A cost evaluation of treatment alternatives in mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Turkey

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 recombinant activated Factor VII (rFVIIa), high-dose Factor VIII, prothrombin complex concentrate (PCC) and activated PCC (aPCC) for the treatment of acute bleeding episodes in haemophilia patients with inhibitors.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with haemophilia A, and presumably B, with inhibitors who were treated at three representative centres in Turkey. No further information was given.

Setting
The setting was primary and secondary care. The economic study was carried out in Turkey.

Dates to which data relate
The effectiveness and resource data were derived from observational data ranging from January 1996 to December 2002. The effectiveness data were validated on the basis of studies published between 1978 and 2000. The costs were expressed in 2003 prices.

Source of effectiveness data
The effectiveness data were derived from a retrospective analysis, expert opinion and published studies.

Link between effectiveness and cost data
The cost analysis was carried out retrospectively on the same sample as that used for the effectiveness analysis.

Study sample
The study sample comprised 105 bleeding episodes in 24 patients. Bleedings were treated with rFVIIa in 28 events, with PCC in 25, with aPCC in 9, and with high-dose Factor VIII in 43. Sixteen of the 24 patients were adults aged over 17 years. The mean weight was 49 kg. No further information was given.

Study design
The study was a retrospective observational analysis that was carried out by three representative centres in Turkey. No further information was given. The follow-up period was unclear and no blinded assessment was reported.

**Analysis of effectiveness**

The primary health outcome assessed was the effectiveness of the treatment alternatives. Effectiveness was defined as the absence of pain or swelling within 24 hours. The secondary outcomes were the mean time to resolution of bleeding episodes, the probability of switch from one treatment to another, the probability of re-bleeding, and the mean number of days of hospitalisation. No statistical analysis was reported. The patients' characteristics were not compared between groups.

**Effectiveness results**

The percentage of bleedings achieving a successful outcome with each agent was 89.3% with rFVIIa, 71.4% with high-dose FVIII, 66.7% with aPCC and 80% with PCC.

The mean time to resolution of bleeding episodes was 17.3 hours with rFVIIa, 23.0 hours with high-dose FVIII, 43.6 hours with aPCC and 40.2 hours with PCC.

The mean number of days of hospitalisation per bleeding episode was 1.12 with rFVIIa, 1.16 with high-dose FVIII, 1.89 with aPCC and 0.72 with PCC.

The reader is referred to the 'Estimates of Effectiveness and Key Assumptions' section below for the effectiveness estimates included in the model.

No safety issues were reported with any treatment.

**Clinical conclusions**

The results of the observational study suggested that rFVIIa was more effective and provided a faster time to resolution of bleeding than the other agents.

**Modelling**

A decision analytical model was built using DATA 3.5 software. The model was used to sequentially follow patients initially treated with rFVIIa, PCC, aPCC or high-dose Factor VIII. It was assumed that all bleeds would eventually cease, regardless of the treatment given.

**Outcomes assessed in the review**

To establish the outcome data used in the model (i.e. the absence of pain or swelling within 24 hours for the different agents for the treatment of severe haemophilia), the authors performed a non systematic review of the literature.

**Study designs and other criteria for inclusion in the review**

Not reported.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

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

Number of primary studies included
Nine primary studies dating from 1978 to 2000 were included in the review.

Methods of combining primary studies
Individual parameters were mostly taken from one source. Hence, it was not relevant to combine the studies. For those parameters for which more than one source was used, it was unclear what strategy was used to combine the studies.

Investigation of differences between primary studies
Potential differences between the primary studies were not discussed in the analysis.

Results of the review
The percentage of bleedings achieving a successful outcome ranged from 85 to 92% with rFVIIa, from 33.3 to 80% with high-dose FVIII, from 60 to 81.3% with aPCC, and was less than 70% with PCC.

The reader is referred to the 'Estimates of Effectiveness and Key Assumptions' section below for the effectiveness estimates included in the model.

Methods used to derive estimates of effectiveness
Expert opinion was used to validate the results obtained from the review of the literature and the observational data.

Estimates of effectiveness and key assumptions
The effectiveness of rFVIIa (89%) and high-dose Factor VIII (71.4%) were based directly on the patients’ data, as they were in line with published data and had been validated by expert opinion. The effectiveness of aPCC (79%) was based on a review of the literature since patients’ data differed from published information and expert opinion. Finally, a value of 75% was considered for PCC as it was suggested that both the published data and patients’ data were unrealistic.

Measure of benefits used in the economic analysis
No summary measure of health benefits was assessed. The study was, in effect, a cost-consequences analysis.

Direct costs
The direct costs included in the analysis were those of the Turkish Reimbursement Institutions. Resource use was obtained from observational data, with information collected on haemostatic agents, concomitant medications, outpatient administration and hospitalisation. Resource use dated from January 1996 to December 2002. The study was planned to calculate the total cost of a full course of the different agents. The costs and the quantities were not reported separately. The costs were expressed in 2003 prices. The authors acknowledged that the unit costs were obtained from Turkish sources, but provided no further details. It was unclear whether discounting was performed since the time horizon of the model was not defined.

Statistical analysis of costs
The data were treated as point estimates (i.e. the data were deterministic).
Indirect Costs
The indirect costs were not included in the analysis.

Currency
Turkish Lira (TRL) and US dollars ($). No conversion rate was provided.

Sensitivity analysis
A sensitivity analysis was performed on those parameters that were likely to vary among hospitals or with high areas of uncertainty. These included the efficacy of first-line therapy, the length of hospital stay and the probability of a re-bleed.

Estimated benefits used in the economic analysis
See the 'Analysis of Effectiveness' section.

Cost results
The overall total cost was TRL 13,348 (US$9,113) for rFVIIa, TRL 18,370 (US$12,542) for aPCC, TRL 22,080 (US$15,075) for high-dose factor VIII, and TRL 13,639 (US$9,128) for PCC.

The results of the sensitivity analysis showed that varying the parameters with uncertainty always yielded rFVIIa as the cheaper option.

Synthesis of costs and benefits
The costs and effects were not combined. Since the authors assumed equal effectiveness of the agents, they considered the analysis to be a cost-minimisation study. In fact, the model suggested that rFVIIa was more effective than the remaining treatments. Therefore, the study was a cost-consequences analysis.

Authors' conclusions
The results of the study showed that recombinant activated Factor VII (rFVIIa) and prothrombin complex concentrate (PCC) are associated with similar direct treatment costs that are lower than those associated with other first-line options. However, rFVIIa had higher efficacy than PCC and may, therefore, be considered the agent of choice for the treatment of haemophilia patients with inhibitors in Turkey.

CRD COMMENTARY - Selection of comparators
The authors clearly justified their choice of the alternatives, which seemed to represent current practice in the authors’ setting. Moreover, the authors used all the alternatives available to treat haemophilia in Turkey.

Validity of estimate of measure of effectiveness
The authors made use of observational data to determine clinical effectiveness. As haemophilia is a rare condition, the sample size was expected to be small. More information on the baseline characteristics and sample size could help in understanding clinical effectiveness. To improve the information, experts’ opinions and published literature were consulted. However, it was not described how this information was gathered. In addition, there was no statistical analysis of whether the difference in effectiveness was relevant. Therefore, the internal validity of the results was not clear.

Validity of estimate of measure of benefit
Having defined the study as a cost-minimisation analysis, as it was assumed that all bleeds would eventually cease...
regardless of treatment, the authors then focused on comparing the direct costs for the treatment of mild-to-moderate bleeding episodes. However, they also assessed the primary health outcome (i.e. the absence of pain or swelling within 24 hours), showing rFVIIa to be more effective than the other treatment alternatives. Therefore, the study should, in fact, be classified as a cost-consequences analysis.

Validity of estimate of costs
The perspective adopted was that of the Turkish Reimbursement Institutions. As such, it appears that the relevant cost categories have been included. However, although safety issues were not reported, it was unclear how adverse events were handled. It is widely recognised that costs associated with adverse events may have an important impact in the overall calculation of drug costs. The authors should have included more relevant information on the topic. Resource use was reported separately, based on observational data. This design can provide effective estimates but, owing to the small sample size, published literature and expert opinion were also used to provide valuable information on the parameters of the model. The sources of the unit cost estimates and the price year were reported. The costs and the quantities were not reported separately. Conversion rates were not reported. Sensitivity analyses on cost parameters were performed. However, the ranges used were not justified on the basis of the literature. These limitations may well influence the internal validity of the model, as well as its transferability to other settings.

Other issues
The authors should have combined the costs and effects in an incremental analysis, as one of the agents was estimated to be more effective. The authors compared their results with similar published studies outside Turkey. They suggested that their results may help decision-making in their setting, as well as in other countries in the region. This statement was not addressed in the sensitivity analysis, or in any other analysis of uncertainty. Moreover, the limitations mentioned already suggest that the internal validity of the model should be revised carefully before making any generalisation to other settings. The authors did not report any further limitations of their study.

Implications of the study
rFVIIa was estimated to be more effective at a lower cost than the alternatives considered. The authors suggested that their results should improve the development of clinical guidelines in Turkey, as well as in other countries with similar treatment options. They also suggested that the decision to use rFVIIa or PCC should be based on clinical criteria, rather than the cost per vial or the cost per individual bleed.

Source of funding
Financed by Novo Nordisk, Turkey.

Bibliographic details

Other publications of related interest
Odeyemi IO, Guest JF. Modelling the economics impact of recombinant activated Factor VII and activated prothrombin-complex concentrate in the treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX at a comprehensive care centre in the UK. Journal of Medical Economics 2002;5:51-64.


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