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ORIGINAL ARTICLE *Inhibitors*

Cost and effectiveness of treatments for mild-to-moderate bleeding episodes in haemophilia patients with inhibitors in Korea

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Summary. First-line treatment for mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors in Korea is currently activated prothrombin complex concentrate (aPCC) with recombinant activated factor VII (rFVIIa) as second-line therapy or as a last resort. The aim of this study was to estimate the cost and effectiveness of aPCC vs. rFVIIa for treating mild-to-moderate bleeds in inhibitor patients from the Korean reimbursement authorities' perspective. Clinical outcomes and resource utilization data (number of doses, average dose, number of outpatient visits, inpatient stays, ambulance transport and concomitant medications) were collected from an observational study involving four Korean paediatric haemophilia centres. Cost-effectiveness was modelled using a decision analysis approach and sensitivity analyses undertaken. rFVIIa was a more effective haemostatic therapy (87.1% efficacy in bleed resolution) than aPCC (64.0%). rFVIIa effected more rapid haemostasis, resolving bleeding in a mean of 6.6 h vs. 25.2 h for aPCC. Fewer rFVIIa doses were required per bleed vs. aPCC (means 1.7 and 2.3). Mean total direct medical costs from bleed initiation to cessation were estimated at Korean Won (KRW)12 460 thousand (US$12 311) for rFVIIa given as first-line therapy and KRW18 304 thousand (US$18 085) for aPCC given as first-line therapy. Sensitivity analyses confirmed the cost-effectiveness of rFVIIa vs. aPCC given as first-line therapy. In Korea, use of rFVIIa as first-line therapy for treatment of mild-to-moderate bleeding episodes in inhibitor patients is both clinically effective and cost-effective compared with initial aPCC treatment. rFVIIa should be considered as the first-line treatment for mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors in Korea.

Keywords: activated prothrombin complex concentrate, bleeds, cost, inhibitor patients, Korea, recombinant activated factor VII

Introduction

Haemophilia is a rare, inherited blood disorder characterized by impaired clotting for which there is currently no cure. It is a life-long condition which affects females as carriers and males who inherit the condition [1–3]. Haemophilia A is owing to the lack of clotting factor, factor VIII (FVIII), and haemophilia B is due to a lack of factor IX (FIX). To avoid excessive internal and external bleeding, patients require life-long treatment involving clotting factor replacement therapy [4–6]. Development of neutralizing antibodies to factor replacement therapy is a serious complication for haemophilia patients [7]. Patients with high-titre inhibitors to coagulation factors, FVIII and FIX, can develop serious bleeding complications, which do not respond to standard factor replacement therapy. This compromises the ability to effectively manage haemorrhage, resulting in a greater rate of disability, risks of complications and higher economic consequences [8–10]. The reasons why some people develop inhibitors and others do not remain unclear, although a number of risk factors have been identified for haemophilia A, including severity of disease, age, genetics and exposure to FVIII replacement therapy. For patients

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with haemophilia B, a number of factors are associated with an increased risk for developing inhibitors, such as auto-immune disease, malignancy and exposure to a number of therapeutic drugs [2,11–14].

Patients with inhibitors must be treated for their bleeding episodes with the so-called bypassing agents, such as recombinant FVIIa (rFVIIa) (active ingredient – eptacog alpha [activated]) and activated prothrombin complex concentrates (aPCC; active ingredient – aPCC) [15–17]. These agents effectively bypass the coagulation pathway that normally utilizes FVIII by supplying activated or partially activated forms of factor VII (FVII) and/or factor X [18,19].

The clinical effectiveness of rFVIIa for control of bleeding episodes has been demonstrated in the medical literature on treatment of patients with haemophilia and inhibitors [20–24].

A number of health-economic studies and models have looked at the cost-effectiveness of treatment options for patients with haemophilia with inhibitors and suggest that rFVIIa offers a cost-effective option compared with aPCC [10,17,25–28]. Recombinant FVIIa has been available to clinicians since 1996 and has an excellent safety record after almost three-quarters-of-a-million doses have been administered [16]. Use of rFVIIa compared with usual therapy is clearly associated with improvements on a number of outcomes, including speed of bleed resolution, duration of pain and quality of life (QoL), and the extra costs of rFVIIa can be justified by benefits achieved in terms of quality-adjusted life years gained (QALY) [26]. Indeed, in a recent cost-effectiveness model comparing rFVIIa, aPCC and FEIBA VH in a mild-to-moderate inhibitor patient population, it was shown that in the majority of the cases, using rFVIIa as a first-line therapy was a less expensive treatment option than using other bypassing agents as first-line therapies [17].

South Korea has a well-defined haemophilia population and programme for care of haemophilia patients [29–31]. Despite implementing the separation of responsibility for prescribing and dispensing medication, including imported pharmaceuticals in the national reimbursement list, and developing a faster drug approval process, there remain financial issues within the healthcare and insurance system affecting therapeutic choice. In Korea, the first-line treatment (the first treatment provided after diagnosis) for mild-to-moderate bleeding episodes in patients with inhibitors is currently aPCC, with rFVIIa used as a second-line therapy or as a last resort. It is estimated that there are around 1423 patients with haemophilia A and 301 with haemophilia B in Korea at present; 54% of whom are aged less than 25 years [32]. Of this total haemophilia population, approximately 10–15% might be expected to develop inhibitors at some time. This paper describes the results of an observational study of Korean clinical practice in the management of haemophilia patients with inhibitors, and cost-effectiveness modelling of those data to determine and evaluate the comparative direct costs of rFVIIa compared with aPCC as an initial therapy for mild-to-moderate bleeding episodes.

Methods

The objective of the study was to estimate the costs of treating patients with haemophilia and inhibitors with rFVIIa compared with aPCC (for mild-to-moderate bleeding), to manage a bleeding episode in adults and children with high-titre, high-responding inhibitors from the perspective of the Korean National Health Service. Thus, the analysis was limited to a comparison of the direct medical costs of the management of mild-to-moderate bleeding episodes and excluded the costs attributable to patients and their families, indirect costs and difficult-to-quantify intangible costs such as those related to changes in QoL.

A cost-effectiveness model based on previously published methods [27] using a decision analysis approach (see Fig. 1) was constructed to assess total direct costs, including cost of treatment failures and re-bleeds from initiation to cessation of a bleed using either aPCC or rFVIIa as a first-line treatment for bleeding in haemophilia with inhibitors. DATA™ 3.5 (TreeAge Software, Williamstown, MA, USA) was used to develop the model. It was assumed that all bleeds would eventually stop regardless of last-line therapy and thus the model was one of cost minimization.

The basic model structure is a decision tree which was used to simulate the management of mild-to-moderate bleeding episodes occurring in patients with haemophilia and inhibitors in Korea. The model comprised: an initial treatment for a bleed, further treatments for a bleed, the probability of switching from one treatment to another, duration of each treatment, effectiveness of each treatment, probability of a re-bleed, and the treatment of a re-bleed. Where possible, the probabilities used in the model were derived from the empirical data. An expert panel consisting of four Korean haematology specialists (Drs You, Lee, Park, and Yoo from the centres involved in the study) was created to fulfil the

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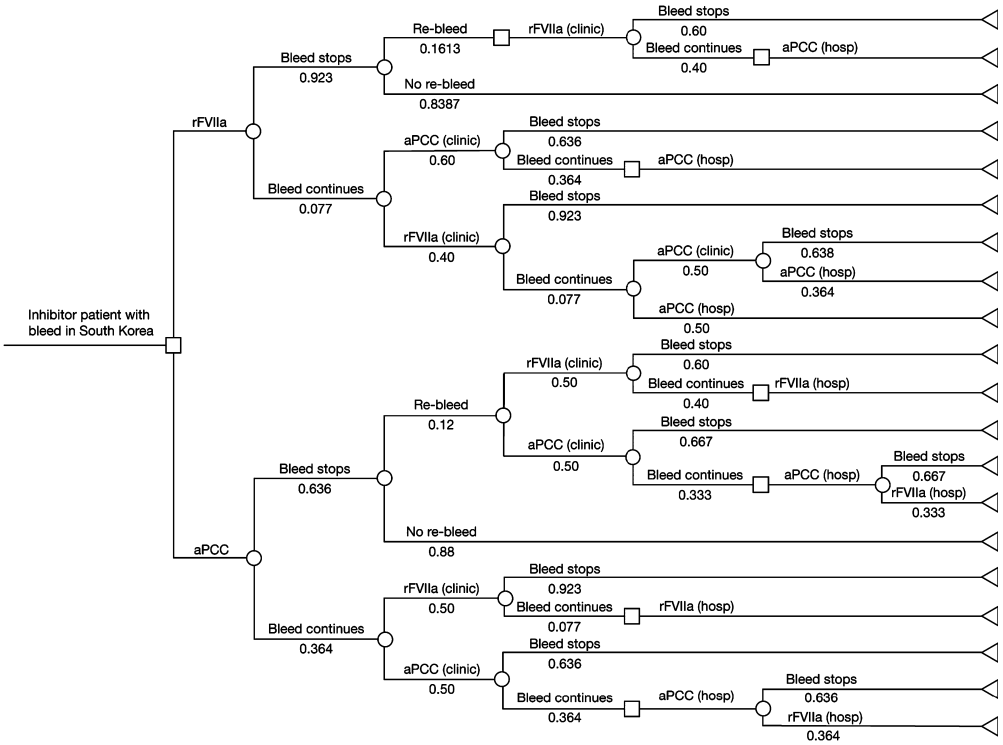

Fig. 1. Decision model structure.

following tasks: (i) comment on and validate the structure of the decision model to best reflect Korean clinical practice; (ii) reach consensus about each case inclusion; and (iii) analyse the study results.

Owing to the current treatment guidelines in place, clinical outcomes and resource utilization data for the model were obtained both retrospectively (aPCC) and prospectively (rFVIIa) from an observational study of Korean clinical practice, as described next.

Unit costs were collected from the local Ministry of Health and Welfare sources, valued at 2005 values. These unit costs are described in Table 1. The expert panel of Korean haematologists provided information for use in the model on re-bleed rates and probabilities of patients switching treatments.

Observational study of Korean clinical practice

Clinical outcome and resource data were obtained from an observational study involving four centres: the Korea Hemophilia Foundation, Seoul; Department of Pediatrics, Inje University College of Medicine, Busan; Department of Pediatrics, University of Ulsan College of Medicine, Ulsan, and the Department of Pediatrics, University of Eulji College of Medicine, Daejeon.

Table 1. Unit costs and associated sources.

Cost item	Unit cost (KRW)	Source
rFVIIa (cost per μg)	1376	MOHW health insurance drug list
aPCC (cost per IU)	1420	MOHW health insurance drug list
Concomitant medication	579 (one vial of tranexamic acid, 500 mg)	MOHW health insurance drug list
One day in treatment centre	14 700	MOHW health insurance drug list

MOHW, Ministry of Health and Welfare; rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate; KRW, Korean Won.

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The data were collected by physicians from patient records and were validated by the consensus of the expert panel of Korean haematologists.

Only mild-to-moderate bleeds, i.e. ecchymosis, epistaxis, superficial cuts, acute haemarthrosis (except hip), gross haematuria (>48 h duration), all haematomas (except iliosoas bleeding), minor surgical initiatives (e.g. urethral catheter placement), and radionucleid synovectomy, were included in the study. A re-bleed was defined as bleeding at the same location between 24 h and 5 days of the last effective treatment dose.

Clinical outcomes included the effectiveness of therapies and the mean time to resolution of the bleeding episode. The therapy was defined as effective when the pain was relieved, swelling decreased and joint movement improved within 24 h of medication in the case of joint bleeding. For other non-severe bleeding we defined the treatment as effective when the bleeding stopped within 24 h. Effectiveness was evaluated by healthcare professionals based on the earlier definition in medical centres. When patients were not able to come to the clinic after the doctor's consultation and injection of rFVIIa, effectiveness was evaluated by a phone call.

Resource utilization included the number of doses and average dose of haemostatic agent, number of outpatient visits and inpatient stay, ambulance transportation, and use of concomitant medications.

Univariate and bivariate sensitivity analyses were conducted on the values of key variables that were likely to vary between hospitals, or for which there were uncertainties. These include the efficacy of first-line therapy, probability of a re-bleed and the probability of effectiveness of treatment after a re-bleed. Sensitivity analyses were conducted by varying the re-bleeding rates and dosing within realistic ranges (10–20% and ±20%, respectively) to ascertain robustness of the model inputs.

Results and sensitivity analyses

Observational study

Patient data were obtained from a retrospective analysis of 25 bleeding episodes in 16 patients treated with aPCC as a first-line therapy between May 2003 and May 2005, and from a prospective analysis of 31 bleeding episodes in 11 patients treated with rFVIIa as a first-line therapy between July 2005 and December 2005 provided by the four representative centres.

A total of 56 bleeds occurring in 21 patients (12 patients aged over 17 years; 57.1% of the patients were aged under 26 years) were included in the observational study. Some 31 bleeds were managed initially with rFVIIa (mean time to treatment 10 h 23 min) and 25 bleeds were managed initially with aPCC (mean time to treatment 6 h 23 min; see Table 2). Owing to the restrictive guidelines on the use of rFVIIa in Korea, most of the patients treated initially with rFVIIa (96.8%) were treated on an

Table 2. Observational study results.

First-line therapy	rFVIIa (n = 31)	aPCC (n = 25)
Mean time to resolution of bleeding episode (h) (min–max)	6.6 (2–22)	25.2 (1–95)
Mean time to treatment (h) (min–max)	10.4 (0–40)*	6.4 (0.1–32.0)
Mean effectiveness for new and re-bleeds (%)	87.1 (92.3 for new bleeds; 60.0 for re-bleeds)	64.0† (63.6 for new bleeds†; 66.7 for re-bleeds)
Mean number of doses per bleeding episode‡ (min–max)	1.7 (1–3)	2.3 (1–4)
Number of days in treatment centre (min–max)	0.95 (0.08–0.92)	1.88 (0.04–3.96)
Number of patients requiring ambulance transportation	0§	0§
Mean treatment dose per bleeding episode per body weight (min–max)	0.136 mg kg^{-1} (0.083–0.253) (0.135 mg kg^{-1} for new bleeds; 0.137 mg kg^{-1} for re-bleeds¶)	168.3 IU kg^{-1} (49–364) (171.4 IU kg^{-1} for new bleeds; 145.5 IU kg^{-1} for re-bleeds)
Episodes treated on a home basis (%)	3.23	68.0
Episodes treated on an outpatient basis (%)	96.8	8.0
Episodes treated on a home and outpatient basis (%)	0.0	24.0

*In the case of aPCC, all cases had valid data. In the case of rFVIIa, there was one missing value; so n = 30 instead of 31.
†In three episodes of treatment (new bleeds) with aPCC, rFVIIa was also used (owing to the ineffectiveness of treatment with aPCC). The use of rFVIIa contributed to the treatment being classified as effective in one of these three episodes, the remaining two episodes continued to be classified as ineffective. These three cases have been excluded from the calculation of effectiveness.
‡From start to cessation of the bleeding episode.
§Patients requiring transportation used their car, a taxi or public transport.
¶One re-bleed required an additional dose of aPCC (1900 IU) owing to lack of availability of rFVIIa.
rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate.

outpatient basis as they could not receive rFVIIa at home. In contrast, most of the patients initially treated with aPCC (68%) could receive their treatment at home. It was found that rFVIIa used as a first-line therapy was a more effective haemostatic therapy than aPCC, resolving the bleeding episode in 87% of the cases as compared with 64% efficacy for aPCC.

The expert panel considered that these rates of treatment success for rFVIIa were comparable and in line with published literature [22]. Patient outcome data for aPCC were at the lower end of the estimates from the literature and expert opinion, which were between 64% and 88% [20,21,33,34]. However, owing to the observational nature of this study and the wish to reflect effectiveness of treatment in a real-life clinical setting in this study, it was decided to use the figure of 64% as the baseline value. Sensitivity analysis was undertaken to observe the impact of changing the value of this variable within a realistic range from the literature.

First-line treatment with rFVIIa was also found to result in a more rapid haemostatic effect than aPCC, resolving bleeding in a mean time of 6.6 h compared with 25.2 h for aPCC (see Table 2).

Physicians tended to give a smaller number of doses of rFVIIa per bleed when it was used as a first-line therapy (a mean of 1.7 doses) compared with aPCC used as a first-line therapy (mean 2.3 doses) (see Table 2). Specifically, the mean dose per bleed was 6.75 mg and 8381 IU for rFVIIa and aPCC, respectively, based on a mean weight of 49.8 kg (mean dose per bleed per kg: 0.136 mg per bleed per kg and 1.68.3 IU per bleed per kg). This result is consistent with observational studies from other parts of the world [35,36].

Modelling of total direct medical costs

Mean total medical costs are detailed in Table 3. The mean cost of rFVIIa given as a first-line therapy per individual bleeding episode was lower than the mean cost for aPCC (KRW9388 thousand [US$9276] vs. KRW11 928 thousand [US$11 785], respectively). Mean total direct medical costs from initiation to cessation of bleeding were estimated to be KRW12 460 thousand (US$12 311) for rFVIIa and KRW18 304 thousand (US$18 085) for aPCC (see Table 3).

Sensitivity analyses

Because the effectiveness of aPCC measured in the observational study and used in the base case was found to be at the lower end of the published data range, a one-way sensitivity analysis on this value was conducted (see Fig. 2). This analysis supported the cost-effectiveness of using rFVIIa as a first-line therapy: rFVIIa was actually cost-effective when simulating any value of the effectiveness of aPCC between 50% and 100%.

Table 3. Mean medical costs per bleeding episode associated with both treatment sequences.

First-line therapy	rFVIIa (n = 31)	aPCC (n = 25)
Mean drug cost for first-line therapy (1000 KRW)	9388 (9276 for new bleed; 9968 for re-bleed)	11 928 (12 147 for new bleed; 10 318 for re-bleed)
Cost of subsequent therapy* (1000 KRW)	3058	6348
Treatment centre stay (1000 KRW)	13.9	27.6
Ambulance transportation cost (1000 KRW)	0†	0†
Concomitant medication	3 7.4‡	–
Total medical cost (1000 KRW)	12 460	18 304

*This cost includes the cost of therapies given after first-line treatment.
†Patients requiring transportation used their car, a taxi or public transport.
‡One vial of tranexamic acid (500 mg) was given in two bleeding episodes in rFVIIa first-line treatment.
rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate; KRW, Korean Won.

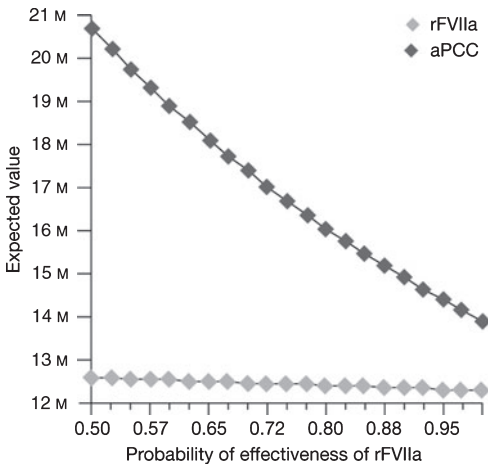

Fig. 2. One-way sensitivity analysis of the effectiveness of activated prothrombin complex concentrate.

1. **Modelling of total direct medical costs**

Mean total medical costs are detailed in Table 3. The mea...

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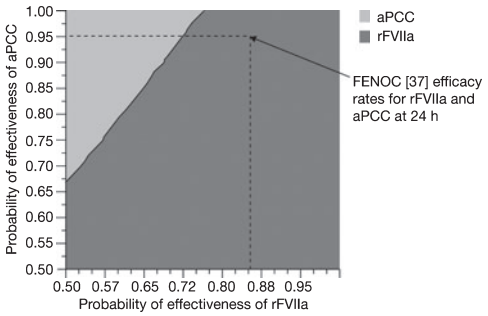

Fig. 3. Sensitivity analysis of the effectiveness of activated prothrombin complex concentrate and recombinant activated factor VII.

Table 4. Costs results and sensitivity analysis.

Initial haemostatic agent	Overall cost/1000 KRW (US$)
Baseline case	
rFVIIa	12 460 (12 311)
aPCC	18 304 (18 085)
Sensitivity analysis Re-bleed rate: 10%	
rFVIIa	11 662 (11 522)
aPCC	18 121 (17 908)
Re-bleed rate: 20%	
rFVIIa	12 963 (12 808)
aPCC	19 037 (18 809)
Dose: −20%	
rFVIIa	9968 (9849)
aPCC	14 644 (14 469)
Dose: +20%	
rFVIIa	14 952 (14 773)
aPCC	21 965 (21 702)

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

Although the FEIBA NovoSeven Comparative (FENOC) study [37] failed to show equivalence between rFVIIa and aPCC, a bivariate sensitivity analysis using efficacy data from this trial was conducted. Results from this analysis supported the cost-effectiveness of using rFVIIa as a first-line therapy in Korea (see Fig. 3). Results were also found to be robust to the extensive sensitivity analyses conducted on other key parameters (re-bleed rates at 10% and 20%, dose adjustment by ±20%), which confirmed the cost-effectiveness of rFVIIa over aPCC (see Table 4).

Discussion

Cost analysis data are valuable for the development of treatment guidelines and help address questions concerning the allocation of limited resources [38]. Increasingly, it is suggested that models of cost-effectiveness ranking should be used to set budgets for specific areas of healthcare intervention [39]. This is particularly important when considering the cost-effectiveness of therapies for rare, chronic conditions such as haemophilia patients with inhibitors, in which novel technologies may play a role in improving patient management and outlook.

Results from this pharmacoeconomic analysis support the cost-effectiveness of giving rFVIIa first-line to treat mild-to-moderate bleeding episodes in patients with haemophilia and inhibitors in Korea, and are based on the current price of rFVIIa. Furthermore, this study highlights a need to modify the current treatment guidelines in Korea, allowing physicians to choose between rFVIIa and aPCC as first-line treatment for their patients.

Currently in Korea, it is recommended that the first-line treatment for mild-to-moderate bleeding episodes in patients with inhibitors is aPCC. At present, rFVIIa is recommended as a second-line therapy or as a last resort, principally on the grounds of the acquisition costs of therapies, rather than on clinical assessment or cost-effectiveness assessment of this treatment option.

Our cost-effectiveness evaluation, based on real clinical practice data from Korea, revealed that the more effective, and more rapid, effects of rFVIIa therapy to control haemophilia bleeds, were associated with a reduction in mean total direct medical costs of care for patients with inhibitors. Considering the direct healthcare cost alone, there was clearly a difference between the costs of rFVIIa and aPCC when used first-line. Costs of treatment were more than 30% lower when rFVIIa was the first-line treatment compared with aPCC. The actual costs for use of rFVIIa were KRW12 460 thousand (US$12 311 at 2005 exchange rates) as compared with KRW18 304 thousand (US$18 085) for aPCC. Neither treatment was associated with any safety issues.

The greater efficacy of rFVIIa, shown by the larger percentage of bleeds stopped within 24 h and the much lower time to resolution, were factors that influenced the cost-effectiveness of therapy. In this study, it was found that rFVIIa resolved bleeds in around a quarter of the time taken for aPCC to result in haemostasis. Bleeding was controlled by rFVIIa within a mean of 6.6 h after administration of therapy, compared with a mean time to bleed resolution of 25.2 h for aPCC.

Time to resolution of bleed is a very important measure of treatment efficacy and a driver of treatment cost-effectiveness. Prolonged bleeding

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often results in greater morbidity, prolonged hospitalization, and in some cases results in the need for surgery [40]. Such increases in morbidity and healthcare utilization are associated with higher medical costs of care, which when considered against the acquisition costs of drug therapy, have great bearing on the costs of managing haemophilia bleeds.

Indeed, one of the major implications of our study is that the decision to use rFVIIa or aPCC should be based on clinical criteria for treatment success and cost-effectiveness, rather than based only on the acquisition cost for a given treatment. The analysis showed that the key economic drivers are the cost of the study medications (rFVIIa and aPCC), the dose used, and the probability of first-line effectiveness. In our study and model, the probability of first-line effectiveness of a treatment was based on the analysed data and verified by expert opinion founded on clinical evidence. By ensuring that baseline effectiveness values could be supported by the results from established clinical trial results, it was intended to avoid possible bias that could be attributed to any of the alternatives being compared. A Korean panel of experts assessed the data based on their clinical expertise and understanding of the literature and evidence on treatment of haemophilia with inhibitors.

Given the restrictive guidelines in Korea on the use of rFVIIa, the product was supplied by the manufacturer and therefore given in an outpatient setting instead of at home. Consequently, most of the patients receiving rFVIIa as a first-line therapy were treated in outpatient centres. This also explains why the average time to treatment was longer for those patients as most of them had to reach their outpatient centres; whereas, patients treated with aPCC as first-line therapy received it at home. However, despite this difference, time to resolution of the bleeding episode was shorter in patients receiving rFVIIa as a first-line therapy.

The cost implications of the difference in treatment settings are limited because the total cost of the bleeding episode is driven mainly by the cost of therapies, representing more than 90% of the total cost of the bleeding episode, as described in other publications [35,36].

It should also be noted that the average outpatient cost (i.e. treatment centre stay in Table 3) is higher for patients treated with aPCC as first-line therapy, compared with patients treated with rFVIIa as first-line therapy. This is because few patients receiving aPCC as first-line therapy were not controlled and had to reach the outpatient centre, where they stayed for a couple of days. However, this had a very limited impact on the total cost per bleeding episode, as explained before.

The results of our study are consistent with other published studies that have compared the total direct medical costs per bleed associated with the use of either rFVIIa or aPCC as first-line therapies (see Fig. 4) [17,35,36,41–46]. These reports in the literature of rFVIIa cost-effectiveness in other health economies and counties lend validity to our findings of rFVIIa cost-effectiveness in Korea. Studies in

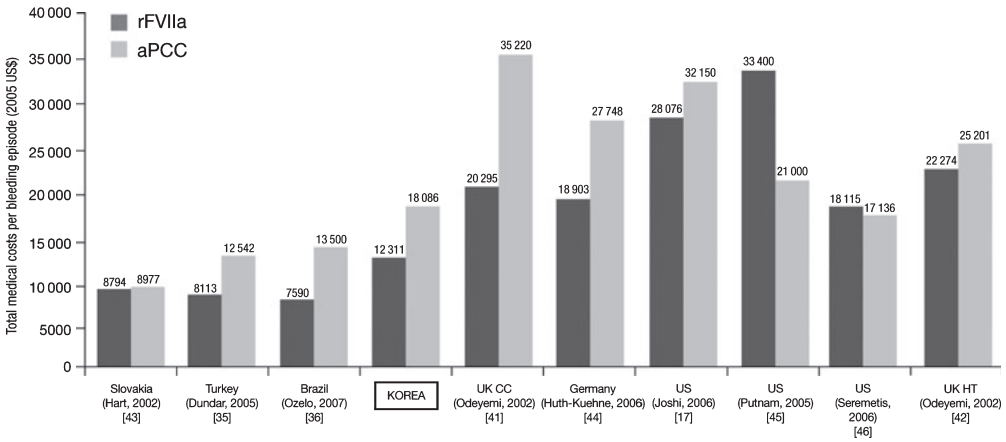

Fig. 4. Worldwide pharmacoeconomic evidence on recombinant activated factor VII. CC, comprehensive care centre; HT, home treatment.

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Brazil, Turkey, Germany, the United Kingdom, and United States have all noted higher costs when using aPCC. Our cost findings are supported, e.g. by results from a study undertaken in the United Kingdom [41], which actually showed higher first-line costs with rFVIIa but equivalent or lower overall costs. The main difference between this Korean study and the UK study is that actual resource utilization data were made available for patients treated in Korea as opposed to the exclusive expert panel approach based on clinical experience and opinion used in the UK investigation.

In another study looking at US$ costs, in the base-case analysis, the average cost per resolved bleed using rFVIIa as first-, second-, and third-line treatment was US$28 076 [17]. In contrast, using aPCC as first-line and rFVIIa as second- and third-line treatments resulted in an average cost per resolved bleed of US$30 883. 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 US$32 150 [17]. These authors clearly identified that management of minor-to-moderate bleeds extends beyond the initial line of treatment. They concluded that the true costs of treatment needs to include the economic impact of re-bleeding and failures over multiple lines of treatment, and based on this, they found that rFVIIa was the least expensive strategy more than 68% of the time.

Such findings mirror those of this Korean study, which demonstrates that the current practice of keeping rFVIIa for second-line therapy or treatment failures is not only associated with high rates of re-bleeding but is also linked with higher direct medical costs. Interestingly, we found that only a minority of bleeds were treated in an inpatient setting in Korea and thus hospitalizations contribute less to the overall costs than in similar studies in other countries, e.g. the United Kingdom [41,42].

As described, the data analysed in this study were derived from real clinical practice reported in an observational study. Ideally, cost data should be obtained in prospective studies. However, the limited number of patients with inhibitors in Korea makes such a study difficult and thus we chose to use a decision analysis model combining both retrospective and prospective data. This study design lends itself to bias in the evaluation of bleeding episodes, although the results are supported by the literature. The analysis here was based on data relating to 21 Korean patients. While a small population in terms of numbers, this actually represents 60% of the total population of treated patients with high-titre inhibitors in Korea, and data were collected from a sample of representative study centres.

Indeed, we believe that the strength of this study is that most of the data put into the model were collected from clinical practice in Korea, and therefore reflect the real-life clinical practice and treatment patterns in Korea. This makes the model more relevant to the resources used in Korea than would have been the case if data from other countries had been used in the model but with Korean pricings, as clinical practice and treatment patterns can vary between different regions and countries. Use (in the base case) of effectiveness data from an observational study of Korean clinical practice could be criticized. Given the treatment guidelines in place at the time of the study, data for use of aPCC could be collected retrospectively, while data for rFVIIa had to be collected prospectively. This could introduce a bias in the study. Despite this, effectiveness rates for treatments were found to be consistent with those reported in the literature, and further, the sensitivity analyses on the effectiveness rates showed that when simulating data from the literature (e.g. FENOC efficacy rates), giving rFVIIa as a first-line treatment was still the dominant strategy.

The study reported here is a cost minimization analysis. It does not assume equivalence of treatments but equivalence of treatment sequences. It is reasonable to consider that after 3–4 lines of therapies, a bleeding episode will be resolved, an assumption that has been used in most other studies assessing cost-effectiveness of therapy for patients with inhibitors [17,27,35,36,41,42].

It could be argued that the time frame used in this study may not be appropriate to capture all costs associated with haemophilia management. It might be assumed that the greater effectiveness of rFVIIa in achieving rapid and effective haemostasis, reducing morbidity, and cutting the need for hospitalization is likely to have an impact in terms of patient QoL and, potentially, the societal costs of managing haemophilia with inhibitors. In reality, the comparative benefits of available treatments for this condition in the long-term remain largely unknown. To date, one study commissioned by the UK National Health Service that estimated costs and outcomes over the lifetime of the patient, also showed that rFVIIa given as a first-line therapy was cost-effective [27].

From the perspective of a national health insurance payer, it could have been informative to run a cost-utility study, but as has been noted by other studies in the literature, the evidence documenting utility value is scarce, and such an approach would have added some uncertainty to the results [27]. Owing to

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the lack of information, the study by Knight *et al.* [27] actually assumed the same level of utility gained for both rFVIIa and aPCC [27]. A study conducted in Australia assessed the cost utility of switching patients to rFVIIa [25]. This study actually showed that switching patients to rFVIIa was associated with an improvement of the health-related QoL of patients and was a cost-effective strategy compared with other healthcare interventions such as dialysis.

Our analysis had not compared the cost-effectiveness of rFVIIa with other health interventions but has compared two options for the first-line management of haemophilia with inhibitors. It is based on Korean patient data, clinical evidence, and experience of treatment efficacy and has used Korean care costs to compare the cost-effectiveness of rFVIIa relative to aPCC. The study concludes that rFVIIa has a good safety profile and has a higher effectiveness relative to other treatment options in the management of haemophilia patients with inhibitors in Korea. Furthermore, despite the perceived differences in acquisition costs between rFVIIa and aPCC, the use of rFVIIa on a first-line basis in Korea would appear to be justified from an economic perspective. This result is relevant for the development of management guidelines which would ensure the best treatment of haemophilia patients in Korea and other countries in the region with similar treatment options.

Further prospective study and monitoring of the effectiveness and cost of treatment should be conducted on a continuous basis to ensure optimal and most cost-effective care for patients.

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The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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