Pharmacoeconomic analysis of recombinant factor Vlla versus APCC in the treatment of minor-to-moderate bleeds in hemophilia patients with inhibitors

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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 study examined three regimens for home treatment of minor-to-moderate bleeds in haemophilia patients with inhibitors. The regimens consisted of first-, second- and third-line treatments using recombinant activated Factor VII (rFVIIa) and activated prothrombin-complex concentrate (APCC).

The first regimen (APCC-APCC-rFVIIa) was APCC (first-line), followed by another APCC (second-line) in case of failure of the first-line treatment, and then rFVIIa (third-line) in case of failure of the second-line treatment.

The second regimen (APCC-rFVIIa-rFVIIa) was APCC (first-line), followed by rFVIIa (second-line) in case of failure of the first-line treatment, and then by another course of rFVIIa (third-line) in case of failure of the second-line treatment.

The third regimen (rFVIIa-rFVIIa-rFVIIa) was rFVIIa as first-, second- and third-line treatments.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of haemophilia patients with inhibitors, who were experiencing minor-to-moderate bleeds. A mild-to-moderate bleed was defined as one which could initially be treated at home.

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

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1998 and 2003. The price year was 2005.

Source of effectiveness data
The effectiveness data were obtained from a synthesis of published studies.

Modelling
A published decision analysis model was adapted to the US context to assess the cost of treating a bleed for the three on-
demand treatment regimens using rFVII and APCC for home treatment of mild-to-moderate bleeds in a hypothetical cohort of patients. The model was based on a decision tree. All patients received a first-line treatment and bleeding could be resolved. In the case of failure of the first-line treatment (re-bleeding), a second-line therapy was given, followed by a third-line treatment in the case of a further failure. Continued bleeding was defined as a bleed that did not initially resolve after treatment had been administered (primary failure). Re-bleeding was defined as a bleed that was initially resolved with treatment but which then recurred. The structure of the decision tree was reported graphically. A short time horizon was used, although it was not explicitly reported.

Outcomes assessed in the review
The outcomes estimated from the literature were efficacy of each single agent, the efficacy of each strategy after third-line treatment, and the re-bleeding rate.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively rather than through a systematic review of the literature. No information on the design or other characteristics of the primary studies was provided. Some evidence came from the published decision model.

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
Six primary publications provided clinical data.

Methods of combining primary studies
The efficacy data were pooled across studies of each agent, and weighted averages were calculated to combine the primary estimates. Ninety-five per cent confidence intervals (CIs) for the proportions of controlled bleeds were estimated using a normal approximation of the binomial distribution.

Investigation of differences between primary studies
Not reported.

Results of the review
The efficacy was 92% with rFVIIa (95% CI: 89 to 93) and 78% with APCC (95% CI: 77 to 84).

The efficacy after the third-line treatment was 100% with all regimens.

The re-bleeding rate was 15% (range: 10 to 20) with both rFVIIa and APCC.

Measure of benefits used in the economic analysis
The summary benefit measure was the success rate (bleeding resolved) of the three regimens. This was derived directly from the effectiveness analysis. The authors stated that the final efficacy was 100% with all three regimens.

**Direct costs**

The perspective taken in the analysis of effectiveness was not explicitly stated, but only drug costs were included in the analysis. Since treatments were administered at home, other resources such as physician visits or hospitalisations were not considered in the base-case. The unit costs and the resource quantities were presented separately. Resource use was estimated using data derived from the literature, while costs were estimated from average wholesale prices. Average doses for treatment regimens depended on the patient's weight, which was based on authors' assumptions (70 kg; range: 66 to 82). Discounting was not relevant as the costs were incurred during a short time. The price year was 2005.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not considered in the economic evaluation.

**Currency**

US dollars ($).

**Sensitivity analysis**

Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the estimated costs to variations in the efficacy rates, re-bleeding rates, dosing, drug costs and patient weight. Alternative ranges of values were derived from the literature. Hospitalisation costs were also considered in the sensitivity analysis. A threshold analysis on efficacy rates and drug costs was performed to determine hypothetical cost-neutrality between treatment strategies. A probabilistic sensitivity analysis was also carried out using a Monte Carlo simulation with 10,000 replications.

**Estimated benefits used in the economic analysis**

The effectiveness of the three regimens (from first-line to third-line treatment) was 100%.

**Cost results**

Total home treatment costs after three lines of treatment were $32,331 with APCC-APCC-rFVIIa, $30,951 with APCC-rFVIIa-rFVIIa, and $28,101 with rFVIIa-rFVIIa-rFVIIa.

The rFVIIa only strategy was less expensive because of the lower re-bleeding rates, which led to lower requirements for second- and third-line treatments.

The results of the univariate sensitivity analysis corroborated the base-case findings since the rFVIIa-rFVIIa-rFVIIa regimen was the least expensive treatment in most scenarios.

The APCC-rFVIIa-rFVIIa regimen was never the cheapest treatment, and was preferred only when the mean dose of APCC decreased by 20% or when the mean dose of rFVIIa increased by 20%.

The threshold analysis showed that keeping the APCC efficacy at the base-case rate, the rFVIIa efficacy rate should decrease to 82% (92% in the base-case) for the overall cost of the treatment regimens to be the same between the rFVIIa-only strategy and APCC-continuing strategies.
The probabilistic analysis showed that the rFVIIa-rFVIIa-rFVIIa regimen was less expensive than the other two regimens in 68% of simulations. The APCC-rFVIIa-rFVIIa regimen was less expensive in 14% of simulations, and the APCC-APCC-rFVIIa regimen was less expensive in 18% of simulations.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant as the three regimens were equally effective when the third-line treatment was administered. Consequently, all patients were assumed to finally resolve the bleeding episode.

Authors’ conclusions
The use of a recombinant activated Factor VII (rFVIIa) regimen for the home treatment of minor-to-moderate bleeds in haemophilia patients in the USA led to cost-savings in comparison with strategies involving activated prothrombin-complex concentrate (APCC), through the avoidance of second- and third-lines of treatment. The results were robust to variations in some clinical and economic data.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as the three regimens based on both APCC and rFVIIa were widely used in the USA for the treatment of mild-to-moderate bleeds in haemophilia patients with inhibitors. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were estimated from published studies. It was not stated whether a systematic review of the literature was undertaken to identify the primary studies, which appear to have been included selectively. There was no information on the studies used to estimate the clinical inputs, thus it was difficult to assess the validity of the primary estimates. The issue of uncertainty in the data was addressed through sensitivity analyses. The authors reported the approach used to combine the primary estimates and the sources of studies from which the alternative values used in the sensitivity analysis were derived.

Validity of estimate of measure of benefit
No summary benefit measure was actually used in the analysis, as the authors assumed equal effectiveness of the three regimens at the end of the three-line treatments. Please see the comments in the ‘Validity of estimate of measure of effectiveness’ field (above).

Validity of estimate of costs
The cost analysis was restricted to the cost of the agents. Other resources associated with different aspects of treatment were not included. This was justified on the basis of the equal effectiveness of the two treatments and on the lack of associated side effects. Potential hospitalisations (2 days) were only included in the sensitivity analysis, and they had no impact on the results. The unit cost of the preparations was provided, as was the source, which represented a typical source of US costs. The quantities of resources used were also provided, which enhances the possibility of replicating the analysis in other settings. The authors carried out some statistical analyses of the costs, and the cost estimates were varied in the sensitivity analysis. The price year was reported, which will enable the results of the study to be reflated in other time periods.

Other issues
The authors reported the results from other studies carried out in several countries. Studies performed in the USA appear to supported APCC strategies. However, it was noted that such studies failed to take failure and re-bleeding into account. The issue of the generalisability of the study results was not explicitly addressed, but extensive sensitivity analyses were performed, which enhance the validity and robustness of the model results. The authors noted that the main drawback of the modelling exercise was the lack of published head-to-head randomised clinical trials.
directly comparing the alternative regimens. The authors pointed out, as a strength of the analysis, that the decision model accounted for the complexity of treating bleeds in inhibitor patients.

**Implications of the study**
The study results supported the use of rFVIIa regimens for the home treatment of minor-to-moderate bleeds over multiple lines of treatment in haemophilia patients with inhibitors. The authors suggested that future studies should examine not only variables such as time to bleed resolution, but also patient- and caregiver-reported outcomes.

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