A cost minimization model for the treatment of minor bleeding episodes in patients with haemophilia A and high-titre inhibitors

Putnam K G, Bohn R L, Ewenstein B M, Winkelmayer W C, Avorn J

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
Two haemostatic agents for the home treatment of minor bleeding episodes in paediatric patients with haemophilia A and inhibitory antibodies to factor VIII (FVIII) were examined. The haemostatic agents studied were activated prothrombin complex concentrates (aPCC) and recombinant factor VIIa (rFVIIa).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of paediatric patients with haemophilia A and inhibitory antibodies to FVIII.

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

Dates to which data relate
The dates to which the effectiveness and resource use data related were not reported. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from experts’ opinions.

Modelling
A cost-minimisation model was constructed to determine the most economical strategy for treating patients who present with high-titre inhibitors to FVIII. The scenario considered in the study was that of a 10-year-old patient with severe haemophilia A, who developed a shoulder haemarthrosis with symptoms that began approximately 1 hour prior. The patient had a history of frequent minor bleeds that had been treated with either rFVIIa or aPCC. In addition, 2 months prior the patient had experienced a major iliopsoas bleed for which a protracted course of porcine FVIII was administered.

The time horizon of the model was 24 hours. The structure of the decision tree was reported. The two main branches of the tree (treatment with aPCC or rFVIIa) were identical. Patients could either improve or not improve (thus experiencing deterioration) at 8 to 12 hours. Patients who improved received no further treatment or continued the initial treatment, and could either improve or not improve at 24 hours. Patients who did not improve either continued
treatment with the initial haemostatic agent or were switched to the competing one, and could either improve or not improve.

**Methods used to derive estimates of effectiveness**
A Delphi panel framework was used to derive clinical estimates. The authors stated that, as background to development of the model, an extensive review of the literature was carried out. However, owing to the limited number of studies retrieved and the high heterogeneity of the literature, it was preferred to contact 11 US-based haemophilia experts. The panel was asked to provide clinical information to populate the decision model. To provide robust estimates, two rounds of questionnaires were used.

**Estimates of effectiveness and key assumptions**
The initial probability of success (at 8 to 12 hours) was 0.90 (range: 0.60 - 0.95) with rFVIIa and 0.75 (range: 0.50 - 0.90) with aPCC.

The initial dose was 270 microg/kg rFVIIa and 75 units/kg aPCC.

For subsequent treatment after initial improvement:
- 27% discontinued with rFVIIa, but 73% continued treatment (270 microg/kg in the next 12 to 16 hours);
- 9% discontinued with aPCC, but 91% continued treatment (120 units/kg in the next 12 to 16 hours).

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic analysis because it was assumed that the two treatments were clinically equivalent. In effect, a cost-minimisation analysis was performed.

**Direct costs**
The authors stated that the cost analysis was carried out from a societal perspective, but only the costs of the two haemostatic agents were included. The unit costs were presented separately from the quantities of resources used. The resource use data were based on experts’ opinions. The costs were estimated using average wholesale prices, which were derived from a study published in 2000. The price year was not explicitly stated. Discounting was not relevant because of the short timeframe of the analysis.

**Statistical analysis of costs**
No statistical analyses of the costs were performed.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was carried out to assess the threshold values at which the preferred strategy changed. The ranges of values were derived from the literature for the clinical data and were varied by +/- 20% for product costs. Two-way sensitivity analyses on the drug costs and doses were also carried out.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The estimated cost of a home treatment course was $21,000 with aPCC and $33,400 with rFVIIa. The sensitivity analysis showed that the base-case cost-difference was not sensitive to plausible variations in clinical data, prices and doses. The preferred strategy changed only when clinically unlikely changes in baseline values were considered. When panelists were asked to estimate the overall dosage for each treatment strategy, the total regimen costs were still lower with aPCC.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-minimisation analysis was performed.

Authors' conclusions
The use of activated prothrombin complex concentrates (aPCC) as the first-line home haemostatic treatment for minor bleeding episodes in children with haemophilia A and inhibitory antibodies to factor VIII (FVIII) led to cost-savings in comparison with recombinant factor VIIa (rFVIIa).

CRD COMMENTARY - Selection of comparators
The selection of the comparator was appropriate since the two treatments would appear to represent commonly used haemostatic agents for patients with haemophilia A and inhibitory antibodies to FVIII. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was based on the opinions of a panel of experts. The choice of this approach was justified on the basis of the scarcity of comparative literature on rFVIIa and aPCC. A Delphi framework was used to derive valid clinical estimates and some information on the approach used to elicit the model inputs was reported. Some sensitivity analyses were carried out to examine the uncertainty surrounding clinical data. Expert opinion represents a weak source of data, but the authors stated that the estimates used in the model were consistent with the published literature, which could not be used because of the lack of comparative clinical trials. In fact, the authors noted that the bulk of the evidence came from observational studies.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-minimisation analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The cost analysis considered only the cost of the haemostatic agents, although the authors stated that a societal perspective had been adopted. The authors stated that the costs of hospitalisation were not included because studies had shown that drug costs accounted for over 80% of the total costs for the treatment of inpatient and outpatient bleeding episodes. Information on the unit costs and resource consumption was provided, which will help others to replicate the cost analysis in other settings. The cost estimates were treated deterministically but extensive sensitivity analyses were carried out. The source of the data was reported, but not the price year. This limits the possibility of performing reflation exercises in other time periods. The authors noted that the difference in costs was attributable primarily to the higher cost of rFVIIa, which appears quite straightforward since only drug costs were considered.

Other issues
The authors stated that their findings were not consistent with those from a published study, mainly because initial treatment was defined differently. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the authors noted that the use of the shoulder as the site of the bleed in the clinical scenario might limit the external validity of the analysis. However, the use of extensive sensitivity analyses, which confirmed the results of the base-case model, was helpful. The reason for choosing a cost-minimisation approach was unclear, as it was stated that the two treatments were equally effective but the rates of success, as defined by the experts, favoured the rFVIIa strategy. The authors noted that the analysis did not consider the "time to resolution" variable, which was relevant when determining the preferred strategy. Finally, the use of quality of life measures could have improved the outcomes of the rFVIIa strategy.

**Implications of the study**
The study results support the use of aPCC for the home treatment of minor bleeding episodes in children with haemophilia A and inhibitory antibodies to FVIII.

**Source of funding**
Supported by an unrestricted research grant from Norvo Nordisk.

**Bibliographic details**

**PubMedID**
15876272

**DOI**
10.1111/j.1365-2516.2005.01098.x

**Other publications of related interest**
Odeyemi IA, Guest JF. Modeling the economic impact of recombinant activated factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting factors VIII and IV in the UK. Journal of Medical Economics 2002;5:119-33.


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Autoantibodies /immunology; Blood Coagulation Factors /administration & dosage /economics /therapeutic use; Child; Drug Administration Schedule; Factor VII /administration & dosage /economics /therapeutic use; Factor VIII /immunology; Factor VIIa; Health Care Costs; Hemarthrosis /drug therapy /economics /etiology; Hemophilia A /complications /drug therapy /economics; Home Care Services /economics; Humans; Models, Economic; Recombinant Proteins /administration & dosage /economics /therapeutic use

**AccessionNumber**
22005000893

**Date bibliographic record published**
31/01/2006
Date abstract record published
31/01/2006