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Section	Value message
Acquired haemophilia	A: NovoSeven® is cost-effective in patients with acquired haemophilia compared to other therapies available due to improved efficacy when used first-line

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The Economic Impact of Different Strategies of Managing Rare Diseases with High Treatment Costs: The Case of Using Activated Recombinant Factor VII in Severe Bleeds in Acquired Haemophilia Patients

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Background

- Acquired haemophilia is a rare bleeding disorder that occurs mainly in young women post partum and in elderly patients without previous history of bleeding disorders (Collins et al).¹ The incidence has been reported to vary from 1–4 per million of the population worldwide (Giangrande)².
- Different haemostatic agents are available to treat bleeding episodes in patients with inhibitors. At lower titres of factor VIII (FVIII) antibodies, FVIII may overcome the inhibitor and provide effective bleed management, but may provoke a further rise in inhibitor level. For high-titre or high-responder inhibitors, activated prothrombin complex concentrates (aPCC), recombinant activated factor VII (rFVIIa), or porcine FVIII have been used.

Objective

- The decision to use a drug first-line instead of second-line could have a significant clinical outcome and economic impact especially in rare diseases with high treatment costs such as acquired haemophilia. The aim of this study is to compare the cost-effectiveness of first-line versus second-line (salvage therapy) use of recombinant activated factor VII (rFVIIa) in the management of severe bleeds in patients with acquired haemophilia.

Methods

- We modelled the economic impact of different treatment strategies reported from the only existing compassionate-use database containing data from 38 patients with acquired haemophilia for whom rFVIIa was used in the management of 78 severe bleeding episodes from 1990–1995. (Hay et al).³

Data

- Data from patients with acquired haemophilia who received rFVIIa as on-demand treatment for bleeds during the 'Compassionate-use Program' (in 32 participating centres in Europe, Canada, the US, Australia, and Malaysia) (1990–1995) were retrieved from the Compassionate-use database and aggregated according to first-line or second-line use of rFVIIa.
- In accordance with the Compassionate-use Protocol, patients with acquired haemophilia received rFVIIa only when other treatment modalities had failed (i.e. as salvage treatment). However, in 14 bleeding episodes, rFVIIa was allowed as first-line therapy. Based on clinical judgement, these cases were considered severe, and patients could not be denied the benefit of treatment on ethical grounds.
- For patients treated with rFVIIa, rFVIIa was administered as an intravenous bolus injection, the dosage, dose interval, and length of treatment being determined by clinical response.

Table 1. Comparison of the treatment regimens

	rFVIIa as first-line strategy			rFVIIa as second-line strategy		
	Mean	Median	Range	Mean	Median	Range
Dose of rFVIIa, µg/kg	89.4	89.9	65.6–100	86.7	90.0	44.8–124.9
Number of doses of rFVIIa	37.4	35.0	2–135	48.6	26.0	1–444
Bleeding episodes	14			60		
Efficacy of treatment	100%			75%		

Source: NovoSeven® Compassionate and emergency use programmes (1990–1995), Hay et al.³

Comparison of treatment strategies

- When used as a first-line therapy for bleeding management, rFVIIa resulted in 100% efficacy. The mean rFVIIa dose was 89.4 µg/kg (range 65.6–100 µg/kg, median 89.9 µg/kg), and the mean number of doses was 37.4 (range 2–135, median 35.0). When rFVIIa was used as second-line treatment (n = 60), the mean treatment efficacy was 75%. For this group, the mean dose of rFVIIa used was 86.7 µg/kg (range 44.8–124.9 µg/kg, median 90.0 µg/kg) and the mean number of rFVIIa doses required was 48.6 (range 1–444, median 26.0) (see Table 1).
- In addition to rFVIIa, more than two haemostatic agents were used in 68% of cases in the attempt to stop bleeding. Table 2 shows the proportion of patients receiving other haemostatic agents before rFVIIa.
- Co-medications used with first-line treatments other than rFVIIa included tranexamic acid, steroids, desmopressin, immunoglobulin, and cyclo-phosphamide.

Table 2. Percentage of patients receiving other haemostatic agents before rFVIIa

	rFVIIa as second-line strategy
FIX	9%
FVIII	50%
Porcine FVIII	47%
aPCC/Autoplex	47%
Two or more agents	68%

Results

- Only drug acquisition costs were considered. Clinician time, haematology tests, hospital bed use, etc., were not included.
- In 14 of the bleeds, rFVIIa was used as first-line therapy with 100% success in controlling the bleeds, while a success rate of 75% was reported for 64 bleeding episodes in which rFVIIa was used as salvage therapy. The mean treatment cost of rFVIIa as the first-line therapy was \$362,906 per bleeding episode compared to \$416,793 when rFVIIa was used as a salvage therapy. Furthermore, the cost per effectively treated bleed for the second-line strategy was \$545,113 compared to \$362,468 for first-line use. (See table 3).
- Based on these results, rFVIIa, as a first-line therapy, is the cost-effective treatment option in the management of severe bleeding episodes in acquired haemophilia patients as compared to second-line treatment strategies.

Table 3. Mean cost distribution for rFVIIa – first-line use vs. second-line use (US\$)

	rFVIIa as first-line strategy	rFVIIa as second-line strategy
Pre-rFVIIa haemostatic therapy	0	117,853
rFVIIa	362,468	278,424
Co-medications	438	20,516
Total	362,906	416,793
Cost per effectively treated bleed	362,906	545,113

Discussions

- This study design permitted only a limited direct comparison of alternative treatment strategies as patients in the Compassionate-use programme had already failed to respond to a median of two blood products given over a median of 4 days. Thus, selection bias is a study limitation in this comparison since the failure of conventional therapy was an entry criterion for the study.
- However, further statistical analysis reveals that there is no correlation between initial inhibitor titre and the number of doses of rFVIIa subsequently administered (r=0.06). Furthermore, there is no significant correlation between the initial inhibitor titre and the final outcome following the use of rFVIIa whether as first-line or second-line therapy (r=0.06).
- A potential limitation of this study is the sample size of the study. However, a recent clinical review provided an overview of the management of acquired haemophilia in a larger number of patients, as reported in an expanded version of the Compassionate-use database, the Hemophilia and Thrombosis Research Society Registry (HTRS) and other independent published reports (Sumner et al).⁴ The efficacy end-points reported for both first-line and second-line use of rFVIIa in these studies were comparable to those reported in the dataset used for this study.
- These results support the view that rFVIIa is efficacious for the management of bleeding episodes in acquired haemophilia when used for both first- and second-line therapy, irrespective of initial bleed severity or inhibitor titre.

Conclusions

- The results of this study suggest that rFVIIa is highly effective in controlling bleeding episodes in patients with acquired haemophilia.
- Based on these results, rFVIIa, as a first-line therapy, is the cost-effective treatment option in the management of severe bleeding episodes in acquired haemophilia patients as compared to second-line treatment strategies.

References

1. Collins P et al. Blood 2007;109(5):1870-75. 2. Giangrande P. Acquired Haemophilia. Treatment of haemophilia. December 2005;38. 3. Hay CR, Negrier C, Ludlam CA. Thromb Haemost 1997; 78: 1463-7. 4. Sumner MJ, Geldziler BD, Pedersen M, Seremetis S. Haemophilia 2007; 13: 451-61.

1. The decision to use a drug first-line instead of second-line could have a significant clinical out...

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2. Anchor Name: Because of NovoSeven's high efficacy and a median time to...

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3. Based on these results, rFVIIa, as a first-line therapy, is the cost-effective treatment option in ...

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4. Anchor Name: (/p2/table3) [NHSM (Neha Sharma)]