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ORIGINAL ARTICLE *Clinical haemophilia*

Cost-effectiveness of recombinant activated factor VII vs. plasma-derived activated prothrombin complex concentrate in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors in Spain

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Summary. Several analyses have shown that recombinant activated factor VII (rFVIIa) is a cost-effective intervention compared with plasma-derived activated prothrombin complex concentrate (pd-aPCC) for the on-demand treatment of mild-to-moderate bleeds in haemophilia patients with inhibitors. The aim of the study was to assess the cost-effectiveness of rFVIIa vs. pd-aPCC in the treatment of bleeding episodes in severe haemophilia A patients with inhibitors in Spain. A decision analytic model was designed to evaluate the costs and clinical outcomes of using rFVIIa or pd-aPCC to treat mild-to-moderate joint bleeds in children (≤14 years old) and adults with inhibitors. Data were obtained from a published meta-analysis and a panel of haemophilia experts. The analysis was conducted from the perspective of the Spanish National Healthcare System. One-way sensitivity analyses were performed to assess the impact of model assumptions on study results. In the Treur meta-analysis, rFVIIa resulted in cumulative joint bleed resolution of 88% and 95% after 24 and 36 h, respectively, compared with 62% and 76%, respectively, with pd-aPCC (Treur *et al. Haemophilia* 2009; **15**: 420–36). Here, the mean cost per bleed was estimated at €8473 and €15 579 in children and adults treated with rFVIIa, vs. €8627 and €15 677 in children and adults treated with pd-aPCC. rFVIIa treatment was found to be the dominating option (cheaper and more effective). The one-way sensitivity analysis also confirmed that rFVIIa was less costly than pd-aPCC. The model suggests that rFVIIa is a cost-effective option compared with pd-aPCC for the treatment of mild-to-moderate bleeding episodes in a Spanish setting.

Keywords: congenital haemophilia with inhibitors, cost-effectiveness, plasma-derived activated prothrombin complex concentrate, recombinant activated factor VII, Spain

Introduction

Haemophilia is a hereditary disease caused by a deficiency in coagulation factors VIII (FVIII) (haemophilia A) or IX (FIX) (haemophilia B) [1]. The estimated annual incidence in Europe is 1 per 10 000 for haemophilia A and 1 per 60 000 inhabitants for haemophilia B [1]. In Spain, 86.7% of patients with haemophilia have haemophilia A [2,3].

Haemophilia A is treated using FVIII-replacement therapy [4], but administration of the factor can lead to the development of anti-FVIII antibodies, commonly known as inhibitors, which interfere with FVIII function and prevent coagulation. Haemophilia patients with inhibitors are at a higher risk of experiencing a bleeding episode and are more difficult to treat [5]. Treatment of acute bleeding episodes in patients with high-responding inhibitors most often involves the use of bypassing haemostatic agents, such as plasma-derived activated prothrombin complex concentrates (pd-aPCC; FEIBA®; Baxter International Inc., Deerfield, IL, USA) or recombinant activated Factor VII (rFVIIa; NovoSeven®; Novo Nordisk A/S, Bagsværd, Denmark).

Two prospective, randomized clinical studies have been conducted and provide information on the relative efficacy of pd-aPCC and rFVIIa in the management of acute bleeds [6,7]. However, these studies reported

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varying efficacy (bleeding resolution) rates for both products, which likely stem from differences in study design. Specifically, bleeds were treated with differing doses of both rFVIIa or pd-aPCC, therapy was administered at different intervals as a single or repeat dose and bleed resolution was assessed at varying time points (ranging from 1 to 72 h postdose) with different measures of efficacy (e.g. controlled vs. not controlled or effective vs. partially effective vs. ineffective).

A recent Bayesian meta-analysis conducted by Treur *et al.* investigated published studies reporting on the efficacy of on-demand rFVIIa and/or pd-aPCC for the treatment of joint bleeds in patients with inhibitors. In total, data on over 2000 joint bleeds from 17 different studies were included in the analysis and results indicated that a typical regimen of rFVIIa is likely to be significantly more effective than a typical pd-aPCC regimen at 12, 24 and 36 h after treatment [8].

Using the efficacy results from this analysis, we aimed to assess the cost-effectiveness of rFVIIa vs. pd-aPCC in the treatment of mild-to-moderate bleeding episodes in patients with severe haemophilia A and inhibitors. The analysis was carried out from the perspective of the Spanish National Healthcare System (NHS).

Materials and methods

Methods

Haemophilia medical experts from Spain were surveyed in a Delphi panel to customize and develop the model from the perspective of the physician and the NHS. Haemophilia A was assessed in the study as it is the most common form of the disorder. Expert opinion was provided based on their experience with the dose-utilized efficacy (response) and the rebleed rates achieved at 24 and 48 h. Mean patient weight and dose for each bypassing agent in the first 24 h of treatment, as well as subsequent doses, were defined by experts (Table 1). Based on their practice, 60% of children and 85% of adult patients would start treatment at home within the 24- and 48-h time periods and those patients who had not responded after 48 h would require hospital admission. Patients initiating treatment with either rFVIIa or pd-aPCC who still had unresolved bleeds after 24 and 48 h would also require further treatment, as described in Tables 2 and 3.

Model structure

A decision analytic model [9] was developed to evaluate the costs and clinical outcomes of treating mild-to-moderate joint bleeding episodes with either rFVIIa or pd-aPCC in children (≤14 years old) and adults with severe haemophilia A (<1% of factor activity) with high-titre, high-responding inhibitors (≥5 Bethesda Units).

Table 1. Base-case assumptions: mean weight, dose regimens and rebleed rate.

	Children (≤14 years)		Adults	
	Base case	Sensitivity analysis	Base case	Sensitivity analysis
Mean weight (kg)	27	7–60	67	50–90
Total daily dose per kg body weight				
Initial dose				
rFVIIa (μg kg^{-1})	360	270–600	300	180–480
pd-aPCC (IU kg^{-1})	150	100–200	120	50–200
Increased dose after 24 h				
rFVIIa (μg kg^{-1})	700	270–1080	675	270–1260
pd-aPCC (IU kg^{-1})	225	140–245	195	100–245
Increased dose after 48 h				
rFVIIa (μg kg^{-1})	875	360–1750	750	360–1200
pd-aPCC (IU kg^{-1})	240	140–245	212	150–245
Rebleed rate (%)	15	10–20	15	10–20

rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; IU, international unit.

The model structure (Fig. 1) is adapted from previously published models [10–12] and adjusted to reflect the routine clinical management of patients with severe haemophilia A and inhibitors in Spain. The model follows patients through initial and subsequent treatment until the bleed is resolved. The structure also includes assumptions around switch of therapy, dose increase and occurrence of rebleeds. Patients entering the model are treated with either pd-aPCC or rFVIIa as the first-line agent when the bleeding episode occurs. The model assumes that all patients will receive treatment with either pd-aPCC or rFVIIa for 24 h as the first-line therapy. If the bleed has not resolved after 24 h, clinicians can choose to continue with current treatment, elevate the dose or switch to the alternative bypassing agent as second-line therapy. After 48 h if the bleed still has not resolved, the model again presents the same choices. Those patients who have switched to the other agent after 24 h and continue with an unresolved bleed after 48 h, only can maintain the current treatment or receive an increased dose.

Based on published data [10,11] and expert opinion, the model assumed that patients not responding to treatment after 48 h would remain on the same treatment for an additional 2.5 days. The model also assumed that if a second bleed (or rebleed) occurred within 7 days, it would be directly related to the first bleeding episode rather than a second bleed. Rebleeds would be managed using the same drug as was used to control the initial episode.

Costs and clinical outcomes were calculated for both paediatric and adult patients. Paediatric patients were considered to be ≤14 years of age to align with treatment practice, as patients above 14 years old are considered adults in Spain.

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Table 2. Base-case assumptions: treatment patterns to manage episodes of mild-to-moderate joint bleeding with rFVIIa.

Patients with unresolved bleeds after 24 h	Children (%)	Adults (%)	Patients with unresolved bleeds after 48 h	Children (%)	Adults (%)
Initiated with rFVIIa and continued with same treatment at 24 h	10	20	Continue with current treatment	40	20
			Continue with same agent, but increase dose	50	60
			Switch bypassing agent	10	20
Initiated with rFVIIa and increased dose at 24 h	80	50	Continue with current treatment	15	20
			Continue with same agent, but increase dose	45	35
			Switch bypassing agent	40	45
Initiated with rFVIIa and switched bypassing agent at 24 h	10	30	Continue with current treatment	50	55
			Continue with same agent, but increase dose	50	45

rFVIIa, recombinant activated factor VII.

Table 3. Base-case assumptions: treatment patterns to manage episodes of mild-to-moderate joint bleeding with pd-aPCC.

Patients with unresolved bleeds after 24 h	Children (%)	Adults (%)	Patients with unresolved bleeds after 48 h	Children (%)	Adults (%)
Initiated with pd-aPCC and continued with same treatment at 24 h	10	25	Continue with current treatment	10	30
			Continue with same agent, but increase dose	50	50
			Switch bypassing agent	40	20
Initiated with pd-aPCC and increased dose at 24 h	50	45	Continue with same treatment	33	37
			Continue with same agent, but increase dose	33	3
			Switch bypassing agent	33	60
Initiated with pd-aPCC and switched bypassing agent at 24 h	40	30	Continue with same treatment	30	40
			Continue with same agent, but increase dose	70	60

pd-aPCC, plasma-derived activated prothrombin complex concentrate.

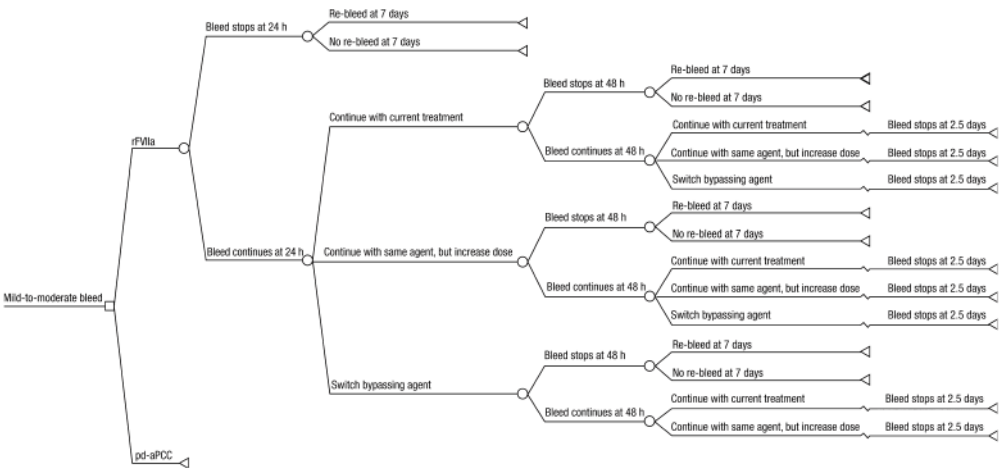

Fig. 1. Decision tree used to represent the management of a mild-to-moderate bleeding episode.

Model parameters

Information to populate the model was obtained from the published literature and the mentioned Delphi panel of five Spanish haemophilia experts. Interviews including standard questions on patient management, treatment pathways and resource use, as well as open-ended questions to elicit any additional important information, were performed.

The response rates used in our model were taken from Treur *et al.* [8], who used a systematic review to identify studies reporting on the dosage and efficacy of rFVIIa or pd-aPCC for treating joint bleeds in haemophilia patients with inhibitors. Pooled efficacy levels for typical rFVIIa and pd-aPCC regimens were estimated from the 17 studies identified, which collectively reported on >2000 joint bleeds and were adjusted for any potential heterogeneity. Treur *et al.* [8] predicts that a typical regimen of 3×90 μg kg^{-1} rFVIIa repeated every 3 h if needed would result in cumulative joint bleed resolution of 88% and 95% after 24 and 36 h, respectively, as based on meta-analysis of key studies. In comparison, a typical regimen of 75 IU kg^{-1} pd-aPCC repeated every 12 h if needed would result in cumulative joint bleed resolution of 62% and 76% respectively. Difference in resolution rates between the

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two regimens were statistically significant and were also found to be robust in sensitivity analyses [8].

In our cost-effectiveness model, the results at 12 h were excluded from the model as clinicians in Spain measure the response at 24 h and 48 h. We used the response rate observed at 24 h and assumed that the response rate at 48 h would be the same as that at 36 h. The probability of developing a rebleed was derived from previous studies [13,14] and expert opinion and was assumed to be equal for both treatments (Table 1). The mean costs take efficacy (e.g. bleed resolved, rebleeds at 24 and 48 h) and the resulting treatment regimen into consideration.

The analysis was performed from the perspective of the Spanish NHS and only direct costs (drug and hospitalization costs) were considered. Drug costs were based on the ex-factory price provided in the medication database of the General Council of Official Colleges of Pharmacists (€0.523 per μg for rFVIIa and €0.63 per IU for pd-aPCC). Non-drug direct costs were obtained from a database of Spanish health care costs [15]. All costs were adjusted to reflect 2011 prices using the Spanish Consumer Price Index.

Sensitivity analysis

Multiple one-way sensitivity analyses were conducted to incorporate parameter uncertainties mainly due to the variability in patient management with respect to unresolved bleeds, and resulting treatment which could be maintained, increased or result in therapy switch.

Key model inputs were varied individually within the clinically appropriate range for the variable in question [16]. Specifically, the one-way sensitivity analysis varied one parameter whereas all others were held constant. Efficacy rates, cost of first dose, rebleed rate and the rate of switching between the rFVIIa and pd-aPCC were all included in the sensitivity analysis.

Results

The model showed that the cost of treating a mild-to-moderate joint bleed with rFVIIa was €8473 and €15 579 for paediatric and adult patients, respectively, for high-titre, high-responding severe haemophilia A patients with inhibitors in Spain (Table 4). Total cost to treat the same type of bleed with pd-aPCC in both subgroups was €8627 and €15 677. In the model, first-line use of rFVIIa led to cost savings of €154 and €98 per episode as compared with pd-aPCC in children and adults. These cost benefits, coupled with the available clinical data and corresponding Treur *et al.* [8] meta-analysis, demonstrate that rFVIIa is the dominant option (both cheaper and more effective). Table 4 shows the estimated cost for different patient groups and the contribution of each of those groups to the mean overall cost to the NHS.

Results of the differences in cost per bleed from the one-way sensitivity analysis are summarized in Table 5. This analysis indicated that the key drivers in the model were cost of first dose, efficacy of pd-aPCC and switch rate. The results were relatively sensitive to rebleed rate.

Discussion

In Spain, first-line treatment with rFVIIa (vs. pd-aPCC) could be a cost-saving alternative in the treatment of mild-to-moderate bleeds for patients with severe haemophilia A and inhibitors. The mean costs are driven primarily by a higher percentage of patients responding to rFVIIa within 24 h (see Table 4 and Fig. 1).

Faster bleed resolution with rFVIIa means that patients are more likely to require fewer doses, only one line of therapy and fewer (or no) hospitalizations [17]. Moreover, a study by Lusher [18] has shown that prolonged bleeding often leads to greater morbidity

Table 4. Results of the base-case analysis.

	rFVIIa as first-line therapy				pd-aPCC as first-line therapy			
	Children		Adults		Children		Adults	
	Cost (€)	% of patients	Cost (€)	% of patients	Cost (€)	% of patients	Cost (€)	% of patients
Resolved bleed at 24 h without rebleed*	5153	74.80	10 533	74.80	2620	52.70	5084	52.70
Resolved bleed at 24 h with rebleed*	12 468	13.20	17 849	13.20	8175	9.30	10640	9.30
Resolved bleed at 48 h								
Continued with current treatment after 24 h	12 054	0.70	22 860	1.40	6724	1.40	11 698	3.50
Increased dose after 24 h	16 852	5.60	35 992	3.50	7988	7.00	14 859	6.30
Switched bypassing agent after 24 h	9257	0.44	17 147	1.30	9521	8.90	17 411	6.60
Unresolved bleed at 48 h								
Continued with current treatment after 24 h	32 221	0.50	69 435	1.00	23 930	2.40	39 444	6.00
Increased dose after 24 h	39 973	4.00	81 728	2.50	19 663	12.00	37 426	10.80
Switched bypassing agent after 24 h	19 027	0.76	35 155	2.30	32 428	6.30	65 183	4.75
Mean cost per bleeding episode	8473	–	15 579	–	8627	–	15 677	–

rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate.
*In a period of 7 days after the initial bleed was resolved.

Table 5. Sensitivity analysis results.

Sensitivity analysis	Value for sensitivity analysis	Children costs (€)			Value for sensitivity analysis sensitivity analysis	Adults costs (€)		
		rFVIIa	pd-aPCC	Difference		rFVIIa	pd-aPCC	Difference
Base case		8473	8627	−154		15 579	15 677	−98
Initial cost of rFVIIa (first 24 h)								
Min	3810 €	7181	8373	−1192	6303 €	11 255	14 999	3744
Max	8467 €	11 917	9302	2615	16 809 €	22 065	16 696	5370
Initial cost of pd-aPCC (first 24 h)								
Min	1698 €	8455	7740	715	2107 €	15 380	12 314	3066
Max	3396 €	8492	9513	−1021	8429 €	15 806	19 521	−3715
Efficacy rate of rFVIIa at 24 h								
Min	68.00%	12 179	8627	3552	68.00%	22 160	15 677	6483
Max	100.00%	6250	8627	−2377	100.00%	11 630	15 677	−4047
Efficacy rate of pd-aPCC at 24 h								
Min	39.00%	8473	11 758	−3285	39.00%	15 579	21 585	−6006
Max	82.00%	8473	5904	2569	82.00%	15 579	10 541	5038
Switch rate to pd-aPCC after no-response at 24 h with rFVIIa								
Min	0.00%	8288	8627	−339	0.00%	14 552	15 677	−1125
Max	50.00%	9214	8627	587	50.00%	16 263	15 677	586
Switch rate to rFVIIa after no-response at 24 h with pd-aPCC								
Min	0.00%	8473	5729	2745	0.00%	15 579	11 423	4156
Max	50.00%	8473	9351	−878	50.00%	15 579	18 514	−2935
Probability of developing a rebleed in pd-aPCC first-line arm								
Min	10.00%	8118	8553	−435	10.00%	15 231	15 608	−377
Max	20.00%	8829	8700	129	20.00%	15 927	15 747	179
Probability of developing a rebleed in rFVIIa first-line arm								
Min	10.00%	8465	8405	60	10.00%	15 565	15 453	112
Max	20.00%	8481	8849	−368	20.00%	15 593	15 902	−309

Min, minimum; max, maximum; rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate.

and prolonged hospitalization, as well as the potential for corrective surgical procedures. Using rFVIIa instead of pd-aPCC to resolve a mild-to-moderate bleeding episode could therefore lead to lower overall treatment costs and a reduction in longer term morbidity. Reduced morbidity could also have positive economic repercussions for the NHS as well as lead to improvements in patients' quality of life.

Our results differ from previous studies which found pd-aPCC was less costly than rFVIIa [10,19]. However, our findings cannot be directly compared with these due to variations affecting overall costs, such as clinical practice patterns, average dosage required and the cost of haemostatic agents. Moreover, these economic evaluations performed a cost-minimization analysis, where only the costs of both therapeutical strategies were compared, whereas our study determined cost-effectiveness of both treatments. In contrast, the results generated by our model are similar to those reported in other countries like Korea [14], Turkey [20] or Brazil [21], which showed that rFVIIa is a cost-effective intervention compared with pd-aPCC when used as on-demand treatment for spontaneous mild-to-moderate bleeds in haemophilia patients with inhibitors [10–12,21,22].

Data on the effectiveness of rFVIIa and pd-aPCC were obtained from a published systematic search and meta-analysis [8], which used a Bayesian approach to pool data from randomized and non-randomized, single arm or head-to-head studies. Systematic review and meta-analysis techniques provide the highest level of evidence as statistical methods allow the results of independent clinical studies to be combined and analysed [23].

As in previous studies [10–12], we found that the results were very sensitive to the parameters used in the base-case values. Much of the uncertainty associated with cost estimates in haemophilia stems from the clinical variability around treating the disease. The fact that haemophilia is a rare disease, clinical outcomes data are limited, and bleeds are unpredictable leads to considerable heterogeneity in terms of clinical experience and treatment. For example, due to the variability between patients, it is difficult to identify a single estimate around the mean volume of haemostatic agents required to stop a bleed. The use of expert opinion to validate and complement information drawn from the literature is necessary when clinical information is limited. However, to reduce the uncertainty associated with the additional data assumptions in this study, it would be useful to conduct a retrospective chart review or prospective study of paediatric and adult patients in Spain. Studies should pay special attention to key clinical variables such as the relative efficacy of each treatment, dosage and rebleeding. The full treatment course should be followed to ensure optimal and cost-effective care for patients.

Conclusions

In conclusion, clinical results indicate that treatment with rFVIIa given first-line is more likely to resolve

mild-to-moderate bleeds and therefore could reduce NHS costs as compared with pd-aPCC. Hence, rFVIIa is a more cost-effective option compared with pd-aPCC based on our clinical and cost assumptions.

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Author contributions

All authors provided substantial contributions to the design of the study, analysis and interpretation of data and to writing and critically reviewing the manuscript. We have all approved the final version.

Disclosures

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