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

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Summary. The first-line treatment for mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors in Brazil is currently activated prothrombin complex concentrate (aPCC), with recombinant activated factor VII (rFVIIa) used as second-line therapy or as a last resort. The aim of this study was to determine the cost and effectiveness of these treatments from the perspective of the Brazilian National Health Service. A decision analysis model was constructed to assess total direct medical costs (including drug costs, costs of outpatient or inpatient care, ambulance transportation and cost of concomitant medications) of first-line treatment with aPCC or rFVIIa. Clinical outcome and resource utilization data were obtained both retrospectively and prospectively and validated by the consensus of an expert panel of Brazilian haematologists. A total of 103 bleeds in 25 patients were included in the analysis. rFVIIa resolved bleeds more quickly (4.4 h) than aPCC (62.6 h) and was more effective (100% vs. 56.7% respectively). Mean total direct medical costs (from initiation to cessation of bleed) were estimated to be US$13 500 (aPCC) and US$7590 (rFVIIa). Extensive sensitivity analyses confirmed the cost-effectiveness of rFVIIa. Compared with aPCC, rFVIIa was more effective and less expensive when used as first-line treatment for mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors in Brazil. rFVIIa should be considered a first-line treatment for the management of these patients.

Keywords: activated prothrombin complex concentrate, bleeds, economic, haemophilia, inhibitor, recombinant activated factor VII

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Introduction

Haemophilia is an inherited bleeding disorder caused by deficiency of factor VIII (haemophilia A) (FVIII) or factor IX (FIX) (haemophilia B) that occurs at a rate of approximately 10–20 in every 100 000 live births [1–3]. The primary treatment for haemophilia is replacement of the missing factor. However, patients may develop inhibitors (antibodies) to the infused FVIII or FIX, making the management of bleeds more difficult and in some cases more expensive [4–8]. In Brazil, there are currently 5411 patients with haemophilia A and 886 patients with haemophilia B; 366 of these patients have inhibitors [9]. Comparing the cost-benefits of different treatment options for patients with inhibitors is therefore of great interest.

In Brazil, the current first-line treatment for mild-to-moderate bleeds in patients with inhibitors is activated prothrombin complex concentrate [aPCC (FEIBA®; Baxter, Vienna, Austria)]. Alternatives, which are used to treat acute bleeding episodes when aPCC is not available, include recombinant activated factor VII [rFVIIa (NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark)], prothrombin complex concentrate (PCC) and high-dose FVIII or FIX. Because of its higher cost, rFVIIa is currently used in Brazil as

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second-line therapy, or in cases of last resort where all other methods have failed to achieve haemostasis. When evaluating the merits of these management strategies, it is important to consider not only the direct cost of acquisition, but also the effectiveness, because an expensive treatment that works better and more quickly may be more cost-effective than an inexpensive product that requires multiple doses to achieve haemostasis. The management of minor-to-moderate bleeds extends beyond the initial line of treatment and consideration of the economic impact of re-bleeding and failures over multiple lines of treatment is required [10]. Therefore, it is important to take into account the total cost associated with the complete resolution of a bleed, as this is the true cost burden.

It was therefore hypothesized that despite the increased acquisition cost, the higher first-line efficacy of rFVIIa would mean that the total cost of managing a bleed (from initiation of symptoms to resolution) would be comparable with, or less than, that of aPCC. The aim of this study was to evaluate the direct medical cost of therapy with rFVIIa compared with aPCC for managing mild-to-moderate bleeding episodes in children and adults with haemophilia and inhibitors, from the perspective of the Brazilian National Health Service.

Materials and methods

Study design

This study used a decision analysis model to assess the total direct medical costs of different treatment options for the management of mild-to-moderate bleeds in patients with haemophilia and inhibitors. Clinical and resource utilization data were mostly obtained retrospectively.

Because of the current prescription guideline in place, the sample size of patients initially treated with rFVIIa in the retrospective cohort was limited. Further specific data on patients initially treated with rFVIIa were therefore prospectively obtained. Data on patients initially treated with aPCC were obtained retrospectively.

Study cohort

Patients were included in the analysis if they had congenital haemophilia A or B with high-titre (>5 BU mL^{-1}) or high-responding (historical peak >5 BU mL^{-1}) inhibitors, and had presented with at least one mild or moderate bleed requiring bypassing treatment in the previous 12 months (retrospective cohort) or during the study period (prospective cohort). A bleed was defined as mild if signs and symptoms of haemorrhage were evident but did not prevent the patient from performing normal activities (e.g. ecchymoses). A bleed was defined as moderate if signs and symptoms of haemorrhage were evident and prevented patients from performing normal activities [including acute haemarthrosis (except hip), gross haematuria (lasting >48 h), muscle haematoma (except iliopsoas bleeding), minor surgical procedures (e.g., placing urethral catheter) or radionuclide synovectomy]. Severe bleeds [including epistaxis (lasting >6 h), gastrointestinal haemorrhage, suspicion of head trauma, intracerebral haemorrhage, compartment syndrome, hip haemarthrosis, iliopsoas haematoma, deep cuts, orthopaedic and other major surgery or tooth extraction] were excluded. Patients who were undergoing immune tolerance induction protocols, or who were receiving prophylactic treatment, were also excluded.

The retrospective cohort (initially treated with aPCC, PCC, high-dose FVIII or rFVIIa, between August 2002 and May 2004) was compiled from the records of four representative centres (Hemocentro da UNICAMP, Centro de Hemofilia da USP, Hospital de Apoio do DF and Hemocentro de Pernambuco).

The prospective cohort was provided by three representative centres (Hemocentro da UNICAMP, Centro de Hemofilia da USP and Hemocentro de Pernambuco) between July 2004 and February 2006.

Clinical outcomes

Clinical data (including demographics, bleed location, time of onset of symptoms, time of treatment and resolution and type and amount of treatment) were collated by clinicians using a standard questionnaire, from the retrospective records and prospective data collection of the patients included in the analysis.

Effectiveness was defined clinically, based on pain relief, reduction of swelling, improvement of joint mobility or cessation of bleeding, occurring within 48 h of treatment initiation. Haemostasis was considered to be maintained if the symptoms did not recur at the same location within 5 days of the last effective treatment dose; a re-bleed was the occurrence of bleeding at the same location within 5 days of the last dose. Treatment was considered ineffective if bleeding, pain or swelling persisted for more than 48 h.

All completed charts and questionnaires were reviewed by the investigators if discrepancies were

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identified during data analysis: if these could not be clarified, the questionnaire was excluded.

Decision analysis model

Decision analysis modelling based on previously published methods [11,12], using Data™ 3.5 (TreeAge Software, Williamstown, MA, USA) was used. The model enabled a cohort of individuals to be followed sequentially, from bleed initiation, taking into consideration first-line efficacy, bleed continuation, switching to other products, re-bleeds and bleed cessation. It was assumed that all bleeds would eventually cease after three courses of therapies regardless of treatment. To reflect Brazilian clinical practice, the decision model (Fig. 1) was validated with input from a panel of Brazilian experts and compared strategy (i) rFVIIa, rFVIIa, aPCC with strategy (ii) aPCC, aPCC, rFVIIa.

Resource utilization and unit costs

Data on resource utilization (including doses of each treatment and total number of doses, number of outpatient visits, days of hospitalization, transportation and concomitant medicine use) were obtained from the retrospective records and prospective data collection of the patients included in the analysis.

Unit costs, obtained from the Federal Official Diary (product costs), Brazilian Medical Association Procedures List 2003 (medical costs) and Brasíndice Medicines List (medication) with 2005 values (exchange rate US$1 = R$2.38, an average value for mid-2005), were assigned for each component of the analysis. An outpatient visit costs US$17.6, with the cost of outpatient nursing care US$6.7, the cost of inpatient care (in a general hospital ward, including physician visit and hospital costs) US$84 per day, and the cost of ambulance transportation based on twice the approximate distance of the patient from the treatment centre multiplied by the estimated cost per km, plus an additional estimate (US$29) for ambulance personnel. In Brazil, the acquisition cost of rFVIIa was US$0.692 per μg whilst the cost of aPCC was US$0.61 per IU. For those patients who required concomitant medications, the cost was determined from utilization derived from the questionnaire multiplied by the published national unit cost.

Analyses

The primary analysis compared the total direct medical costs [drug costs (mean cost of drug treatment per bleeding episode, based on mean total dose per kg and the mean cost of drugs), outpatient or inpatient care, ambulance transportation and concomitant medication costs] of treating a bleeding episode (from initiation to cessation) with aPCC or rFVIIa. A subgroup analysis was also undertaken on patients treated with either aPCC or rFVIIa in ≤12 h after the initiation of symptoms. A secondary analysis was planned, to incorporate the limited data available for PCC and high-dose FVIII.

The outcome data were discussed with experts and compared with previously published literature to establish that they were consistent with clinical practice and published evidence and could be confidently used in the model. The figures for effectiveness of rFVIIa were subsequently based directly on the current patient data. The figures for effectiveness of aPCC in the current patients were at the lower end of those previously published (between 64% and 88% [13–17]) and were used in the baseline analysis. To confirm the applicability of these data, a sensitivity analysis was undertaken to observe the impact of changing this variable.

Sensitivity analyses were also conducted on the values of key variables that were likely to vary

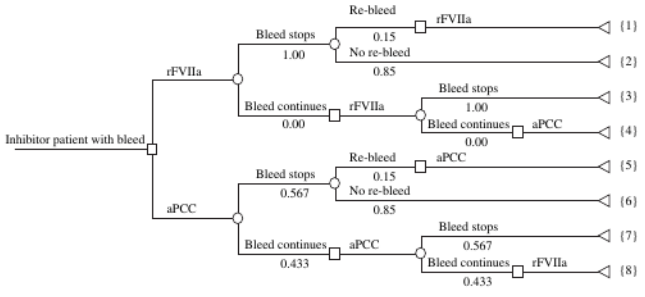

Fig. 1. Baseline decision tree structure for comparing recombinant activated factor VII and activated prothrombin complex concentrate as first-line therapies.

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between hospitals, or for which there were uncertainties. These included the length of hospital stay and the probability of a re-bleed.

Results

Patient demographics

In total, 130 bleeds in 27 patients were documented. The retrospective cohort comprised 108 bleeding episodes in 24 patients. The prospective cohort comprised 22 bleeding episodes in nine patients; six of these patients had historical bleeds also included in the retrospective cohort and three were new patients.

Of the 27 patients, 15 (55.6%) were aged ≥17 years at the first treatment date and 12 (44.4%) were <17 years of age.

Of the 130 bleeding episodes, 67 were initially treated with aPCC, 16 with PCC, 11 with high-dose FVIII and 36 with rFVIIa.

Outcome of bleeding episodes treated with aPCC or rFVIIa – all bleeds (prospective and retrospective)

A total of 103 bleeds in 25 patients were treated with aPCC or rFVIIa (Table 1) and bleed severity was similar in both groups. Of the 67 bleeding episodes treated with aPCC, 37.3% were of mild severity and 62.7% were of moderate severity. Of the 36 bleeding episodes treated with rFVIIa, 33.3% were mild and 66.7% were moderate (Table 1). The effectiveness of rFVIIa (100% for new bleeds, 100% for bleeds treated in ≤12 h of onset and 100% for re-bleeds) was higher than that of aPCC (corresponding values: 56.7%, 63.6% and 40.0% respectively). The mean

Table 1. Treatment, outcomes and resource utilization data from the analysis of 103 bleeds in 25 patients.

	Initial treatment with	
	aPCC	rFVIIa
Total number of bleeding episodes	67	36
Mild bleeds (%)	25 (37.3)	12 (33.3)
Moderate bleeds (%)	42 (62.7)	24 (66.7)
Mean number of doses per treatment (range)*:		
Mild	3.6 (1–8)	1.6 (1–3)
Moderate	3.9 (1–13)	2.3 (1–4)
All	3.8 (1–13)	2.0 (1–4)
Mean dose size per kg body weight per dose and per treatment (range)*:		
Mild	57.7 (26.3–86.2) U	91.8 (82.8–103.2) μg
Moderate	74.8 (36.2–128.6) U	92.2 (80.0–120.0) μg
All	68.5 (26.3–128.6) U	94.5 (80.0–120.0) μg
Mean total dose per kg body weight (to bleed resolution or switch to next line of therapy) (range)*:		
Mild	207.6 (44.1–494.1) U	146.9 (84.7–248.3) μg
Moderate	291.6 (72.4–1383.0) U	212.1 (80.0–363.6) μg
All	260.2 (441.1–1383.0) U	189.9 (80.0–363.6) μg
Mean treatment dose per bleeding episode per mean body weight (52.6 kg)	13 687.5 U	9.99 mg
All bleeds		
Mean time to treatment (range)*	19.6 (1.0–168) h	8.6 (1.0–29) h
Mean time to resolution (range)*	62.6 (12–168) h	4.4 (0.3–11) h
Effectiveness (%)	56.7	100.0
Bleeds treated in ≤12 h of onset (*n*)	(33)	(33)
Mean time to treatment (range)*	4.6 (1.0–12) h	7.0 (1.0–12) h
Mean time to resolution (range)*	56.8 (12–120) h	4.2 (0.3–11) h
Effectiveness (%)	63.6	100.0
Bleeding episodes treated at home (%)	16.4	16.7
Bleeding episodes treated as inpatient or outpatient (%)	83.6	83.3
Mean time at hospital per bleeding episode (range)*	0.6 (0–7) days	0.3 (0–5) days

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.
*Ranges are provided instead of CI because statistics were only descriptive.

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time to resolution of bleeding was less for rFVIIa (4.4 h) compared with aPCC (62.6 h) and was achieved using fewer doses (mean 2 vs. 3.8 respectively, Table 1). Most patients were treated as inpatients or outpatients rather than at home (Table 1).

The outcomes and characteristics of patients who were treated within 12 h following the bleeding episode are presented in Table 2 (prospective data, rFVIIa only) and Table 3 (prospective and retrospective data, aPCC and rFVIIa).

Outcome of bleeding episodes treated with rFVIIa – prospective bleeds only

All nine prospective patients were treated on an outpatient basis with rFVIIa. Of the 22 bleeding episodes documented prospectively, nine were mild (40.9%) and 13 were moderate (59.1%). All bleeds resolved with one to four doses of rFVIIa (mean 2.05) and all bleeds treated in <6 h resolved with one to two doses of rFVIIa (mean 1.67, Table 2). The majority of bleeding episodes (20/22, 90.9%) resolved with three doses of rFVIIa; two bleeding episodes (9.1%) required four doses. Haemostasis was maintained for 5 days in 18/22 (81.8%) bleeding episodes. Four bleeds recurred: these were moderate in severity and were treated 6–12 h after the initiation of symptoms.

Outcome of bleeding episodes treated with PCC or high-dose factor VIII

Of the 16 bleeds treated with PCC, 56.3% were mild and 43.7% were moderate. Of the 11 bleeds treated with high-dose FVIII, 72.7% were mild and 27.3% were moderate. Effectiveness values for new bleeds were 62.5% for PCC and 63.6% for high-dose FVIII. Because of the small sample size and high proportion of mild bleeding episodes, these data were not incorporated into the cost comparison.

Cost of drug treatment per bleeding episode

The mean cost of drug treatment per bleeding episode for bleeds treated with rFVIIa was lower than for bleeds treated with aPCC, for all new bleeds (US$7010 vs. US$8227 respectively per bleed), for bleeds treated up to 12 h from onset (US$6727 vs. US$7916 respectively per bleed) and for re-bleeds (Table 4).

Total direct medical costs

Based on the decision analysis model, mean total direct medical costs per bleed were lower when rFVIIa was the first-line treatment (US$7590) than if aPCC was the first-line treatment (US$13 500). For bleeds treated up to 12 h from onset, rFVIIa had

Table 4. Cost of drug treatment per bleeding episode.

Haemostatic agent	Type of bleed	Cost of drug treatment per bleeding episode (US$)
aPCC	All bleeds	8227
	Bleeds treated in ≤12 h	7916
	Re-bleed	4664
rFVIIa	All bleeds	7010
	Bleeds treated in ≤12 h	6727
	Re-bleed	3868

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

Table 2. Treatment characteristics and outcome of 22 prospective bleeds treated with rFVIIa.

Time to treatment	Number of bleeds	Time to treatment, mean hours (range)*	Time to resolution, mean hours (range)*	Mean number of doses (range)*	Body weight (kg), mean (range)	Dose (mg), mean (range)*	Effectiveness (%)	Re-bleeds
Up to 6 h	6	5 (3.6–5.7)	3.4 (2.0–4.0)	1.67 (1–2)	57.1 (46.5–68.0)	9.0 (4.8–12)	100	0/6
6–12 h	16	10.3 (6.3–12.0)	4.9 (0.3–11.0)	2.19 (1–4)	60.9 (36.5–82.0)	12.5 (4.8–24)	100	4/16
Up to 12 h	22	8.7 (3.6–12.0)	4.5 (0.3–11.0)	2.05 (1–4)	59.6 (36.5–82.0)	11.5 (4.8–24)	100	4/22

*Ranges are provided instead of CI because statistics were only descriptive.

Table 3. Treatment characteristics and outcome of bleeds treated with aPCC and rFVIIa up to 12 h (all bleeds).

Treatment	Number of bleeds	Time to treatment, mean hours (range)*	Time to resolution, mean hours (range)*	Mean number of doses (range)*	Body weight (kg), mean (range)	Effectiveness (%)	Re-bleeds
rFVIIa	33	7.0 (1–12)	2.7 (0.3–6)	1.6 (1–4)	53.3 (15.0–85.0)	100	4/33
aPCC	33	4.6 (1.0–12.0)	56.8 (12–120)	3.7 (1–10)	55.2 (12.5–85.0)	63.6	0/33

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.
*Ranges are provided instead of CI because statistics were only descriptive.

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similar cost-savings (US$7307 and US$12 134 for rFVIIa and aPCC respectively, Table 5).

Sensitivity analysis using first-line efficacy rates based upon published data (rFVIIa 92% and aPCC 80%, Fig. 2) confirmed that the total direct medical costs per bleed remained lower for rFVIIa (US$8157 for all bleeds and US$7850 for bleeds treated in ≤12 h) compared with aPCC (US$10 712 for all bleeds and US$10 328 for bleeds treated in ≤12 h).

The majority (>98%) of total direct medical costs were attributable to the drug (aPCC or rFVIIa). Hospitalization, ambulance travel and concomitant medications represented <2% of total costs for rFVIIa and aPCC.

Table 5. Total direct medical costs per bleed (from initiation to cessation) treated with aPCC or rFVIIa.

Bleeding episodes included in model	Initial haemostatic agent	Total direct medical cost (US$) per bleed
All bleeds	aPCC	13 500
	rFVIIa	7590
Bleeds treated in ≤12 h	aPCC	12 134
	rFVIIa	7307

aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

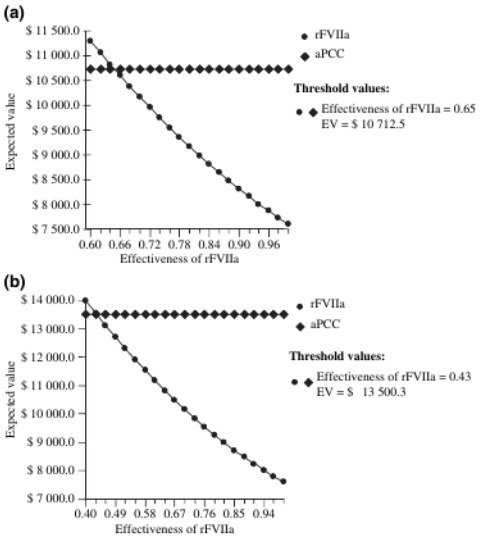

Fig. 2. Break-even analysis between recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) as the probability of the effectiveness of rFVIIa is varied from 40% to 100%: (a) using values for the effectiveness of aPCC derived from those previously published and (b) using values for the effectiveness of aPCC derived from the current study.

Sensitivity analyses

Varying the figures for effectiveness of rFVIIa and aPCC showed that as effectiveness of rFVIIa was decreased, the total direct medical costs for rFVIIa as first-line therapy approached the total direct medical costs for aPCC as first-line therapy. The break-even point, where total direct medical costs of rFVIIa and aPCC were the same, was reached when the effectiveness of rFVIIa was valued at 66% and that of aPCC was assigned a fixed value of 80%. If an effectiveness value of 56.7% was used for aPCC, a break-even point was achieved at a very low effectiveness value for rFVIIa (43%). In fact, rFVIIa was always the lowest cost option compared with aPCC where rFVIIa effectiveness was >66% (with aPCC effectiveness of 80%) or >43% (with aPCC effectiveness of 56.7%, Fig. 2). The effect of varying the effectiveness of aPCC between 40% and 100%, whilst fixing the effectiveness of rFVIIa at 100%, demonstrated that within a realistic range of effectiveness values, first-line treatment with rFVIIa will always be the lowest cost option compared with first-line treatment with aPCC (Fig. 3). The effect of varying the effectiveness of both drugs simultaneously was determined using two-way sensitivity analysis (Fig. 4). The diagonal hashed area indicates the combination of values that results in a total direct medical cost lower for rFVIIa (Fig. 4). This analysis is further validated by the finding that recently published data fall within the hatched area [18].

Other sensitivity analyses confirmed the validity of the data used in the model (data not shown).

Safety

No safety issues were identified with any first-line treatment, including those cases prospectively treated with rFVIIa.

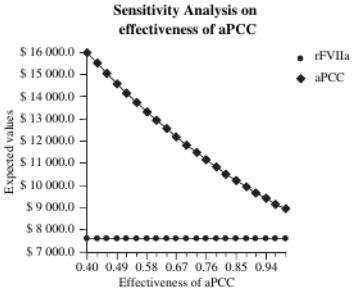

Fig. 3. Impact of changing the probability of effectiveness of activated prothrombin complex concentrate from 40% to 100%.

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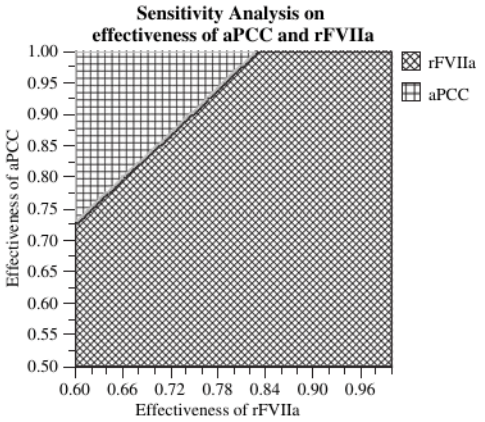

Fig. 4. Impact of simultaneously changing the probability of effectiveness of activated prothrombin complex concentrate from 50% to 100% and recombinant activated factor VII (rFVIIa) from 60% to 100% (hashed area indicates when rFVIIa is the cheaper option).

Discussion

The results of the current analysis suggest that compared with aPCC, rFVIIa is more effective, and costs less, when used as first-line treatment for mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors. This is the first such analysis of the use of rFVIIa as first-line therapy in patients in Brazil. Contrary to current practice, this study confirms that in Brazil, rFVIIa may be considered a realistic first-line treatment in most patients. However, data for other treatment alternatives (PCC and high-dose FVIII) were not sufficient to allow comparison.

The effectiveness of rFVIIa in the current study was slightly higher than that reported previously (92%) [13], probably because of the small sample size (particularly the prospective cohort). Early treatment is clearly advantageous as indicated by the lower mean number of doses and the absence of re-bleeds in patients treated in <6 h. The greater effectiveness of rFVIIa is also likely to have a positive impact on quality of life and, potentially, on societal costs. These factors warrant further study and should be considered when selecting appropriate treatment options.

In this study, the time taken to initiate treatment was longer for aPCC compared with rFVIIa, a finding that might be expected to influence cost and effectiveness. However, after comparing bleeds treated ≤12 h from onset, the superior effectiveness and cost-effectiveness of rFVIIa remained. The less favourable performance of aPCC cannot therefore be explained by the delay in initiating treatment in these patients.

The lower total direct medical costs of first-line treatment with rFVIIa compared with aPCC are supported by results from studies in the UK [11,12,19], Turkey [20] and the US [10].

The key economic drivers in the current study were drug costs, the dose used and the probability of first-line effectiveness. This last component in the baseline scenario was based on the obtained data and verified by expert opinion. Mean aPCC doses used in the current study were in line with those reported in a recent review of aPCC efficacy in Europe and the US [21]. The dose of aPCC used in the current study reflects current clinical practice in Brazil and is in line with aPCC prescribing information that recommends the use of doses of 50–100 units per kg body weight [22]. In the current study, only a minority of bleeds were treated in an inpatient setting, so hospitalization contributed less to the overall costs than in similar studies in other countries [11,12,19].

Cost analysis data are extremely valuable for the development of treatment guidelines where there is debate over the most appropriate treatment in terms of cost-effectiveness. Such information also helps to address questions concerning the allocation of limited resources [23]. Indeed, in some countries it has been suggested that models of cost-effectiveness ranking be used to set specific healthcare budgets [24]. The current study demonstrates the importance of considering more than just the direct acquisition cost per vial.

The original design of this study was to retrospectively evaluate treatment of mild-to-moderate bleeds in patients with inhibitors in Brazil. However, the limited number of bleeding episodes initially treated with rFVIIa (only 14) in the period August 2002–May 2004 meant it was necessary to collect more data for rFVIIa (prospectively). Ideally, cost data should be obtained in prospective studies. However, retrospective data were considered valid because the pattern of use of aPCC had not changed significantly in Brazil during this period. Extensive sensitivity analysis of the effect of varying effectiveness values and other parameters confirmed the validity of the current findings, showing that the fundamental conclusions were not subject to bias from these factors.

Conclusion

In conclusion, the effectiveness of rFVIIa was higher than that of aPCC. Although the acquisition cost of rFVIIa was higher than that of aPCC, the total direct medical costs of treating an individual bleed were lower when rFVIIa was used as first-line therapy

compared with aPCC. From this study, it is clear that both from a clinical and an economic position, rFVIIa should be recommended as the first-line treatment for bleeds in patients with haemophilia and inhibitors. These findings are relevant for the development of management guidelines to ensure the best treatment of haemophilia patients, both in Brazil and in other countries in the region with similar treatment options.

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[no notes on this page]