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ORIGINAL ARTICLE

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

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Key words: Activated prothrombin complex concentrate – APCC – Economic model – FEIBA – Hemophilia with inhibitors – Monte Carlo simulation – NovoSeven – Probabilistic sensitivity analysis – rFVIIa

ABSTRACT

Objective: To compare the cost-effectiveness of three treatment regimens using recombinant activated Factor VII (rFVIIa), NovoSeven†, and activated prothrombin-complex concentrate (APCC), FEIBA VH‡, for home treatment of minor-to-moderate bleeds in hemophilia patients with inhibitors.

Methods: A literature-based, decision-analytic model was developed to compare three treatment regimens. The regimens consisting of first-, second-, and third-line treatments were: rFVIIa-rFVIIa-rFVIIa; APCC-rFVIIa-rFVIIa; and APCC-APCC-rFVIIa. Patients not responding to first-line treatment were administered second-line treatment, and those failing second-line received third-line treatment. Using literature and expert opinion, the model structure and base-case inputs were adapted to the US from a previously published analysis. The percentage of evaluable bleeds controlled with rFVIIa and APCC were obtained from published literature. Drug costs (2005 US$) based on average wholesale price were included in the base-case model. Univariate and probabilistic sensitivity analyses (second-order Monte Carlo simulation) were conducted by varying the efficacy, re-bleeding rates, patient weight, and dosing to ascertain robustness of the model.

Results: In the base-case analysis, the average cost per resolved bleed using rFVIIa as first-, second-, and third-line treatment was $28 076. Using APCC as first-line and rFVIIa as second- and third-line treatment resulted in an average cost per resolved bleed of $30 883, whereas the regimen using APCC as first- and second-line, and rFVIIa as third-line treatment was the most expensive, with an average cost per resolved bleed of $32 150. Cost offsets occurred for the rFVIIa-only regimen through avoidance of second and third lines of treatment. In probabilistic sensitivity analyses, the rFVIIa-only strategy was the least expensive strategy more than 68% of the time.

Conclusions: The management of minor-to-moderate bleeds extends beyond the initial line of treatment, and should include the economic impact of re-bleeding and failures over multiple lines of treatment. In the majority of cases, the rFVIIa-only regimen appears to be a less expensive treatment option in inhibitor patients with minor-to-moderate bleeds over three lines of treatment.

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‡ FEIBA VH is a registered trademark of Baxter, Deerfield, Illinois, USA

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[NHSM (Neha Sharma)]

Introduction

Approximately 20–30% of hemophilia A and 2–5% of hemophilia B patients eventually develop antibodies (or inhibitors) to traditional clotting factor replacement with Factor VIII (FVIII) or Factor IX (FIX)[1]. These inhibitors bind to FVIII and FIX and neutralize their effect on hemostasis, resulting in major difficulties in controlling bleeding.

Treatments used for managing bleeds in patients with high titer or high responder (> 5 Bethesda units) inhibitors work through bypassing the normal coagulation cascade. Agents used for managing bleeds in patients with inhibitors primarily include recombinant activated Factor VII (rFVIIa), NovoSeven*, and the activated prothrombin complex concentrate (APCC), FEIBA VH†, which differ in terms of their mechanism of action, efficacy, safety, and administration profiles[2,3].

APCC is a freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity[2]. It works by shortening the activated partial thromboplastin time (APTT) of plasma containing FVIII inhibitor. Disadvantages associated with the use of APCC include the potential for anamnestic responses due to FVIII in the APCC preparation, and possible transmission of human pathogens[2].

The human recombinant activated coagulation Factor VII (rFVIIa) binds to tissue factor, and in pharmacologic doses it binds to the surface of activated platelets found at the site of vascular injury and directly activates Factor X, promoting localized thrombin generation and fibrin clot formation[4,5]. Because rFVIIa is a recombinant product, there is no potential for human pathogen transmission. Its use is not associated with an anamnestic response; inhibitor titers have actually been noted to decrease during rFVIIa therapy[6].

Managing bleeds in patients with hemophilia and inhibitors is challenging and can be expensive[7]. Costs may be up to three times higher for patients with high responding inhibitors than those with no or low responding inhibitors[8,9]. High costs of this nature are typical for drug therapies with orphan indications for rare disorders such as hemophilia with inhibitors. Although inhibitor patients have minor as well as major bleeds, minor-to-moderate bleeds (e.g., joint bleeds, soft tissue, and muscle bleeds) are the primary cost driver since the patients typically experience up to 15 minor bleeds and 0.2 major bleeds per year[10]. Home treatment for minor-to-moderate bleeds is now the standard of care in the US to more quickly control the bleeding instead of waiting until the patient arrives at a treatment center. In addition, earlier treatment with a more effective drug is likely to reduce the need for further hospitalizations, and possibly require fewer doses in further treatment. As the hospital care component has shifted from being a major to now a minor cost driver, home treatment now represents approximately 90% of the total cost of care, made up almost entirely by the cost of the agents themselves[9]. Attention has now been shifted to the pharmacy budget impact of various agents for home treatment.

A pharmacoeconomic analysis of the available treatment options, taking into account different clinical and cost profiles, would be helpful to decision makers when selecting therapies. Therefore, the objective of this study was to conduct a pharmacoeconomic analysis that compares the cost of treatment of rFVIIa with APCC for home treatment in hemophilia patients with inhibitors experiencing minor-to-moderate bleeds. The focus of the analysis was on the entire cost of managing a bleeding episode, thus taking into consideration the costs associated with treatment failures, re-bleeding, and re-treatments.

Methods

Model framework

A decision-analytic model was used to compare the cost of treating a bleed for three 'on-demand' treatment regimens using rFVIIa and APCC for home treatment of minor-to-moderate bleeds. The model structure and parameter values for the base-case analysis were adapted to a short-term US perspective from a previously published model in the UK[10], after consultations with experts regarding practice patterns in the US. A minor-to-moderate bleed was defined as one which could initially be managed at home (e.g., joint bleeds, soft tissue, and muscle bleeds, etc.) in hemophilia patients with inhibitors (not being treated with immune tolerance therapy [ITT])[10]. Continued bleeding was defined as a bleed that does not initially resolve after administration of a treatment strategy (primary failure) and re-bleeding was defined as a bleed that initially resolves with treatment but recurs.

The model followed patients through three lines of treatment to address costs of failures and re-bleeding. Three 'on-demand' treatment regimens (regimens adopted from the UK analysis)[10] were compared in the model (from first-, to second-, to third-line treatments) (Figure 1):

- Regimen 1: APCC (first line) followed by another course of APCC (second line) in case of failure of the first line, and then by rFVIIa (third line) in case of failure of the second line.

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† FEIBA VH is a registered trademark of Baxter AG, Deerfield, Illinois, USA

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- Regimen 2: APCC (first line) followed by rFVIIa (second line) in case of failure of the first line, and then by another course of rFVIIa (third line) in case of failure of the second line.
- Regimen 3: rFVIIa as first-, second-, and third-line treatments.

As shown in Figure 1, initial re-bleeding in any line of treatment was managed with a repeat dose of the same agent in that line of treatment.

Clinical inputs

The treatment algorithm, dosing, and base-case efficacy rates and probability of re-bleeds were adapted from a previously published model in the UK (see Table 1)[10]. Evaluable bleeds were used as the basis for success rates in the studies. In all 3 strategies, efficacy was assumed to be 100% after third-line treatment[10].

Table 1. *Model assumptions*

Model parameter	Base-case analysis*		Range tested in sensitivity analyses	
	rFVIIa[7]	APCC[7]	rFVIIa[8–10]	APCC[11,12]
Efficacy	92%	78%	88–93%, pooled: 91% (CI: 89–93%)	78–81%, pooled: 81% (CI: 77–84%)
Re-bleed rate	15%	15%	10–20%	10–20%
Mean total dose				
Line 1	207 μg/kg	180 IU/kg		
Line 2	207 μg/kg	180 IU/kg	± 20%	± 20%
Line 3	414 μg/kg	n.a.		
Drug cost†	$1.54/μg	$1.68/IU	± 10%‡	± 10%‡
Hospital costs	$0	$0	$1500/day × 2 days for line 3‡	$1500/day × 2 days for line 3‡
Patient weight	70 kg	70 kg	20 kg‡, 66–82 kg	20 kg‡, 66–82 kg

*Base-case analysis assumptions from Knight *et al.*[7]
†AWP from August 2005 for rFVIIa and APCC[18]
‡Univariate sensitivity analyses only

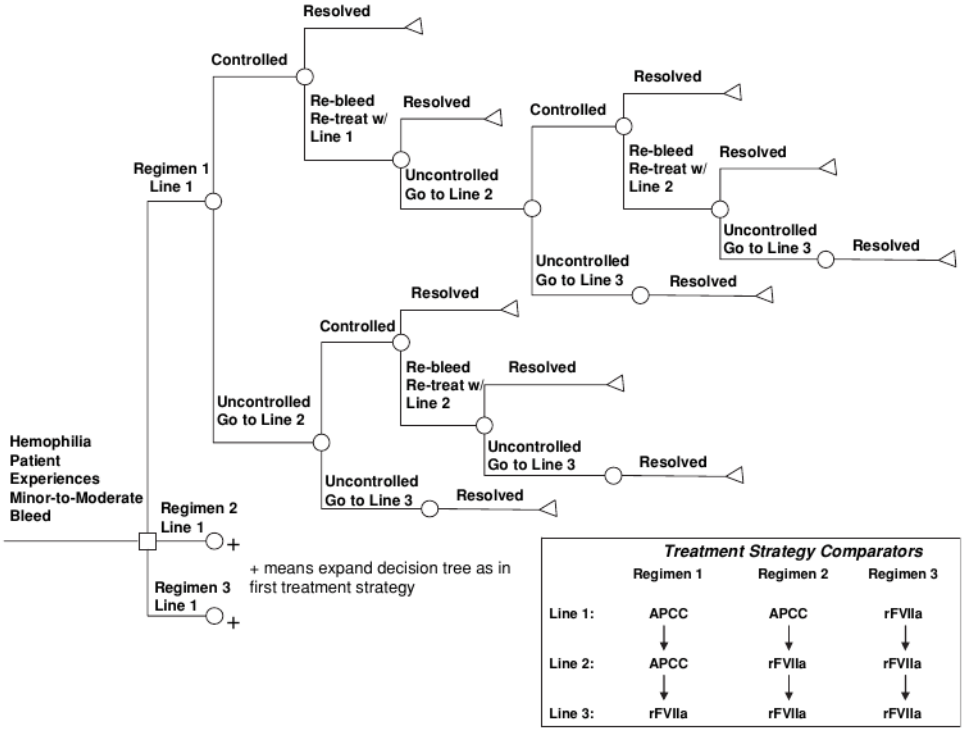

Figure 1. *Model structure and treatment strategy comparators*

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Because the agents are dosed by weight, we assumed the mean patient weight was 70 kg in the base-case analysis. Each line of treatment consisted of multiple doses/infusions as is common in clinical practice. Total mean dose per line of treatment was adapted from the literature-based assumptions used in the Knight *et al*. economic analysis[10]. In each line of treatment, the average treatment cycle consisted of slightly more than two infusions per patient. Specifically, the mean total dose per line of treatment for rFVIIa was 207 µg/kg (approximately 2.3 doses of 90 µg/kg), and for APCC, the mean dose was 180 IU/kg per line of treatment (approximately 2.4 doses of 75 IU/kg). In general, the base-case assumptions reflected the previous Knight *et al*. analysis when possible to keep in the spirit of a US adaptation[10].

In the sensitivity analyses, data from the various studies were combined (whenever possible) to generate probable ranges of average values for the model parameters[11–15]. Specifically, for rFVIIa and APCC, efficacy data were pooled across studies of each agent[16] to calculate their weighted average efficacy rate, defined as the cumulative number of successfully controlled bleeds divided by the cumulative number of evaluable bleeds across all studies of each agent. Ninety-five per cent confidence intervals for the proportion of successfully controlled bleeds were estimated using a normal approximation of the binomial distribution. From published literature, the percentage of evaluable bleeds controlled with rFVIIa and APCC ranged from 88% to 93% (pooled average and 95% confidence interval: 91% [89–93%])[11–13] and 78–81% (pooled average and 95% confidence interval 81% [77–84%])[14,15], respectively (Table 1). Pooled re-bleeding rates were not used because the definitions of re-bleeding varied dramatically across studies. Instead we assumed that the re-bleeding rate would range ±5% around the base-case re-bleeding rate of 15%[10]. In the absence of sufficient data, the re-bleeding rates were also assumed to be equal for both agents. Dosing variability for the sensitivity analyses was assumed to be ±20% based upon a review of the studies[11–15]. Patient weight was varied based on the 25th–75th percentiles of average weight for a US adult 20 year old male (range 66–82 kg)[17].

Costs

Only drug costs based on August 2005 US$ average wholesale prices (AWP) were included in the base-case model, since the patients or their caregiver administered the treatment at home[18]. Hospital costs were excluded from the base-case analysis because patients are routinely treated at home for minor-to-moderate bleeds in the US, even for second- and third-line treatments. Potential hospitalization costs for third-line treatment were included in sensitivity analyses and were assumed to be incurred for 2 days at a general ward cost of $1500/day (adjusted to 2005 US$), with costs taken from a study comparing changes in intensive care unit and ward costs[19]. Costs were not discounted due to the short-term nature of the model.

Analyses

For the base-case analysis, the model reports the average cost per bleeding episode over three lines of treatment for each of the three regimens. Costs were broken down by overall and within each line of treatment for comparisons.

Since uncertainty exists regarding the precise value that should be taken by most parameters of the model, univariate and multivariate sensitivity analyses were conducted to test the robustness of the results.

Specifically, univariate sensitivity analysis, in which one parameter is varied at a time while holding all other parameters constant, were conducted on the efficacy rates, re-bleed rates, dosing, drug costs, and patient weight for all three lines of treatment. Potential hospitalization costs for third-line treatment were also included in univariate sensitivity analyses to demonstrate that this had a limited effect on the cost of treatment. As part of the univariate analyses, threshold analyses were also conducted on efficacy rates and drug costs to hypothetically determine cost neutrality between the treatment strategies when holding other variables constant.

A probabilistic sensitivity analysis (PSA) was also conducted. PSA is a form of sensitivity analysis designed to test whether a model produces consistent results and conclusions when multiple parameters are varied simultaneously. The values taken by each of the model parameters in the PSA are selected from their assumed and pre-specified probability distributions (e.g., normal, uniform, or other). Monte Carlo simulations are then used to generate and summarize the results of a large number of model replicates (e.g., 10 000), in which different values for each parameter are being drawn from their distributions. The results of these 10 000 replicates can then be analyzed in terms of their own distribution using simple descriptive statistics. This provides an indication of level of uncertainty associated with the results (e.g., in what percentage of the model replications do we find cost savings with one strategy over another). In the present analysis, 10 000 replicates of the model were generated, using a random selection of values within the range specified.

Following recommendations by Briggs[20], only those parameters that were uncertain, unknown, or could not be controlled by decision makers, such as efficacy, re-bleeding, dosing, and patient weight were included in the PSA. Drug costs were excluded from the PSA

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because these are known and controllable by decision makers[20]. Finally, the cost of hospitalization was also excluded from the PSA because there is little evidence that patients with mild to moderate bleeding require hospitalizations (as mentioned earlier, hospitalizations were included in univariate sensitivity analyses to illustrate their lack of impact on the results).

The base-case model and univariate sensitivity analyses were conducted in Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). The PSA, including two- and three-way comparisons, were conducted using @RISK (Palisade Corporation, Ithaca, New York, USA).

Results

Main results

Given the higher efficacy of rFVIIa, the base-case analysis showed decreasing costs with subsequent lines of treatment with rFVIIa, while showing increasing costs in subsequent lines of treatment with APCC strategies. Specifically, in the base case, the average cost per resolved bleed was the lowest using rFVIIa-only (Regimen 3) at $28 076 per bleed over three lines of treatment (Figure 2). Using APCC as a first-line strategy was more expensive by $2807 (Regimen 2) and $4074 (Regimen 1) per bleed, representing a 10–15% increase compared to the rFVIIa-only regimen. As shown in Figure 2, the cost of first-line treatment was approximately $1700 higher for the rFVIIa-only strategy, however, when re-bleeding rates were accounted for, the costs for an rFVIIa-only strategy were substantially lower than other strategies in second and third lines of treatment.

Sensitivity analyses

Univariate sensitivity analyses indicated that the model's findings were generally consistent with the base-case results (Table 2). The model was relatively sensitive to variations in the mean number of doses in univariate sensitivity analyses, and was, therefore, further tested in the PSA to allow for an analysis of extremes and maximum uncertainty (e.g., simultaneously testing an rFVIIa mean dose at +20% of base-case value, while APCC dose at –20% of base-case value). The 20% variability criterion for the number of doses was derived from the average variation in mean doses from published efficacy studies[11–15].

The threshold analyses showed that when holding APCC efficacy rates at the base-case levels, the rFVIIa efficacy rate would need to be as low as 82% for the overall cost of treatment to be the same between an rFVIIa-only strategy and APCC-containing strategies. In addition, the threshold analysis for drug price showed that the rFVIIa cost per unit would need to be as high as $1.79 (holding APCC costs at base-case level) to reach cost neutrality between the treatment strategies.

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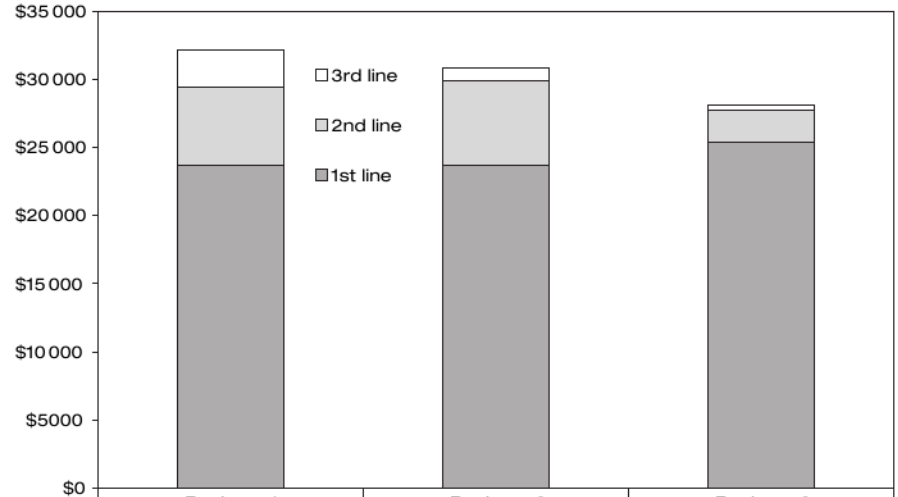

	Regimen 1	Regimen 2	Regimen 3
3rd line	$2695	$998	$370
2nd line	$5810	$6240	$2312
1st line	$23 645	$23 645	$25 394

Figure 2. *Cost of managing a minor-to-moderate bleed. Note: second- and third-line treatment costs are calculated after factoring in efficacy rates and re-bleed probabilities, based on an average scenario for a certain number of patients. Regimen 1 = APCC/APCC/rFVIIa; Regimen 2 = APCC/rFVIIa/rFVIIa; Regimen 3 = rFVIIa/rFVIIa/rFVIIa*

The probabilistic sensitivity analysis using 10 000 Monte Carlo simulations demonstrated that in three-way comparisons rFVIIa-only (Regimen 3) was less expensive than APCC-based Regimen 2 or Regimen 3 in 68% of simulations; Regimen 2 was less expensive than Regimen 3 or Regimen 1 in 14% of simulations; Regimen 1 was less expensive than Regimen 3 or Regimen 2 in 18% of simulations. In order to compare average treatment costs of one regimen vs. another, pair-wise analyses were carried out (Figure 3), which provide

Table 2. *Results of univariate sensitivity analyses*

Parameter	Treatment strategy		
	Regimen 1	Regimen 2	Regimen 3
Base case	$32 150	$30 883	$28 076*
Efficacy APCC 81%	$30 825	$30 017	$28 076*
Efficacy rFVIIa 88%	$32 150	$31 342	$29 515*
Efficacy rFVIIa 93%	$32 150	$30 768	$27 740*
Re-bleed rate 0%	$27 985	$26 863	$24 385*
Re-bleed rate 10%	$30 741	$29 523	$26 837*
Re-bleed rate 20%	$33 580	$32 265	$29 323*
AWP APCC + 10%	$35 131	$33 276	$28 076*
AWP APCC – 10%	$29 170	$28 491	$28 076*
AWP rFVIIa + 10%	$32 413	$31 589	$30 589*
AWP rFVIIa – 10%	$31 888	$30 178	$25 341*
Mean dose APCC + 20%	$38 041	$35 612	$28 076*
Mean dose APCC – 20%	$26 259	$26 155*	$28 076
Mean dose rFVIIa + 20%	$32 689	$32 331*	$33 691
Mean dose rFVIIa – 20%	$31 611	$29 436	$22 461*
Patient weight = 66 kg	$30 313	$29 119	$26 471*
Patient weight = 82 kg	$37 662	$36 178	$32 889*
Patient weight = 20 kg	$9186	$8824	$8022*
Hospitalization for 2 days ($1500/day) in line 3	$32 331	$30 951	$28 101*

*Least expensive regimen; AWP = average wholesale price
Regimen 1 = APCC/APCC/rFVIIa
Regimen 2 = APCC/rFVIIa/rFVIIa
Regimen 3 = rFVIIa/rFVIIa/rFVIIa

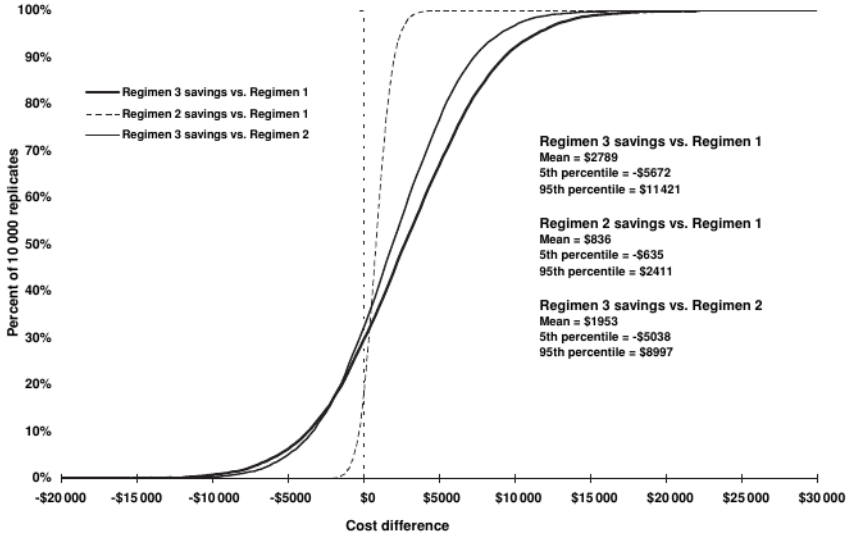

Figure 3. *Cumulative distributions of net cost differences from 10 000 Monte Carlo simulations between 3 treatment strategy comparators (pair-wise comparisons). Regimen 1 = APCC/APCC/rFVIIa; Regimen 2 = APCC/rFVIIa/rFVIIa; Regimen 3 = rFVIIa/rFVIIa/rFVIIa. For example, Regimen 3 cost savings vs. Regimen 1 are calculated as follows: Regimen 1 cost – Regimen 3 cost*

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the cumulative distributions of cost differences from 10 000 Monte Carlo simulations between each regimen. Mean cost savings with the rFVIIa-only (Regimen 3) strategy ranged from $1953 (vs. Regimen 2) to $2789 (vs. Regimen 1). In two-way comparisons, the rFVIIa-only strategy was the least expensive in 70–80% of the 10 000 model replicates.

Discussion

To our knowledge this is the first US economic model to address the full drug therapy cost of managing minor-to-moderate bleeds in patients with hemophilia and inhibitors. This clinically relevant approach, adapted from a previously published model in the UK[10], addresses both initial efficacy and cost of treatment failures and re-bleeding and subsequent management over multiple lines of treatment. Thus, the approach accounts for the complexity of managing bleeds in inhibitor patients.

Decision makers are naturally inclined to select the treatment with the lowest acquisition cost as the first-line agent; however, our model suggests that using the more effective treatment as the first-line strategy may save money when the costs of treating failures and re-bleeds are factored into the analysis. More specifically, the model demonstrated that using an rFVIIa-only regimen provides cost offsets through avoidance of second and third lines of treatment when compared to using APCC strategies. These results were consistent in a variety of scenarios, including probabilistic sensitivity analysis, suggesting that the model results are robust.

In other countries, several economic analyses have been conducted on the management of patients with inhibitors from government payer perspectives[10,21–23]. Ekert *et al*. assessed the cost-utility of using rFVIIa compared to 'usual care' with plasma derived agents in Australia using a combination of medical chart review and patient/caregiver-reported data collection on quality of life[21]. This study examined the period before and after the introduction of rFVIIa in Australia. Following introduction of rFVIIa , researchers found a 92% reduction in the number of re-treatments, 85% reduction in the duration of painful episodes, 84% reduction in the delay to initiation of treatment, and 60–70% reductions in days requiring wheelchairs or crutches, lost caregiver time, and emergency room visits. The Ekert study concluded that the use of rFVIIa was cost-effective (at an incremental cost per QALY of ≈A$51 000), with this cost effectiveness ratio being lower than other well-accepted treatments in Australia, such as dialysis. In the UK, Knight *et al*. conducted a detailed modeling study designed in part to compare a variety of 'on demand' regimens[10]. They found that an rFVIIa-only strategy had a lower average lifetime cost per patient, making it a cost-saving option compared to treatment with APCCs. These results were also consistent with short-term analyses by Odeyemi and Guest evaluating home-based treatment of mild to moderate bleeds in patients with inhibitors from a UK National Health Service (NHS) perspective[22]. In this short-term study, the time to resolve a bleed was faster and the expected NHS cost of managing the bleed was lower with an rFVIIa strategy compared to APCC. Likewise, a recent Turkish economic analysis found lower direct medical costs, higher efficacy, and faster time to bleed resolution with an rFVIIa strategy compared to APCC[23]. Overall, the results of economic analyses in other countries suggest that rFVIIa improves quality of life and is a cost-effective treatment option compared to plasma-derived agents.

Though important to establish cost-effectiveness from a government policy perspective, short-term analyses from a payer perspective are also very relevant for the US in an era of tightened healthcare budgets. Two previous US economic analyses were identified, both adopting a short-term perspective[24,25]. These studies concluded that APCC was less expensive in the initial line of treatment; however, both studies failed to account for treatment failures and re-bleeding and its associated costs in subsequent lines of treatment, thus underestimating the true costs of managing a bleed. In addition, these economic studies conducted limited sensitivity analyses or did not use probabilistic sensitivity analysis over a broad range of variables to generate a reasonable level of certainty with their results. Our model addressed the limitations of these previous analyses through the use of a more appropriate sensitivity analysis and treatment algorithm (which addressed both continued bleeding and re-bleeding over multiple lines of treatment [continued bleeding is a bleed that does not resolve initially (primary failure) and re-bleeding is a bleed that initially resolves but re-bleeding occurs within a set time period]). Unlike previous studies, we used rigorous testing of model robustness using a variety of sensitivity analyses, including PSA. Our model suggests cost offsets are achieved with rFVIIa, leading to an overall lower cost through the entire bleeding episode.

To strengthen our analysis, uncertainty regarding efficacy, re-bleeding, and dosing was tested via probabilistic sensitivity analysis. In this analysis, the model was run 10 000 times using, for each run, a different combination of model parameters selected from their pre-specified distribution. This analysis supported the base-case model findings that the rFVIIa-only strategy would be more likely to demonstrate cost savings than APCC strategies.

The main methodological challenge of this analysis (and of most modeling studies) was the lack of published head-to-head randomized controlled trials

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directly comparing the agents and treatment strategies. Without direct comparative trial data, decision makers are left to make value judgments on products based upon best available information (e.g., separate clinical trials, observational studies, etc.). However, economic modeling provides a way to make systematic comparisons among various products when comparative studies are unavailable and is a method commonly employed in decision-making in other therapeutic areas[26]. Until head-to-head outcomes studies become available, economic modeling (taking into account uncertainty in the assumptions) is one of the best options to compare therapeutic strategies.

Future observational studies should examine treatment strategies through multiple lines of treatment beyond the first 24 h, taking into account key clinical variables such as efficacy, primary failure, re-bleeding, and dosing variability among the agents. Future studies should also examine the time to bleed resolution. Since the labeled dosing for rFVIIa is every 2–3 h and for APCC is 8–12 h, three doses of rFVIIa would resolve a bleed in 6–8 h whereas three doses of APCC would require 36 h to resolve the bleed. A shorter time to bleed resolution may have economic implications in terms of time taken away from school/work or other activities and should ideally be factored into a pharmacoeconomic analysis adopting a societal perspective. Faster resolution of bleeding episodes could also have other important clinical benefits such as fewer doses required for resolution, fewer lines of treatment, and ultimately less joint damage. In addition, future studies should include patient- and caregiver-reported outcomes which would be essential for measuring the entire value of the different treatment strategies available.

Conclusions

The management of minor-to-moderate bleeds in patients with hemophilia and inhibitors is clinically challenging and extends beyond the initial line of treatment. Our model demonstrates that simply focusing on drug cost per dose or per first line of treatment may be short sighted, when in fact the economic effects of treatment failures and re-bleeding and subsequent lines of treatment are important in the overall cost impact.

In conclusion, after accounting for uncertainty in efficacy, re-bleeding, patient weight, and dosing, the rFVIIa-only regimen (compared to APCC strategies) was the most effective and least expensive strategy in the treatment of minor-to-moderate bleeds over multiple lines of treatment in hemophilia patients with inhibitors in the majority of cases.

Acknowledgments

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