported.

Estimated benefits used in the economic analysis
The reader is referred to the effectiveness results reported above.

Cost results
Individual monthly costs and total costs for months two through six were lower for the study regimen compared with the control regimen. The cost difference was statistically significant by the third month and remained so for the remainder of the study, (p<0.02). There were potential savings of $109/month or $1,308/year per patient with maintenance of the TSAT between 30 and 50%.

Synthesis of costs and benefits
Consistent with the cost-consequences analysis, costs and benefits were not combined into cost-effectiveness ratios.

Authors' conclusions
Maintenance of TSAT between 30 and 50% reduces the rhEPO requirement significantly over a six-month period. The lower Epoetin requirements when maintaining TSAT above 30% can potentially result in significant cost savings.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used, namely that it was a current treatment alternative. You, as a user of the database, should decide if these health technologies are relevant to your setting.
Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial, which was appropriate for the study question. The study sample was representative of the study population. Groups were shown to be comparable at analysis. The analysis of effectiveness was handled credibly. These attributes suggest that the effectiveness results have high validity.

Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis. These were left disaggregated according to the cost-consequences approach that was adopted.

Validity of estimate of costs
More details could have been provided about which direct cost categories were included. The price year was not reported, and quantities and costs were not reported separately. No statistical or sensitivity analyses were reported on quantities or costs. Charges were not converted into costs and, hence, true opportunity costs were not estimated. These features of the cost analysis tend to limit the generalisability of the results to other settings.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but did not address the issue of generalisability to other settings. The authors did not present their results selectively. The study considered patients receiving chronic hemodialysis, and this was reflected in the authors’ conclusions. The authors noted that the sample size was small and that the observation period was short. Patients in the study were heterogeneous with considerable co-morbidity. This introduces potential bias and confounding which, in turn, may have influenced some of the effectiveness results.

Implications of the study
The authors suggested that maintenance of TSAT between 30 and 50% reduces rhEPO requirement significantly over a six-month period. The lower Epoetin requirements when maintaining TSAT above 30% can, potentially, result in significant cost savings. ZPP was not useful in the evaluation or serial evaluation of iron delivery to the erythron in the study. Changes in CHr correlated with changes in Epoetin dose, and this parameter should be evaluated further as a primary determinant of iron need in patients on Epoetin.

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