Novo Nordisk Limited
Haematology Business Unit Telephone: +44 (0)1293 762 002
Broadfield Park Brighton Road Crawley West Sussex RH11 9RT England
Telephone: +44 (0)1293 613 555 Facsimile: +44 (0)1293 613 535 Internet: www.novonordisk.co.uk
Registered Office: As above Reg. No: 1118740

[no notes on this page]

Modelling 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 IX in the UK

Isaac A O Odeyemi[1], Julian F Guest[1]

Summary

This study estimated the costs and consequences of using recombinant activated Factor VII (rFVIIa; NovoSeven®*) at home, compared to activated prothrombin-complex concentrate (aPCC; FEIBA®*) at home, to manage a minor (i.e. mild to moderate) bleeding episode in adults with high titre, high responding inhibitors (>10 BU). The analysis was performed from the perspective of the UK's National Health Service (NHS).

Clinical outcomes and resource utilisation attributable to managing a minor bleed were obtained from published literature, supplemented with information about treatment patterns and associated resource utilisation derived from interviews with a panel of 22 consultant haematologists experienced in managing inhibitor patients. Using these data sources a decision tree modelling the management of a minor bleed, initially at home, was constructed. Unit resource costs at 1999/2000 prices were applied to the resource utilisation estimates in the model to estimate the expected NHS cost of managing a minor bleeding episode. Consensus on the probabilities and resource utilisation estimates in the model were reached at a meeting comprising seven panel members.

Key words: activated prothrombin-complex, costs, Factor VII, economics, haemophilia

Accepted for publication: 16th September 2002

[1] CATALYST Health Economics Consultants, Northwood, Middlesex, UK

Address for correspondence: Dr Julian F Guest, CATALYST Health Economics Consultants, 34b High Street, Northwood, Middlesex HA6 1BN, UK. Tel: +44 (0)1923 450045, fax: +44 (0)1923 450046, e-mail: jg.catalyst@dial.pipex.com

* NovoSeven® and FEIBA® are registered trademarks of Novo Nordisk and Baxter Healthcare, respectively.

[no notes on this page]

The expected NHS cost of managing a minor bleeding episode initially treated with rFVIIa or aPCC at home was estimated to be £12,944 and £14,645, respectively. Additionally, the expected time to resolving a minor bleeding episode when initially treated with rFVIIa or aPCC at home was estimated to be 32 hours and 60 hours, respectively. Hence, rFVIIa improves clinical outcome compared to aPCC, but at no additional cost to the NHS, resulting in rFVIIa being the cost-effective treatment. This finding warrants further investigation in a prospective, comparative, randomised, controlled study.

Introduction

There are currently an estimated 6,000 patients with haemophilia A or B in the UK. Up to 15% of severely affected haemophilia A patients develop neutralising antibodies (inhibitors) against Factor VIII and 1% to 5% of patients with haemophilia B develop antibodies to Factor IX. The UK Haemophilia Centre Directors' Organisation reported an average annual incidence of new inhibitors of about 1.5 per 1000 individuals[1].

The development of inhibitors is one of the most serious complications in haemophilia management. In most patients with high titre, high responding inhibitors, the bleeding complications cannot be treated using conventional therapies. Hence, they are treated with activated prothrombin-complex concentrate (aPCC) and recombinant Factor VII (rFVIIa). aPCC has been the subject of several studies. In two studies conducted by Hilgartner *et al* in the US [2,3], a mean 3 doses of aPCC resolved 78% of bleeds after 36 hours and 79% of minor bleeds. In a French multicentre study, aPCC controlled 81.3% of bleeds with fewer than three infusions, although the efficacy of aPCC was assumed in some cases[4]. However, a recent worldwide surveillance study[5] reported efficacy levels of 77% for aPCC, similar to those reported by Hilgartner *et al*[2,3]. The efficacy of rFVIIa increases as the time between bleed onset and the start of treatment shortens[6,7]. This led to suggestions that early treatment at home may improve outcome. In one US home-treatment study[8], Key *et al* reported 92% of bleeds being resolved within 24 hours when a mean 2.3 doses of rFVIIa were administered at a mean 1.2 hours from the start of a bleed.

The difficulty in predicting patterns of bleeding episodes, as well as the effectiveness and duration of treatment options, often hinders budgeting[9]. This has led to geographical variations in the funding of high-cost recombinant and plasma-derived products used to manage and prevent individual bleeding episodes in the UK[10]. Against this background, this study estimated the economic impact of using rFVIIa compared to aPCC at home to manage a minor (i.e. mild to moderate) bleeding episode among patients who have high titre, high responding inhibitors (>10 BU), from the perspective of the NHS in the UK.

[no notes on this page]

Methodology

Clinical outcomes and resource utilisation

There were no published studies directly comparing the home treatment of a minor bleed with rFVIIa and aPCC. Therefore, following a literature review, it was decided that the studies by Hilgartner *et al*[2] and Key *et al*[8] could be used to provide the clinical basis for a decision model pertaining to first-line treatment at home with aPCC and rFVIIa, respectively. These studies were selected because the description of the trial protocol and results were sufficiently informative to enable us to compare the dose, dosage and efficacy of treatments.

Since none of the published studies described the treatment patterns and associated resource use attributable to managing a minor bleed that did not resolve following first-line treatment at home, this was established by interviewing a panel of 22 consultant haematologists from across the UK with experience of managing patients with inhibitors. Haematologists were selected on the basis of being representative of the healthcare they provided for inhibitor patients and of being geographically representative of the UK. These interviews were semi-structured, qualitative and quantitative discussions that evolved with each expert interview. They included standard questions on patient management, treatment paths and resource use as well as open questions that enabled any other information to be recorded. The minutes of each meeting were sent to the panel members for annotation and verification. Consensus on the probabilities and resource utilisation estimates used in the treatment paths were reached at an expert panel meeting comprising seven of the panel members. Expert panel members were selected in accordance with set guidelines for selection of Delphi panel members[11] . The expert panel agreed with our use of the Hilgartner *et al*[2] and Key *et al*[8] studies as the basis for the efficacy and associated resource utilisation pertaining to first-line treatment at home with aPCC and rFVIIa, respectively.

Decision model

Using the decision analysis software package DATA™* 3.5 for Windows and information obtained from the published literature and the panel of haematologists, a decision tree modelling the management of a minor bleed, initially at home, was constructed (Figure 1).

The model comprises: the initial home treatment for a bleed, subsequent treatments for a bleed at a Haemophilia Treatment Centre (Comprehensive Care Centre (CCC)), probability of switching from one treatment to another, duration of use for each treatment, probability that each treatment would resolve a bleed, probability of a re-bleed and treatment for managing a re-bleed.

In addition, the model contains resource utilisation estimates associated with:

* DATA™ is a registered trademark of Treeage, USA

[no notes on this page]

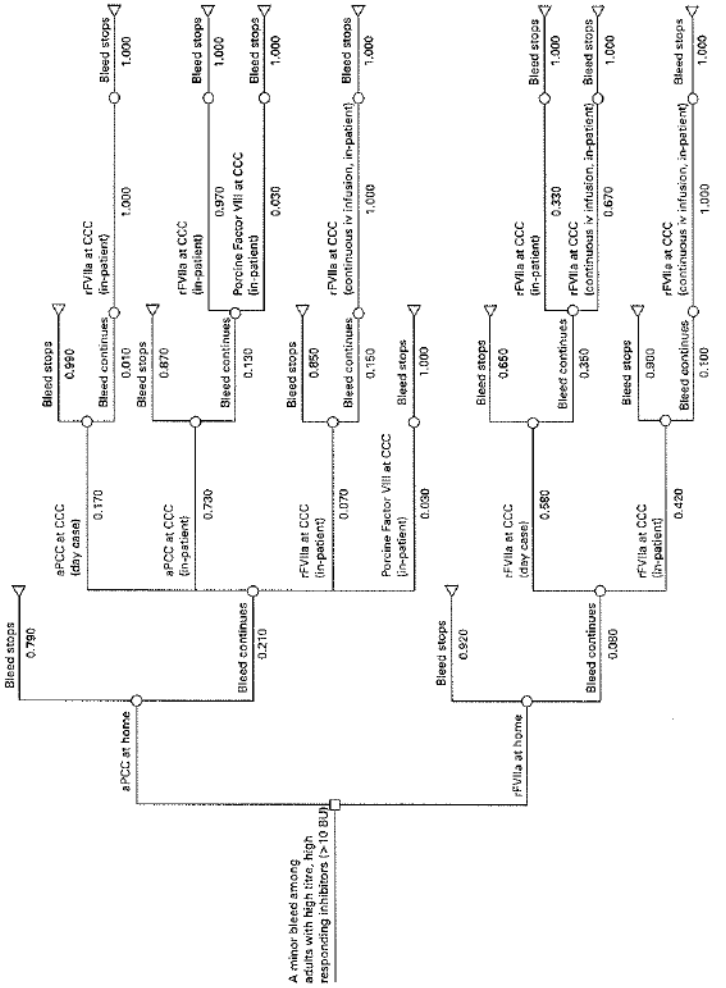


Figure 1. Decision tree modelling the management of a minor bleed among adults with high titre, high responding inhibitors (>10 BU) who start treatment at home with rFVIIa or aPCC. Numbers denote the probability that a patient will follow a particular path

[no notes on this page]

haemostatic drugs, co-medication, outpatient visits, inpatient stay, clinical tests/investigations, and ambulance transport.

Unit resource costs at 1999/2000 prices[12-14] were applied to the resource utilisation estimates in the decision model to determine the expected NHS cost of initially managing a minor bleeding episode at home with aPCC and rFVIIa. The model also estimated the expected time to bleed resolution following initial treatment at home with rFVIIa and aPCC.

Sensitivity analyses

Sensitivity analyses tested the robustness of the results by varying probabilities and resource use values in the model to determine how they affected the economic impact of rFVIIa compared with aPCC. The large values used for these analyses reflect the large range of uncertainties within the model.

Results

Treatment patterns for managing a minor bleed at home

The decision model incorporated the following treatment patterns and associated estimates of resource utilisation.

Management with aPCC

The haematologists considered that following the onset of a minor bleed at home, patients would self-administer a mean 3 doses of aPCC (mean 75 units/kg body weight). On the basis of published data[2], it was assumed that a mean 79% of bleeds would resolve with first-line home treatment and a mean 21% of bleeds would require subsequent treatment at a CCC.

The haematologists considered that of the unresolved bleeds requiring treatment at a CCC:

- A mean 17% would be treated as a day case over a mean 2 days and receive a mean 2.6 doses of aPCC (mean 87.5 units/kg body weight every 12 hours). They also considered that a mean 99% of these bleeds would resolve and the other 1% would result in a patient being admitted for a mean 21.8 days and receiving a mean 9.5 doses of rFVIIa (mean 88.8 mg/kg body weight), after which these bleeds would resolve.
- A mean 73% would be admitted for a mean 3 days and receive a mean 5.4 doses of aPCC (mean 53.1 units/kg body weight), after which a mean 87% of these bleeds would resolve. They also considered that a mean 97% of the unresolved bleeds would be treated with a mean 9.5 doses of rFVIIa (mean 88.8 µg/kg body weight) and a mean 3% would be treated with a mean 5 doses of Porcine Factor VIII (mean 55 units/kg body weight) after which these bleeds would resolve.
- A mean 7% would be admitted for a mean 1.8 days and switched to rFVIIa and receive a mean 9.5 doses (mean 88.8 µg/kg body weight every 2 hours), after which a mean 85% of these bleeds would resolve. The haematologists considered that the other 15% of bleeds would result in further stay at a CCC for a mean 2.5 days and be treated with a continuous iv infusion of rFVIIa (mean

[no notes on this page]

20 μg/kg body weight/hour)*, after which all bleeds would resolve.
- A mean 3% would be admitted for a mean 2 days and switched to Porcine Factor VIII and receive a mean five doses (mean 55 units/kg body weight), after which the bleeds would resolve.

Management with rFVIIa

The haematologists considered that following the onset of a minor bleed at home, patients would self-administer a mean 2.3 doses of rFVIIa (mean 90 μg/kg body weight). On the basis of published data[8], it was assumed that a mean 92% of bleeds would resolve at home without further treatment and a mean 8% of bleeds would require subsequent treatment at a CCC.

The haematologists considered that of the unresolved bleeds requiring treatment at a CCC:
- A mean 58% would be treated with a mean 2.5 doses of rFVIIa (mean 93.8 μg/kg body weight) over a mean 1.2 outpatient visits, after which a mean 65% of bleeds would resolve without further treatment. They also considered that the unresolved bleeds would result in a patient being admitted to a CCC, with a mean 67% of them being treated with a continuous iv infusion of rFVIIa (mean 20 μg/kg body weight every hour) over 2.5 days*. The other mean 33% of unresolved bleeds would be expected to receive a mean 9.5 doses of rFVIIa (mean 88.8 μg/kg body weight) over a mean 1.8 days, after which the bleeds would resolve.
- A mean 42% of patients with bleeds would be admitted for a mean 1.8 days and treated with a mean 9.5 doses of rFVIIa (mean 88.8 μg/kg body weight), after which a mean 90% of bleeds would resolve without further treatment. They also considered that the other 10% would result in further stay at a CCC for a mean 2.5 days and be treated with a continuous iv infusion of rFVIIa (mean 20 μg/kg body weight every hour)*, after which the bleeds would resolve.

Re-bleeds

The haematologists interviewed considered that a second bleed would be directly related to the initial episode if it occurred at the same site within a mean 6.9 days after the initial bleed resolved. Furthermore, they considered that a re-bleed would occur in a mean 15% of bleeding episodes among adult patients. Re-bleeds would be managed using the same treatment as that which controlled the initial episode.

Other resource use

The haematologists considered that tranexamic acid (25 mg/kg body weight, 3 times daily) would be administered to a mean 6% of bleeds treated with aPCC and 28% of bleeds treated with rFVIIa. They also considered that Fibrin Glue (1.5 ml) would be administered to a mean 3% of bleeds regardless of whether the initial treatment was aPCC or rFVIIa.

The haematologists considered that home-treated adults with a minor bleed who

*rFVIIa is not licensed for continuous iv infusion in the UK

[no notes on this page]

subsequently attend a CCC would receive the following medication for pain relief:

- Diamorphine (mean 96 mg daily) would be prescribed to a mean 10% of patients.
- Morphine sulphate (mean 23 mg, 2 times daily) would be prescribed to a mean 4% of patients
- Pethidine (mean 100 mg, 6 times daily) would be prescribed to a mean 4% of patients.
- Dihydrocodeine (mean 57 mg, 5 times daily) would be prescribed to a mean 10% of patients.
- Kapake (codeine phosphate/paracetamol 1.5 tablets, 5 times daily) would be prescribed to a mean 1% of patients.
- Paracetamol (mean 1.5 tablets of 250 mg tabs, 4 times daily) would be prescribed to a mean 9% of patients.

Routine tests

The haematologists considered that adult patients who subsequently attend a CCC would undergo the following tests:

- Bethesda assay for a mean 33% of patients at admission.
- Biochemistry tests for a mean 20% of patients at admission.
- Factor VII plasma level assay for patients who receive a continuous iv infusion of rFVIIa and this would be repeated every 24 hours.
- Ultrasound for a mean 5% of all patients.

Ambulance travel

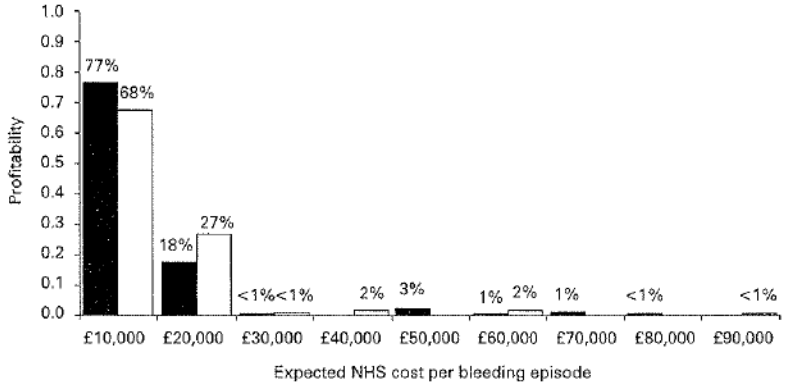
The haematologists considered that 4% of home-treated adults with a minor bleed who subsequently attend a CCC would be transported to hospital by ambulance, irrespective of their initial haemostatic treatment. Patients would generally stay within the vicinity of the hospital until the bleed had resolved and would not make any further use of ambulance transportation.

Table 1. Expected costs of the treatment components attributable to managing adults with a minor bleeding episode, stratified by initial treatment. (Percentage of total expected cost is in parentheses)

	Expected NHS cost (£s) per patient who starts treatment at home with:	
	aPCC	*rFVIIa*
aPCC first-line (at home)	10,254 (70.0%)	-
aPCC (at CCC)	2,462 (17.0%)	-
rFVIIa first-line (at home)	-	10,108 (78.1%)
rFVIIa (at CCC)	1,462 (10.0%)	2,789 (21.5%)
Porcine Factor VIII	240 (1.6%)	-
Ambulance travel	2 (<0.1%)	1 (<0.1%)
Co-medication	5 (<0.1%)	3 (<0.1%)
Inpatient stay	215 (1.5%)	39 (3.0%)
Outpatient consultations	4 (<0.1%)	3 (<0.1%)
Tests	1 (<0.1%)	1 (<0.1%)
Total	14,645	12,944

[no notes on this page]

Figure 2. Distribution of the expected cost of managing adults with a minor bleed at home. ■, rFVII; □, aPCC

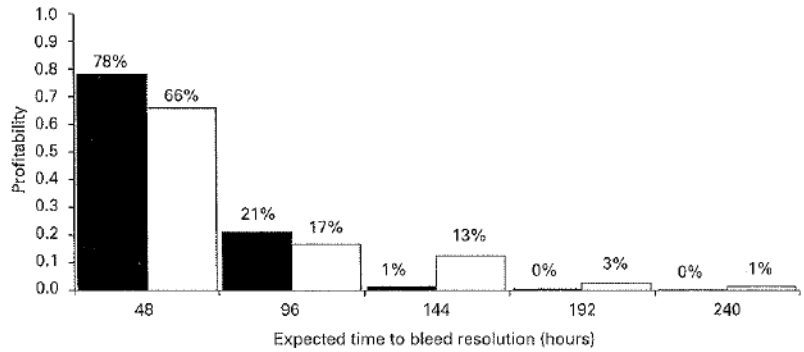


Costs and consequences analyses

The expected cost of managing a minor bleeding episode following initial treatment at home with rFVIIa was estimated to be £12,944. The expected cost with aPCC was estimated to be £14,645. These costs include the probability of a re-bleed occurring and the associated resources that would be consumed.

Table 1 illustrates that drug acquisition costs are the key cost driver associated

Figure 3. Distribution of the expected time to bleed resolution in adults following initial treatment at home. ■ rFVIIa; □, aPCC



[no notes on this page]

with managing a minor bleed at home. Furthermore, the cost of first-line drugs used at home accounts for over 70% of the expected management costs.

Figure 2 shows that in 77% of cases treated with rFVIIa, the expected NHS cost of managing a minor bleeding episode would be no more than £10,000 and in up to 18% of cases the expected cost would be between £10,000 and £20,000. In 68% of cases treated with aPCC, the expected NHS cost of managing a minor bleeding episode would be no more than £10,000 and in up to 27% of cases the expected cost would be between £10,000 and £20,000. Up to 5% of cases treated with either haemostatic would be expected to cost >£20,000.

The expected time to resolving a minor bleed at home with rFVIIa was estimated to be 32 hours and 60 hours when aPCC is used as the first-line treatment. Hence, the time to resolving a minor bleed would take almost twice as long using aPCC at home instead of rFVIIa at home.

Figure 3 illustrates that there is a 78% probability of minor bleeds initially managed with rFVIIa at home being resolved within 48 hours, and another 21% within 96 hours. Fewer than 1% of bleeds initially managed with rFVIIa at home would be expected to require more than 96 hours to resolve. In contrast, there is a 66% probability of minor bleeds initially managed with aPCC at home being resolved within 48 hours, and another 17% within 96 hours. Up to another 17% of bleeds initially managed with aPCC at home would be expected to take longer than 96 hours to resolve.

These distributions were derived from random sampling of the probabilities across all the branches in our decision model. This provides a more realistic estimate of the distribution of costs that would be seen in actual clinical practice, since it takes into consideration the prevailing standard deviations around the means of all the nodes in the model.

Sensitivity analyses

Table 2 shows how the economic impact of rFVIIa compared to aPCC would be altered by varying a number of parameters in the decision model.

Table 2 illustrates that:

- The cost of managing a minor bleed with aPCC would become the lower cost option if the probability of successful treatment at home increases from 79% to above 90% (providing the probability of successful treatment at home with rFVIIa remains unchanged). Alternatively, aPCC would become the lower cost option if the probability of successful treatment at home with rFVIIa falls below 90% (providing the probability of successful treatment at home with aPCC remains unchanged).
- The time to successfully controlling a minor bleed at home following initial treatment with rFVIIa would have to increase from 24 hours to more than 49 hours before the expected time to resolving a minor bleeding episode becomes shorter with aPCC.

1. **Anchor Name: costs effectiveness** *[Agency Switzerland m.waldis@fatzerimbach.ch]*

Table 2. Sensitivity analyses

Parameter	*Baseline value*	*Breakeven value*
Probability of successful treatment at home with rFVIIa ranges from 25% to 100%	92%	90%
Probability of successful treatment at home with aPCC ranges from 25% to 100%	79%	90%
Time to initial bleed resolution with rFVIIa at home ranges from 8 to 72 hours	24 hours	49 hours
Time to initial bleed resolution with aPCC at home ranges from 8 to 72 hours	36 hours	13 hours
Dose of rFVIIa given at home ranges from 1 to 6 doses	2.3 doses 90 μg/kg bw	2.8 doses 90 μg/kg bw
Dose of rFVIIa given to a day case ranges from 1 to 6 doses	2.5 doses 93.8 μg/kg bw	–
Dose of rFVIIa given to an inpatient ranges from 1 to 6 doses	9.5 doses 88.8 μg/kg bw	–
Dose of aPCC given at home ranges from 1 to 9 doses	3 doses 75 units/kg bw	2.5 doses 75 units/kg bw
Dose of aPCC given to a day case ranges from 1 to 9 doses	2.6 doses 87.5 units/kg bw	–
Dose of aPCC given to an inpatient ranges from 1 to 9 doses	5.4 doses 53.1 units/kg bw	–
Dosage of rFVIIa given at home ranges from 50 to 200 μg/kg bw	90 μg/kg bw (2.3 doses)	108 μg/kg bw (2.3 doses)
Dosage of rFVIIa given to a day case ranges from 50 to 200 μg/kg bw	93.8 μg/kg bw (2.5 doses)	–
Dosage of rFVIIa given to an inpatient ranges from 50 to 200 μg/kg bw	88.8 μg/kg bw (9.5 doses)	–
Dosage of rFVIIa given as continuous iv infusion ranges from 10 to 40 μg/kg bw	20 μg/kg bw /hour	–
Dosage of aPCC given at home ranges from 35 to 150 units/kg bw	75 units/kg bw (3 doses)	63 units/kg bw (3 doses)
Dosage of aPCC given to a day case ranges from 35 to 150 units/kg bw	87.5 units/kg bw (2.6 doses)	–
Dosage of aPCC given to an inpatient ranges from 35 to 150 units/kg bw	53.1 units/kg bw (5.4 doses)	–
Probability of a re-bleed ranges from 0% to 25%	15%	–

Additionally, the time to successfully controlling a minor bleed at home following initial treatment with aPCC would have to be less than 13 hours before the expected time to resolving a minor bleeding episode becomes shorter with aPCC.

- If rFVIIa's efficacy remains unchanged,

[no notes on this page]

administering more than 2.8 doses of rFVIIa at a dosage of 90 μg/kg body weight would result in aPCC at home becoming the lower cost option. Similarly, administering a mean 2.3 doses beyond a dosage of 108 μg/kg body weight would result in aPCC at home becoming the lower cost option.

- If aPCC's efficacy remains unchanged, administering less than 2.5 doses of aPCC at a dosage of 75 units/kg body weight would result in aPCC at home becoming the lower cost option. Similarly, administering a mean 3 doses of aPCC below a dosage of 63 units/kg body weight at home would result in aPCC at home becoming the lower cost option.

In summary, the sensitivity analyses demonstrate that the economic impact of initial home treatment with rFVIIa compared to aPCC in the management of a minor bleeding episode among adults is sensitive to the dose and dosage of the haemostatics administered at home, the probability of successful treatment at home and the time to bleed resolution at home following initial treatment with either rFVIIa or aPCC. However, the relative economic impact of rFVIIa is not sensitive to the dose and dosage of any drugs administered second-line or later, or any other component of treatment.

Discussion

Recent guidelines on the management of high responding inhibitor patients by both the UK Haemophilia Centre Directors' Organisation[15] and the Association of Haemophilia Clinic Directors of Canada[16] recommend the use of rFVIIa not only for severe bleeds, but also for minor bleeds. However, the NHS has not advised on implementing the UK guidelines[10] and there is no consensus among haematologists as to the different products' role. Consequently, differences in opinion exist between haematologists and haemophilia funding agencies on the cost-effectiveness of various haemophilia treatments. These differences impact on the quality of care received by haemophilia patients across the UK[17,18].

The cost of managing inhibitor patients has not been widely reported in the published literature. In Canada, the use of aPCC was estimated to cost a mean $107,513 (i.e. £55,591 at 1993 exchange rate) per inhibitor patient per year to manage an unspecified number of bleeding episodes[19]. In the UK, Stewart *et al*[20] estimated that in a haemophilia patient with high titre, high responding inhibitors, the cost of treating bleeding episodes at home with rFVIIa was £12,152 per bleeding episode, which was comparable to our own findings. However, the paper presented insufficient data to enable us to calculate a comparable cost for aPCC[20].

Against this background, we estimated that the expected NHS cost of initially using rFVIIa at home is comparable to that of aPCC when managing a minor bleeding episode among patients who develop high titre, high responding inhibitors (>10 BU). However, using rFVIIa at home instead of aPCC approximately

[no notes on this page]

halves the time to resolving a minor bleeding episode. Hence, compared to aPCC, rFVIIa improves clinical outcome (as found by others[6,7,21]), while being, at the least, cost neutral.

Haemophilia's rarity, the difficulty in predicting patterns of bleeding episodes and their outcomes, as well as the high treatment cost of managing bleeds and associated complications make planning and budgeting for haemophilia problematic[9,10]. Accordingly, predicting the distribution of costs would aid the management of haemophilia patients with inhibitors. According to our analysis, up to 95% of all minor bleeds among adults managed at home with either aPCC or rFVIIa would be expected to cost the NHS less than £20,000. Although spontaneous bleeds are often unpredictable, these data should help in planning haemophilia budgets, thereby minimising geographical variation in the funding of treatment while maximising the quality of care. Nevertheless, it should be recognised that budgets for haemophilia patients would also be influenced by the cost of managing severe bleeds, which have not been included in this particular analysis.

Multicentre studies on haemophilia patients who develop inhibitors show that the shorter the mean time from start of a bleed to onset of treatment with a haemostatic, the higher the efficacy of the treatment and, therefore, the fewer doses needed[6,8,21]. Consequently, the key to successful long-term management is the early administration of a haemostatic following the onset of a bleed, thereby minimising damage to affected joints or tissues[21].

Other studies have shown that prolonged bleeding often results in greater morbidity, prolonged hospitalisation, and in some cases, subsequent need for corrective surgical procedures[6,21]. Since our study shows that rFVIIa resolves a minor bleeding episode in approximately half the time of that with aPCC, rFVIIa has the potential to reduce morbidity over the longer term and this could have a positive economic impact on the NHS and improve the quality of life of patients. Therefore, rFVIIa improves clinical outcome compared to aPCC, but at no additional cost to the NHS, resulting in rFVIIa being the cost-effective treatment.

The results of these analyses can thus be used to inform treatment guidelines and associated decisions regarding resource allocation[22]. This would ensure better targeting of scarce resources, more effective management of bleeds and better quality of life for patients.

This study is subject to a number of limitations. The major limitation was the use of a panel of haematologists to obtain data that were unavailable in published studies. However, there are approximately 200 inhibitor patients in the UK and the haematologists interviewed have collectively managed 84 inhibitor patients over the last 5 years, representing 42% of the total estimated number of such patients. Consequently, the management patterns and resource use

[no notes on this page]

reported in this study are representative of UK clinical practice. Furthermore, the analysis showed that the economic impact of rFVIIa compared to aPCC is most sensitive to parameters pertaining to home treatment that were derived from published trials, and not to those pertaining to subsequent treatment at a CCC which were obtained from the panel.

The protocol in the Key study[8] recommends treatment within 8 hours from the onset of a bleed. However, the Hilgartner study[2] did not specify such time. Consequently, it was not possible to determine the effect of time from the onset of a bleed to treatment on the outcomes of our model.

The limited number of inhibitor patients in the UK and the unpredictable nature of bleeds have meant that there is varied clinical experience and a general lack of consensus among haematologists on best practice.

However, as more experience is gained about managing inhibitor patients and more robust data become available, the decision model should be updated accordingly.

The model estimates the expected cost attributable to resolving a minor bleeding episode following initial home treatment with either rFVIIa or aPCC. Furthermore, the model only considers direct healthcare costs and not the direct costs to patients and their families, indirect costs to society, such as loss of productivity, and intangible costs, such as changes in quality of life. Future analyses should examine the economic and quality of life implications of rFVIIa compared to aPCC in minimising damage to affected joints or tissues in the longer term.

Conclusion

Within the limitations of our model, the costs of initially managing a minor bleeding episode at home with either haemostatic are comparable. However, using rFVIIa at home instead of aPCC is expected to resolve a minor bleeding episode in about half the mean time, but at no additional cost to the NHS. Hence, the decision to use either rFVIIa or aPCC at home for managing a minor bleed should be based on efficacy, safety and patient preferences and not drug acquisition costs. This finding warrants further study in a prospective, comparative, randomised controlled study.

Acknowledgements

The authors thank the following for their contributions: Dr P Bolton-Maggs, Royal Liverpool Children's Hospital Alder Hey*; Dr E Chalmers, Royal Hospital for Sick Children; Dr P Collins, University Hospital of Wales*; Dr G Dolan, Queens Medical Centre, Nottingham; Dr P Giangrande, Oxford Haemophilia Centre; Dr I Haan,

*Participated at the expert meeting.

[no notes on this page]

Great Ormond Sick Children's Hospital; Dr C Hay, Manchester Royal Infirmary*; Dr C Hock Toh, Royal Liverpool University Hospital; Dr P Jones, Royal Victoria Hospital, Newcastle; Professor C Lee, Royal Free Hospital, London; Professor C Ludlam, Lothian University NHS Trust, Edinburgh; Dr M Makris, Royal Hallamshire Hospital, Sheffield; Dr O McNulty, Royal Victoria Hospital, Belfast*; Dr B McVerry, St James University Hospital, Leeds; Dr T Noakes, North Hampshire Hospital,Basingstoke; Dr D Perry, Royal Free Hospital, London*; Dr M Richards, Children's Day Hospital, Leeds; Dr M Smith, St Thomas' Hospital, London*; Dr R Stevens, Manchester Children's Hospital; Dr A Thomas, Lothian University NHS Trust, Edinburgh*; Dr I Walker, Glasgow Royal Infirmary; Dr J Wilde, Queen Elizabeth Hospital, Birmingham.

The authors also thank Novo Nordisk Ltd for their financial support of this study.

References

1. Jones P. Haemophilia: a global challenge. *Haemophilia* 1995, 1: 11-13.
2. Hilgartner M, Aledort L, Andes A, Gill J, and the members of the aPCC Study Group. Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in haemophilia patients. *Transfusion* 1990; 30: 626-630.
3. Hilgartner MW, Knatterud GL and the aPCC Study Group. The use of Factor eight inhibitor by-passing activity (aPCC Immuno) product for treatment of bleeding episodes in haemophiliacs with inhibitors. *Blood* 1983; 61: 36-40.
4. Negrier C, Goudemand J, Sultan Y, Bertrand M, Rothschild C, Lauroua P and the members of the French aPCC study group. Multicenter retrospective study on the utilisation of aPCC in France in patients with Factor VIII and Factor IX inhibitors. *Thrombosis and Haemostasis* 1997; 77: 1113-1119.
5. Negrier C, Lee M *et al.* The FEIBA-VH survey: Initial findings from a world-wide surveillance study. *Haemophilia* 2000; 6 (Suppl. 1): 279-314
6. Lusher JM. Early treatment with recombinant Factor VIIa results in greater efficacy with less product. *European Journal of Haematology* 1998; 61 (Suppl. 63): 7-10.
7. Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated Factor VII in patients with Factor VIII inhibitors: the advantages of early intervention. *British Journal of Haematology* 1999; 104: 22-26.
8. Key NS, Aledort LM, Beardsley D *et al.* Home treatment of mild to moderate bleeding episodes using recombinant Factor VIIa (NovoSeven) in haemophiliacs with inhibitors. *Thrombosis and Haemostasis* 1998; 80: 912-918.
9. Lipton RA. The economics of Factor VIII inhibitor treatment. *Seminars in Haematology* 1994; 31 (Suppl. 4): 37-38.
10. Ludlam C. Funding arrangements within the UK. *Haemophilia* 1998; 4 (Suppl. 1): 13-14.
11. Fink A, Kosecoff J, Chasssin M *et al.* Consensus methods: characteristics and guidelines for use. *American Journal of Public Health* 1984; 74: 979-983.
12. Netten A, Dennett J, Knight J. Unit costs of health and social care 1999. University of Kent, Canterbury, 1999. Personnel Social Services Research Unit.

*Participated at the expert meeting

[no notes on this page]

13. Monthly Index of Medical Specialities (MIMS), 2000 edition. London: Haymarket Publications Ltd, 2000.

14. Department of Health. Drug Tariff, May 2000 edition. London: The Stationary Office, 2000.

15. Hay CR, Baglin TP, Collins PW *et al*. The diagnosis and management of Factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organisation (UKHCDO). *British Journal of Haematology* 2000; 111(1): 78-90.

16. Inhibitor Subcommittee of the Association of Haemophilia Clinic Directors of Canada (AHCDC) (2000). Suggespptions for the management of Factor VIII inhibitors. *Haemophilia*; 6 (Suppl. 1): 52-59.

17. Lee C. Funding rare and expensive treatments: the case of haemophilia. *Haemophilia* 1998; 4 (Suppl. 1): iii.

18. Bolton-Maggs P. The doctor's dilemma. *Haemophilia* 1998 4 (Suppl. 1): 4-5.

19. Rivard G-E, Vick S. Economics of inhibitor treatment in Canada. *Seminars in Haematology* 1994; 31 (Suppl. 4): 41-43.

20. Stewart AJ, Hanley JP, Ludlam CA. Safety, efficacy and cost-effectiveness of home therapy with recombinant activated Factor VII in a patient with severe haemophilia A and an anti-Factor VIII inhibitor. *Blood Coagulation and Fibrinolysis* 1998; 9 (Suppl. 1): S93-S95.

21. Lusher JM. Recombinant activated Factor VII for treatment of intramuscular haemorrhages: a comparison of early versus late treatment. *Blood Coagulation and Fibrinolysis* 1998; 9 (Suppl. 1): S111-S114.

22. Aledort LM. Economic aspects of haemophilia care. *Haemophilia* 1999; 5: 216-219.

[no notes on this page]