

Expert Opinion

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Health economic review of recombinant activated factor VII for treatment of bleeding episodes in hemophilia patients with inhibitors

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Severe hemophilia with inhibitors is a rare disease with substantial clinical, humanistic and economic consequences. This review provides an overview of the role of recombinant activated factor VII (rFVIIa) versus plasma-derived bypassing agents for hemophilia with inhibitors and summarizes the 13 formal economic analyses (6 burden of illness and 7 comparative studies) that have been published in this indication. The findings suggest that the economic impact of rFVIIa has occurred primarily during hospitalization to manage major bleeding episodes and to allow for elective orthopedic surgeries that would not have been attempted prior to rFVIIa. Comparative analyses for on-demand treatment suggest that the total cost of treating a bleeding episode with rFVIIa may be lower than with plasma-based agents due to faster bleeding resolution, higher initial efficacy rates and avoidance of second and third lines of treatment.

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1. Introduction

Hemophilia is a rare, X-linked, recessive, chromosomal disorder that results in excessive bleeding in males. Hemophilia A occurs when there is a decrease in the concentration of clotting factor VIII (FVIII); hemophilia B or Christmas disease occurs when there is a decrease in the concentration of clotting factor IX (FIX). The prevalence of hemophilia A in the US is ~ 20.6 cases per 100,000 males. Hemophilia B is less common, with a prevalence of 5.3 cases per 100,000 males; ~ 44% of patients have severe disease (typically defined as < 1% of normal clotting factor levels) [101]. Typically, patients with hemophilia and inhibitors experience 12 – 15 mild-to-moderate bleeding episodes yearly, and have occasional severe bleeds [1]. Mild-to-moderate bleeding episodes involve the joints, soft tissues and muscles and are commonly treated at home.

As many as 13 to > 30% of patients with hemophilia A will develop inhibitors to FVIII and 2 – 5% of patients with hemophilia B will develop inhibitors to FIX [2,3]. Inhibitors typically develop in patients before they reach 10 years of age. Bleeding does not occur more frequently in patients with inhibitors, but bleeding may be harder to control when it occurs. Inhibitor levels are measured using a Bethesda assay. Approximately 30% of patients who develop inhibitors will have inhibitor levels < 5 Bethesda units (BU) [4]. These patients are classified as having low-responding inhibitors and can typically be treated with increased doses of recombinant FVIII or FIX. In contrast, patients with inhibitor levels of 5 BU or more are classified as having high-responding inhibitors, and cannot be treated with human FVIII or FIX products [4]. Patients with hemophilia A or B and inhibitors compared with patients without inhibitors are more likely to have increased morbidity. In fact, patients with inhibitors (compared with those without) are at an increased risk of having limb- or

life-threatening bleeds, severe arthropathy and physical disability [5].

Although hemophilia is rare, treatment costs are high and patients with hemophilia use a high volume of healthcare resources. Yearly costs for treatment ranges from US\$60,000 – 150,000 without inhibitors [102] to > US\$300,000 with inhibitors [6]. Treatment costs increase exponentially in patients during surgical procedures, major bleeding episodes, occurrence of viral infections such as hepatitis and HIV, or for second-line therapies [7,102].

1.1 Treatment options

In patients with high responding (high titer) inhibitors, several treatment options are available, including immune tolerance induction (ITI) therapy, administration of porcine FVIII (pFVIII) or administration of bypassing agents, such as activated prothrombin complex concentrate (aPCC [FEIBA® VH, Baxter, Deerfield, Illinois, USA]) or recombinant activated factor VII (rFVIIa [NovoSeven®, Novo Nordisk A/S, Denmark]). These bypassing drug therapies are used to bypass the FVIII and FIX role in the coagulation cascade.

During ITI therapy, patients receive frequent doses of FVIII over a prolonged time period in an effort to suppress their inhibitor levels. The length of time required for ITI therapy depends on the protocol used, but can take > 18 months to complete and success rates only range from 43 to 73% [1]. ITI therapy is costly (> US\$1 million for an average 5 year old), but may increase projected life expectancy by almost 5 years and reduce lifetime total costs [8]. Bleeding episodes that occur during ITI therapy need to be treated with an alternative agent, preferably one that does not increase FVIII levels.

Administration of pFVIII is another treatment option for patients with inhibitors, although this is rarely used now, as patients can also develop inhibitors to pFVIII, rendering this therapy ineffective. Thrombocytopenia and allergic reactions can also occur with pFVIII administration [9].

Administration of aPCC is safe and effectively treats ~ 79% of bleeds treated at home and 88% of bleeds in the hospital [1]. All aPCCs contain trace amounts of FVIII and, therefore, can cause an anamnestic response, meaning they can increase FVIII inhibitor levels. In addition, these products are obtained from pooled human plasma and, therefore, have the potential to transmit human viruses such as HIV and hepatitis [9]. In a recent study of 50 patients with a mean age of 35.7 years, a total of 44 patients had concurrent viral infections; hepatitis C was the most common [5].

Administration of rFVIIa is also safe and highly effective, with efficacy rates of > 90% for bleeds treated at home and in the hospital [1]. Unlike aPCCs, human viruses cannot be obtained from rFVIIa. In addition, rFVIIa does not cause an anamnestic response as it does not contain FVIII.

1.2 Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) works by directly activating factor X and thereby eliminating the need for FVIII

and FIX. The exact mechanism by which rFVIIa works is not completely known [10]. However, it is believed that rFVIIa activates factor X by binding to tissue factor; tissue factor is expressed on cells at the injury site. This rFVIIa–tissue factor complex then plays a role in the conversion of factor X to factor Xa. Factor Xa in combination with other factors, enhances thrombin production by converting prothrombin to thrombin, and thus contributing to the formation of a stable fibrin plug or clot [10]. A similar process is also believed to occur on the surface of activated platelets.

Recombinant FVIIa has been used successfully in various clinical situations including the treatment of mild-to-moderate, severe and CNS bleeds [11]. In addition, rFVIIa was used successfully to control bleeding during surgery and also to control bleeding that occurred during ITI therapy [11]. In general, rFVIIa administration was considered to be effective in all of these clinical situations.

In most of the studies evaluating the administration of rFVIIa for mild-to-moderate bleeds, rFVIIa was administered at home. Efficacy rates reported in these studies ranged from 71 to 93% [12-16]. The lowest efficacy rate was reported in a dose ranging study that evaluated 35 and 70 µg/kg rFVIIa doses [13]; both of these doses are less than the currently recommended dose which is 90 µg/kg [17] and existing evidence suggests increased efficacy to 97% with higher bolus doses (> 200 µg/kg) [15]. Home administration of rFVIIa compared with hospital administration allows for earlier treatment of bleeding episodes. Evidence suggests that early, effective treatment not only decreases the amount of drug needed to stop a bleed, but also decreases long-term sequelae, such as synovitis and arthropathy [18]. A decrease in synovitis and arthropathy should ultimately improve quality of life (QoL).

1.3 Rationale and objectives

Regardless of which treatment options are selected for managing bleeds in inhibitor patients, the economic burden is substantial. Drug acquisition costs have become the top cost driver in managing these patients, as treatment protocols have successfully transitioned the management of mild-to-moderate bleeds from the in-patient to the home setting. As a result of substantial drug costs, decision makers have tended to focus on the cost per dose and not examine the full cost per treatment episode, which would ideally consider the efficacy of the agent, the number of doses required, time to bleed resolution and the need for retreatment due to rebleeding or primary failure [19]. Within the past few years, a number of formal economic analyses have emerged that examine the cost of treating bleeding episodes in hemophilia with inhibitors, primarily for rFVIIa versus plasma-derived agents, the two primary treatment options. Thus, the objective of this exercise was to review and summarize these recent health economic analyses of rFVIIa and plasma-derived agents in the management of patients with hemophilia and inhibitors.

1.4 Study selection and data extraction

The authors conducted a systematic literature review of the health economics of using rFVIIa and aPCCs to manage the frequent bleeding episodes that occur in patients with hemophilia and inhibitors. This review focuses on the past 10 years (1996 – 2006, with searches updated in 2007 just prior to publication) in order to identify the most recent economic analyses and trends for the current standards of care. The articles were selected for inclusion in this review because they were formal economic analyses or specifically reported costs or resource utilization trends in a cohort of patients. These key papers were predominantly economic models and/or burden-of-illness studies using retrospective or prospective data collected from hemophilia centers.

The core search terms in MEDLINE/EMBASE were 'hemophilia AND inhibitors' with the following terms added for specificity: 'economics', 'costs', 'cost-effectiveness', 'economic model', 'rFVIIa', 'Novoseven', 'aPCC', 'activated prothrombin-complex concentrate' and 'FEIBA'. In addition, a series of attempts was made to ensure that all potentially relevant information was identified using the MEDLINE 'related articles/links' feature and manual reviews of the bibliographies of relevant, retrieved references.

The combined search strategies resulted in > 70 abstracts 'hits' that were imported into a reference manager database and screened by 2 authors independently to assess relevance. An abstract was deemed relevant and the article retrieved in full text if it had information that addressed formal economic analysis of drug treatment strategies, cost of treatment or illness for patients with inhibitors, healthcare resource utilization patterns or overall cost of treatment for various medication strategies. Abstracts were excluded if the paper was a case report, letter, general review, focused on non-inhibitor patients, or focused on ITI therapy.

After detailed abstract review, ~ 30 articles were selected and retrieved in full text. Once retrieved, many of these articles mentioned economics in the abstract, but did not provide further information beyond simply reporting drug acquisition costs or discussed ITI or non-inhibitor patients. Because the focus of the search was on formal economic analysis of drug treatments, the authors excluded 17 papers that were not formal economic analyses or did not specifically report overall cost of treatment or resource utilization trends for rFVIIa in a cohort of patients.

2. Pharmacoeconomics

A total of 13 studies met inclusion criteria, including 6 cost impact/general burden studies for rFVIIa (3 prospective, 3 retrospective) and 7 comparative economic analyses of rFVIIa versus plasma-derived agents. Of the comparative analyses, one was a combined prospective/retrospective economic and QoL study and six were economic models using various combinations of literature, expert opinion and medical chart data (see Table 1). No articles were identified on the general

burden of plasma-derived agents other than the six burden studies that addressed the more recent impact of rFVIIa in the treatment armamentarium. The seven comparative studies addressed the economics of rFVIIa versus plasma-derived agents, and no additional non-comparative formal economic analyses were identified for plasma-derived agents.

2.1 General burden and cost impact

Six studies were identified that specifically addressed the changing practice patterns, general cost impact or burden related to rFVIIa on hospitals, payers or hemophilia centers treating inhibitor patients [6,15,20-23]. Most of these studies addressed the hospital or payer perspective and had small samples, although they typically included the entire inhibitor population available at a given center.

Galanaud *et al.* conducted a prospective study in a French public hospital to examine cost drivers for 96 patients with hemophilia who were hospitalized (154 hospital stays) in 1999 [20]. The presence of circulating inhibitors was the main independent predictor of high drug costs for hemophilia. The adjusted odds ratio that the drug cost for inhibitor patients was in the highest quartile of expenditures (drug cost > €445/kg/hospital stay) was 16.9 (95% CI = 4.3 – 66) [20]. rFVIIa was used in 20% of hospital stays, but represented > 50% of total annual expenditures. This was useful in that it was one of the first studies that showed that the presence of inhibitors affects high hemophilic drug costs in the in-patient-setting. However, additional descriptive detail about the patients with inhibitor or in the highest quartile was not provided. With the prospective, observational nature of the study, the authors would probably have had information about the specific uses for rFVIIa; however, they did not comment on the type of patient or admission characterized by rFVIIa used.

Goudemand *et al.* retrospectively compared treatment patterns and costs of 144 patients at a French hemophilia center before and after the introduction of rFVIIa [23]. For patients with inhibitors, expenditures increased > 300% after introduction of rFVIIa (mean cost of €186,482 per year per patient) with 52% of those costs associated with hospital treatment. Regarding hospital treatment, the authors noted that rFVIIa allowed surgical procedures to be performed (including elective joint replacements) that would not have been considered prior to the availability of rFVIIa. Limitations of this retrospective cost study include lack of measurement of associated clinical or QoL benefits of rFVIIa, particularly because the authors noted that its use was related to surgical procedures that would probably improve QoL. Although many new therapies increase costs, their clinical and QoL value may indicate that there is good cost-effectiveness.

A prospective, longitudinal study examined the humanistic and economic burden of Italian hemophilia patients with inhibitors over an 18-month time frame [21]. The average monthly cost to Italy's National Health Service was €18,000 per patient per month, primarily for drug products. However, due to the rarity of the disease, the National Health Service

Table 1. Comparative economic analyses of on-demand treatment of mild-to-moderate bleeds in inhibitor patients.

Ref.	Comparisons	Methods	Data source	Key findings
Joshi, 2006 [28]	3 OD strategies for home treatment: i) aPCC/aPCC/rFVIIa ii) aPCC/rFVIIa/rFVIIa iii) rFVIIa/rFVIIa/rFVIIa	Decision model, cost of bleed episode, direct medical costs Adapted Knight 2003 to US payer perspective	Literature	Average cost per resolved bleed was lowest using a rFVIIa-only strategy at US\$28,076 when following patients over three lines of treatment for entire bleed episode. Using aPCC as a first-line strategy was more expensive by ~ US\$2800 – 4000 per bleed. Cost-offsets for rFVIIa-only strategy were seen with reduced need for second and third lines of treatment.
Dundar, 2005 [26]	Initial bleeding treatment: - HD-FVIII/X - PCCs - aPCCs - rFVIIa	Decision model, cost of bleed episode, direct medical costs, Turkish government perspective	Chart review Literature Expert opinion	Total overall costs were lower for rFVIIa and PCC compared with aPCC or HD-FVIII (see Figure 1). More than 97% of total costs were attributable to the drug. Other sensitive variables were dose used and first-line effectiveness.
Putnam, 2005 [27]	aPCC versus rFVIIa for first-line treatment	Decision model, drug cost minimization at 24 h, US drug cost perspective	Expert panel of 11 US experts	aPCC treatment strategy (US\$21,000) cost less than a rFVIIa strategy (US\$33,400). Costs driven by dosing assumptions in first 8 – 12 h (model assumed one dose of aPCC and three doses of rFVIIa). Expert opinion on total average dose for the entire bleeding episode did not match the best-case model assumption. Experts reported that total aPCC dose expected over episode was 300 IU/kg and for rFVIIa was 360 µg/kg.
Knight, 2003 [1]	OD protocols: i) aPCC/aPCC/rFVIIa ii) aPCC/rFVIIa/rFVIIa iii) rFVIIa only	Decision model, CUA, lifetime costs, direct medical costs, UK NHS perspective	Literature	Lifetime costs of treating bleeding episodes were lowest with a rFVIIa-only protocol (£2,047,344) versus aPCC primary strategies (£2,225,755 – 2,255,483). No differences in QALYs were assumed for treating minor bleeds. Study also modeled CE of ITI protocols versus OD treatment.
Odeyemi, 2002 [25]	rFVIIa versus aPCC to manage mild-to-moderate bleeds at a hemophilia treatment center	Decision model, UK NHS perspective, cost of bleed episode, time to bleed resolution	Literature, expert panel of 22 hematologists	Expected cost of managing a minor bleed was 45% lower with rFVIIa (£11,794) versus aPCC (£20,467). Time to bleed resolution was 30 h for rFVIIa and 58 h for aPCC. Patients failing first-line aPCC in a treatment center were more likely to be hospitalized.
Odeyemi, 2002 [17]	rFVIIa versus aPCC to manage mild-to-moderate bleeds at a home	Decision model, UK NHS perspective, cost of bleed episode, time to bleed resolution, 1999/2000 prices	Literature, expert panel of 22 hematologists	Cost of home treatment of minor-to-moderate bleeding was lower with rFVIIa (£12,944) versus aPCC (£14,645). Time to bleed resolution was 32 h for rFVIIa and 60 h for aPCC. Results were most sensitive to dose/dosage and efficacy rates.
Ekert, 2001 [24]	rFVIIa versus usual care with plasma-derived agents: - 6 months before rFVIIa - 12 months after rFVIIa	Longitudinal study before and after introduction of rFVIIa in three 6-month phases, CUA from Australian government perspective	Prospective study, medical charts, patient/family interviews, patient diary perspective	After rFVIIa, utility improvement was +0.58, retreatments were reduced by 92%, duration of painful episodes reduced by 85%, and 60 – 70% reduction in days with mobility accessories, lost caregiver time, and ER visits. The average 6-month cost of treatment per patient was AUS\$94,657 for usual care versus AUS\$109,607 for rFVIIa. The incremental cost per QALY for rFVIIa was AUS\$51,533.

aPCC: Activated prothrombin complex concentrate; CE: Cost-effectiveness; CUA: Cost-utility analysis; ER: Emergency room; FIX: Factor IX; HD-FVIII: High-dose factor VIII; ITI: Immune tolerance induction; NHS: National Health Service; OD: On demand; QALY: Quality-adjusted life year; rFVIIa: Activated recombinant factor VII.

budget impact was < €1 per Italian citizen per year. They found that 50% of drug costs were for rFVIIa, although most of this was related to 19% of patients who underwent surgery (typically joint replacement). Variables noted to adversely affect QoL in inhibitor patients included age and orthopedic joint status (OJS). As OJS increased, representing worsening orthopedic status, patients reported more problems with all domains of the EQ-5D and the Short Form-36 (SF-36) physical functioning domain and physical component score. Health-related QoL for patients with inhibitors was similar to patients with diabetes and dialysis as measured by the SF-36. Patients with hemophilia and inhibitors frequently reported at least some or moderate problems on the EQ-5D with pain/discomfort (71%), usual activities (53%) and mobility (67%) [21].

Hemophilia centers have reported a shift towards increasing recombinant product use, and expect to see continued growth in the cost of replacement products [6,22] particularly as new children developing inhibitors would receive only a recombinant replacement product. A retrospective case-controlled study conducted over 3.5 years in 9 inhibitor patients at the largest hemophilia treatment center in Canada found that aPCC use decreased sharply corresponding to an increase in rFVIIa [6]. A similar retrospective audit was conducted at an Auckland hemophilia treatment center where costs of replacement products were expected to grow by 5% per year related to children with severe hemophilia predominantly being treated with recombinant product [22]. Both of these reports were descriptive in nature, but did specifically address the trends in rFVIIa use after it became available and what the probable future impacts might be.

Finally, a cost per bleeding episode was reported based on prospective registry data for patients in the Hemophilia and Thrombosis Research Society Registry receiving rFVIIa for acute bleeds (most of whom were treated at home) [15]. A total of 555 bleeding episodes treated with rFVIIa were evaluated by dose. Average cost per bleed in children ranged from US\$10,800 to 22,000 (low to highest dose). Average cost per bleed in adults ranged from US\$25,000 to 51,000 (lowest to highest dose). This study is from one of the few published registries on experience with rFVIIa in patients with inhibitors. It provides substantial value in understanding the impact of dosing on efficacy in real-world settings. The limitations of the study included the lack of any comparative data for patients managed with other products and the use of a 72-h time point for 'efficacy' assessment. Thus, the data may not be relevant for incorporation into further economic analyses where shorter timepoints (e.g., 24 h) are often used for assessment of efficacy.

2.2 Comparative economic analyses

2.2.1 Cost utility

An Australian cost-utility analysis assessed the QoL and incremental costs associated with converting patients from plasma-derived agents to rFVIIa [24]. Ekert *et al.* systematically assessed retrospective and prospective data from 6 patients

with inhibitors and numerous bleeding episodes over the course of 18 months. This study consisted of 3 phases. The first phase was a retrospective evaluation of data obtained during the 6 months prior to switching to rFVIIa on-demand therapy. The second phase was a retrospective evaluation of medical chart data obtained during the first 6 months of rFVIIa on-demand therapy. The third phase was a prospective evaluation of clinical outcomes, QoL and resource utilization during the second 6 months of rFVIIa on-demand therapy. In most instances, the patients received rFVIIa therapy at home. Only bleeding in joints, muscle groups, psoas muscle, mucosal bleeding and head injuries were treated using a dose of rFVIIa of 90 µg/kg repeated in 2 h. QoL was assessed using the Australian Authorized Adaptation of the Child Health Questionnaire-Child Form (CHQ-CF80), the CHQ-Parent Form (CHQ-PF50), self-reporting diaries, interrogation of hospital records and the EQ-5D questionnaire. At study endpoint, patients were given three clinical scenarios constructed from information obtained both from the patients' diaries and from questionnaires. For each scenario, patients completed the EQ-5D.

Patients reported an improvement in all components of the CHQ-CF80, with the exception of overall behavior while receiving rFVIIa therapy. Similarly, parents reported an improvement in all components of the CHQ-PF50 with rFVIIa therapy. A utility value of -0.11 was obtained for the scenario representing phase 1 (usual care) of this study. During this phase, there was a 37 h delay to treatment, 131 h of pain per bleed, 28 bleeds, 6 retreatments in initial 24 h, and 96 days when crutches or a wheelchair were required. A mean utility value of 0.47 was obtained for the scenarios representing phases 2 and 3 (rFVIIa treatment) of this study. During these 2 phases (average of the 2 rFVIIa phases), there was only a 5 – 7 h delay to treatment, 12 – 26 h of pain per bleed, 18 bleeds, < 1 rebleed, and between 34 and 36 days when crutches or a wheelchair were needed. The overall incremental utility improvement with rFVIIa was 0.58.

All direct healthcare costs incurred by each patient during all 3 phases of the study were determined and an incremental cost per QALY ratio determined. Not surprisingly, costs during phases 2 and 3 were higher (AUS\$109,607) than during phase 1 (AUS\$94,657). The majority of this difference could be attributed to the cost of rFVIIa. The incremental cost per QALY ratio calculated was AUS\$51,533 which is less than the incremental cost per QALY ratio calculated for hospital dialysis (AUS\$57,053) in Australia. This study was probably the most comprehensive combining retrospective and prospective data collection. However, the key limitation was its small sample size; although this was difficult to avoid with an extremely rare disease in a relatively small country, thus making generalizability difficult.

2.2.2 Cost effectiveness

Knight *et al.* conducted a systematic review of the cost-effectiveness of various strategies used to treat patients with

hemophilia and inhibitors from the perspective of the NHS in the UK [1]. They compared the cost-effectiveness of three ITI and three on-demand strategies using a Markov decision model. This modeling study incorporated outcome, cost and life expectancy information for each of the therapies evaluated. Overall, treatment with any of the ITI strategies was more cost effective than any of the on-demand strategies. However, of the on-demand therapies, rFVIIa had a lower average lifetime cost per patient (~ £200,000 less) than the other on-demand therapy regimens using aPCC. This study was a very comprehensive modeling effort that addressed the lifetime impact of rFVIIa versus other treatments. The main limitation for this study was the lack of head-to-head comparative data.

2.2.3 Cost of bleeding episodes

Odeyemi and Guest performed 2 modeling studies to determine the economic impact of rFVIIa compared with aPCC administration in adult patients with mild-to-moderate bleeds treated either at home [17] or at a comprehensive care center [25]. To construct their model, Odeyemi and Guest obtained clinical outcome and resource utilization data from published literature and supplemented it with information obtained from hemophilia experts. A decision tree modeling the management of a minor bleed treated either at home or at a comprehensive care center was constructed using UK 1999/2000 cost data. Costs included in this analysis included not only drug costs, but also costs for additional therapies, transportation and hospitalization. Using this model, not only was the time to bleeding resolution shorter with rFVIIa compared with aPCC administration, but also costs were less. Patients treated at home with rFVIIa had an estimated bleeding time of 32 h compared with 60 h for patients treated with an aPCC. Likewise, patients treated at a comprehensive care center with rFVIIa had an estimated bleeding time of 30 h compared with 58 h for patients treated with an aPCC. The cost of rFVIIa treatment at home was estimated to be £12,944 and with aPCC £14,645; the cost of treatment at a comprehensive care center with rFVIIa was estimated to be £11,794 and with aPCC £20,467. These studies were unique in that they addressed bleeding time resolution as part of the economic impact. Again, limitations included the available data sources and lack of comparative studies.

Dundar *et al.* constructed a decision-analysis model to determine the economic impact of four different treatment regimens (high-dose factor VIII or IX, prothrombin complex concentrate, aPCC, rFVIIa) for mild-to-moderate bleeds in patients with hemophilia and inhibitors [26]. This model was constructed using data from the literature and from a retrospective medical chart review of 105 bleeding episodes that occurred in 24 patients over a 6-year period at 3 comprehensive care centers in Turkey. The medical chart data showed that fewer doses were required (3.6 versus 4.8), bleeding resolution time was shorter (17 versus 44 h), and efficacy higher (89% rFVIIa versus 67% aPCC) with rFVIIa versus aPCC. Mean treatment dose per bleeding episode was 204 µg/kg for

rFVIIa and 167 IU/kg for aPCC. This medical chart data on outcomes was used as inputs for an economic model, with validation by a panel of hemophilia experts. Because the efficacy results for an aPCC in the retrospective chart review were low (67%) compared with efficacy results reported in the literature (79%), the model assumed the higher literature rates for efficacy in the base case analysis with aPCC, and used the medical chart efficacy rate for rFVIIa (89%), which was generally consistent with literature rates. Total costs were ~ US\$3000 lower per bleeding episode with rFVIIa administration compared with aPCC therapy (Figure 1). This was probably one of the most complete and transparent economic analyses, given the large sample size, variety of data sources (patient chart review, literature, experts) and assumptions that were outlined and tested. This is the only economic analysis that incorporates 'comparative' data collected as part of the sample for the various agents.

Another economic analysis compared rFVIIa and aPCC therapies based on treatment patterns reported by an expert panel of 11 hematologists [27]. Putnam *et al.* constructed a cost minimization model to compare the drug costs of the initial 24 h of treatment with aPCC versus rFVIIa in the home treatment of minor bleeds [27]. Assumptions and base case values utilized in this model were determined using an expert consensus process and not published literature. In this study, treatment costs for a bleeding episode with aPCC were US\$21,000 compared with US\$33,400 for rFVIIa. The analysis results appeared to be driven by the base case dosing assumptions for rFVIIa that were much higher than reported by the primary data source for the analysis or literature. The discrepancies in this study between dosing assumptions as mentioned above, and the sources of drug pricing data (average wholesale price used for rFVIIa versus discount price for aPCC), raises questions about the quality of the methodology.

Finally, Joshi *et al.* compared the cost-effectiveness of three different treatment regimens, consisting of first-, second- and third-line therapies used in the treatment of mild-to-moderate bleeds in patients with hemophilia and inhibitors [28]. In this study, the model proposed by Knight *et al.* [1] was adapted to the US based on data from the published literature and expert opinion. Drug costs utilized were the 2005 average wholesale price for each agent. Although initial treatment costs were higher with rFVIIa therapy, overall treatment costs were lower (Figure 2). The total cost of therapy for an rFVIIa-only strategy was estimated to be US\$28,076 compared with US\$30,883 – 32,150 for aPCC-based strategies. The decrease in cost seen with rFVIIa therapy occurred because additional lines of therapy were often not needed. Probabilistic sensitivity analyses (second-order Monte Carlo simulation) were and evaluated the effects of changing the efficacy rate, re-bleeding rate, patient weight and drug doses needed to determine the robustness of this model. Results from the probability sensitivity analyses using 10,000 Monte Carlo simulations documented that a rFVIIa-only regimen was less expensive than

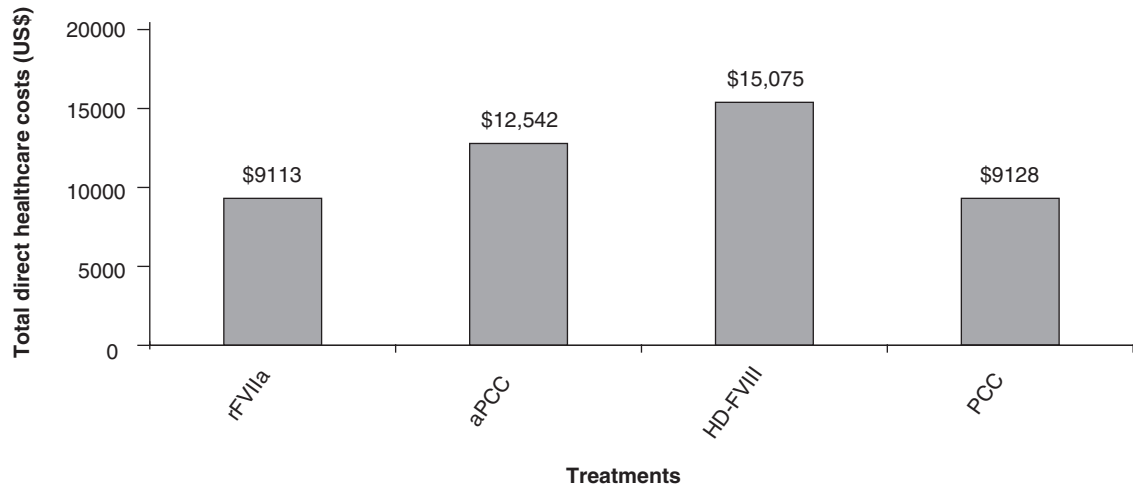


Figure 1. Comparison of total direct healthcare costs (US\$) for four treatments used in patients with hemophilia and inhibitors.

Data from [26]. Costs modeled based on resource utilization data collected directly from patient medical charts.

aPCC: Activated prothrombin-complex concentrate; HD-FVIII: High-dose factor VIII; PCC: Prothrombin-complex concentrate; rFVIIa: Activated recombinant factor VII.

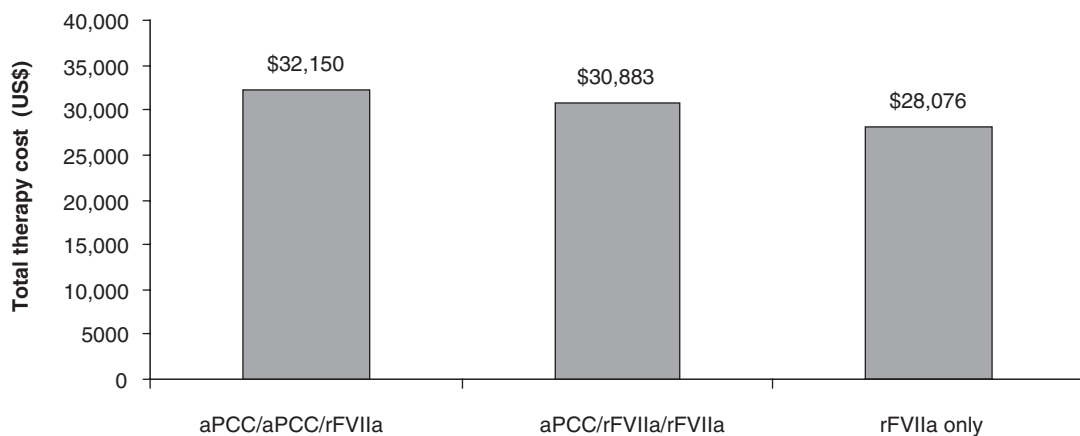


Figure 2. Costs of three different 'on-demand' strategies through three lines of treatment for mild-to-moderate bleeding episodes.

Adapted from [28].

aPCC: Activated prothrombin-complex concentrate; rFVIIa: Activated recombinant factor VII.

aPCC-based strategies in 68% of the simulations. Although the study was comprehensive in assessing total treatment costs, key limitations with this study (similar to other comparative modeling studies) include reliance on literature-based estimates for model assumptions and the lack of published head-to-head trials, thus only indirect comparisons can be made. Ideally, this model should be validated using prospective clinical trial data.

3. Conclusions

Patients with hemophilia and inhibitors are a challenge to treat, requiring high costs over their lifetimes for effective management. The drug acquisition costs of various treatment options must be considered in the context of

patient QoL and management of the entire bleeding episode. Well-designed studies are needed to compare recombinant and plasma-based agents for the treatment of hemophilia patients with inhibitors. In the meantime, decision-makers are left to determine which therapies are most cost-effective based on the best information available. In conclusion, the results of data currently available from a variety of countries suggest that on-demand first-line treatment with rFVIIa may be a less expensive and/or cost-effective option compared with plasma-derived agents.

4. Expert opinion

The use of rFVIIa for an on-demand bleeding episode in hemophilia with inhibitors is either cost saving or

cost-effective compared with plasma-derived agents. This review presents a growing body of global literature suggesting that rFVIIa was a cost-effective treatment for patients with hemophilia and inhibitors compared to plasma-derived agents in almost all analyses [1,17,25,26,28]. Results from the Putnam *et al.* economic analysis showing much higher costs with rFVIIa should be interpreted cautiously [27]. Limitations of this particular study were addressed in a letter to the editor outlining several issues with the analysis including: failure to include costs from treatment failures and rebleeds, dosing assumptions for the agents were not consistent with the study's own expert panel, and drug price sources were not consistent between the comparators (the higher average wholesale price was used for rFVIIa, whereas a discounted price was used for aPCC) [29].

The costs and cost-effectiveness of rFVIIa versus aPCCs is controversial and primarily dependent on dosing requirements to control a bleed. The total dose used to manage a bleeding episode may have profound effects on the overall cost of treatment [30]. Results from the economic analyses presented here are primarily driven by dosing assumptions for the agents. As widely discussed in the hemophilia literature, response to various agents and dosing requirements to control bleeding tend to be different for each patient, and a few outliers may completely drive the cost of care at a particular center [31,32]. Thus, at the patient level, a practitioner is tailoring the patient's on-demand home treatment based on prior success with various therapies. As hemophilia with inhibitors is rare, an individual clinician may only manage one or two patients at a time. The problem of small sample size with this rare disease population is unavoidable (even with multi-center trials), though these patients may have up to 20 bleeds per year and few are lost to follow up as patients usually stay with a hematologist/hemophilia center because of the frequent need for care. Thus, using economic models to understand the larger impact across a health system or country might be helpful in understanding the broader cost-effectiveness issues associated with selection of a preferred drug treatment strategy. Economic analyses from government perspectives conducted to date suggest that rFVIIa is cost-effective despite potentially higher doses (and higher drug costs depending on number of doses required for a particular patient) than older plasma-derived agents [1,17,24-26].

Larger bolus doses of rFVIIa may actually be more cost-effective than smaller, repeated doses due to greater efficacy and faster resolution of bleeding. The most common dose of rFVIIa is generally 90 µg/kg; however, the effective dose of rFVIIa may vary between patients. As mentioned earlier, efficacy rates appear to increase with increasing doses [15,33]. To test this hypothesis, Kenet and coworkers evaluated the efficacy and safety of a single 300 µg/kg rFVIIa bolus dose in the treatment of 114 bleeds. A total of 95 bleeds responded to single-dose therapy; 14 bleeds required a second dose. Patients reported

faster pain relief and shorter treatment durations with bolus therapy [33]. Although more rFVIIa was administered with bolus therapy, patients preferred the convenience of this therapy approach (though report was only in three patients). In addition, results from a recently published retrospective review of data contained in the Hemophilia and Thrombosis Research Society registry database found bleeding cessation rates to be higher with rFVIIa doses > 200 µg/kg compared with < 200 µg/kg [15]. Bleeding cessation occurred in ~ 84% of cases when rFVIIa doses < 200 µg/kg were administered compared with 97% of cases when rFVIIa doses > 200 µg/kg were administered. Most recently, Kavakli *et al.* (2006) reported similar efficacy and patient preference for 270 µg/kg bolus versus 90 µg/kg × 3 regimens in a randomized, double-blind, cross-over trial of 24 patients [34].

In-patient costs associated with rFVIIa in inhibitor patients are related to orthopedic surgery for joint replacement and other surgeries that would not have been attempted prior to the introduction of rFVIIa. In the hospital setting, cost burden associated with rFVIIa for hemophilia with inhibitors was typically ~ 50% of total drug treatment costs. The added cost of rFVIIa on healthcare budgets should be balanced with the value of a life-changing surgery that will improve patient physical function and functional status. The faster time to bleeding resolution for rFVIIa versus plasma-derived agents has resulted in changing practice patterns in multiple countries where rFVIIa is frequently used to manage bleeding for inhibitor patients during hospitalizations for surgeries and major bleeding episodes [35].

As implied in the previous paragraph, the relative value of a newer and recombinant product such as rFVIIa must also be considered in the context of its potential humanistic impact. Now that hemophilia mortality has been reduced, a key goal of treatment is to improve functional status and QoL. To date, very few studies into inhibitors have evaluated how various hemophilia treatments affect QoL and longer-term outcomes, such as joint function, as discussed in the review [21]. Retrospective studies in non-inhibitor patients have found QoL to be negatively influenced by the severity of hemophilia, the frequency of bleeding episodes, and the presence of orthopedic problems or viral infections [5]. In addition, the patient's therapeutic treatment plan, whether it is on-demand or prophylactic, also influences their QoL [5].

Additional studies are needed to determine the impact of different treatments on the QoL of hemophilia patients with inhibitors. The present evidence suggests that orthopedic problems negatively affect the QoL of hemophilia patients with inhibitors. Long-term prophylaxis with aPCC in seven patients did not prevent progression of existing joint disease [36], and additional studies of whether aPCC or rFVIIa prevent arthropathy from developing in the first place, are needed. In another small study, treatment with rFVIIa has been shown to decrease the delay to initiation of treatment by 84%, the duration of pain by 85%, the number of retreatments by 92%

and the number of days required for crutches or a wheelchair by 60 – 70% [24]. However, additional larger studies are needed to determine if these improvements translate to a decrease in orthopedic problems and a reduced need for orthopedic surgery later in life.

In summary, the future direction of outcomes assessment for hemophilia with inhibitors will probably focus on bleeding time comparisons among available treatments and how recurrent joint bleeds affect long-term joint status, QoL and cost-effectiveness. Products such as rFVIIa may provide long-term cost-effectiveness through reductions in bleeding time and superior joint function.

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