

A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors

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Summary. Recombinant factor VIIa (rFVIIa) was developed to provide an improved procoagulant component capable of 'by-passing' inhibitor antibodies in the treatment of haemophilic patients. The primary objective of this study was to compare the efficacy of two dosage regimens of rFVIIa (given intravenously at periodic intervals) in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B with and without inhibitors. The study was designed as a randomized, double-blind, parallel group, international multicenter trial. Patients were randomly allocated to treatment A: $35 \mu\text{kg}^{-1}$ or B: $70 \mu\text{kg}^{-1}$, in blocks of 2. Within each block, one patient was assigned to the $35 \mu\text{kg}^{-1}$ dosing regimen and the other to $70 \mu\text{kg}^{-1}$ dose. One hundred and fifty subjects from 20 sites were screened for this study and 116 had baseline assessments. Of these, 84 were treated on the protocol and 32 were not treated in the study, in most cases because they did not return to the clinic with an eligible bleeding episode. One hundred and seventy-nine bleeding episodes were

treated, of which 145 (81%) were acute haemarthroses. Both treatments were efficacious, with 71% having an excellent (59% and 60%) or effective (12% and 11%) response. Overall, the mean and median number of doses given per episode of joint bleeding were 3.1 and 2, respectively. The mean number of doses was 3.1 for the $70 \mu\text{kg}^{-1}$ group and 2.7 for the $35 \mu\text{kg}^{-1}$ group (P value = 0.142). The study concluded that rFVIIa in a dosage of $35 \mu\text{kg}^{-1}$ or $70 \mu\text{kg}^{-1}$ is both safe and reasonably effective in the treatment of joint or muscle haemorrhages in haemophilic patients with inhibitor antibodies to factor VIII or factor IX. It is concluded that the appropriate dose for the treatment of joint and peripheral muscle bleeding in haemophilic patients with inhibitors is $35\text{--}70 \mu\text{kg}^{-1}$ given at 2–3 h intervals until haemostasis is achieved.

Keywords: acute haemarthroses, FIX inhibitors, FVIII inhibitors, haemophilia, intramuscular haemorrhage, recombinant factor VIIa.

Approximately 20–25% of persons with severe haemophilia A develop inhibitor antibodies to FVIII

[1–5]; treatment options for those with high-titre inhibitors have been limited and each has potential deleterious side-effects [6–9]. Recombinant factor VIIa (rFVIIa) was developed to provide an improved procoagulant component capable of 'bypassing' inhibitor antibodies in the treatment of haemophilic patients.

Both native FVIIa and rFVIIa require tissue factor (TF) exposed at the site of injury to become enzymatically active. FVIIa plus TF is the tinase complex.

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FXa is inhibited by TF pathway inhibitor (TFPI) [10] which then forms a complex with the VIIa TF. In normal haemostasis, TFPI dampens the initial response; the extrinsic pathway is down-regulated by TFPI. The mechanism of action of FVIIa is that FVIIa out competes FVII for TF, so that enough FXa free of TFPI is formed to activate small amounts of prothrombin in the TF milieu. The thrombin formed is sufficient to activate platelets, which then attract the 'TF VIIa' activated FIXa to the platelet surface, which then recruits more FX [11].

The risk of inducing generalized activation of the coagulation cascade and disseminated intravascular coagulation (DIC) with the use of rFVIIa appears to be minimal. It appears that rFVIIa is only active at the site of injury where TF is present [12, 13]. rFVIIa should be effective in persons with haemophilia A and B, irrespective of inhibitor antibody status or titre, and indeed has been effective in achieving and maintaining haemostasis in compassionate use situations including major surgery, central nervous system haemorrhages, severe intra-abdominal bleeding and other life-threatening bleeding episodes [12, 14–21].

In an attempt to determine the optimal dosage regimen for treatment of common types of bleeding in persons with haemophilia, a randomized double-blind study was designed to compare two dosages of rFVIIa: 35 $\mu\text{g kg}^{-1}$ body weight (bw) and 70 $\mu\text{g kg}^{-1}$ bw per dose. These two dosages were chosen because in earlier studies in a small group of subjects single doses of 35 $\mu\text{g kg}^{-1}$ were reportedly effective in some patients [22]. This paper describes the study design, study subjects, observations and data analysis.

Objectives of the study

The primary objective of the study was to compare the efficacy of two dosage regimens of rFVIIa (given intravenously at periodic intervals), in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. Secondary objectives were (1) to compare the short-term safety of the two dosage regimens, (2) to monitor patients for potential development of antibodies to rFVIIa and to contaminants in the rFVIIa preparation such as baby hamster kidney (BHK) cell proteins, and murine IgG as a result of repeated treatment.

Materials and methods

The study was designed as a randomized, double-blind, parallel group, international multicentre trial

to evaluate the efficacy and safety of two dosages of rFVIIa for the treatment of joint, muscle and mucocutaneous bleeding episodes. Patients were randomly allocated to treatment A: 35 $\mu\text{g kg}^{-1}$, or B: 70 $\mu\text{g kg}^{-1}$, in blocks of two. Within each block, one patient was assigned to the 35 $\mu\text{g kg}^{-1}$ dosing regimen and the other to the 70 $\mu\text{g kg}^{-1}$ dose. Randomization was stratified into four groups according to body weight. The dose randomly assigned for each subject was followed for the duration of the study. No control group (placebo) was included since ethical considerations demand treating haemophiliacs during a bleeding episode. Patients received either 35 or 70 $\mu\text{g kg}^{-1}$ bw of reconstituted rFVIIa administered as an i.v. bolus injection over 2–5 min, at intervals of 2.5 ± 0.5 h (which was in keeping with the short half-life of rFVIIa) [19]. The maximum number of doses of rFVIIa which could be given per bleeding episode was six. Timing of the primary efficacy endpoint (cessation of bleeding) was based on the length of time from the first injection of rFVIIa for each bleeding episode.

Patients reported to their respective treatment centres after determining that they were experiencing a joint, muscle or mucocutaneous bleed. Consequently, the length of time from the beginning of the bleeding episode until the first injection of rFVIIa varied with each bleed.

Evaluation of bleeding severity, size of haemorrhage, degree of joint or muscle pain was done at baseline and before each dose of rFVIIa, at 8 h and 12 ± 2 h after the initial dose (unless treatment was discontinued), and at the end of the treatment episode. A second and subsequent doses were given if the clinical response to the first or previous infusion was judged by the investigator as ineffective or partially effective as compared to pretreatment assessment. Treatment of a bleeding episode was terminated when an excellent or effective global evaluation of efficacy was attained or after a sixth dose of rFVIIa had been given.

Immediately before the administration of the initial and subsequent doses of rFVIIa, coagulation tests were performed to monitor for possible intravascular coagulation or DIC. Treatment was allowed to continue if there was no laboratory evidence of activation of coagulation. Samples were also obtained for surveillance for antibody formation against FVIIa. The samples were analysed in an ELISA of the following configuration: rFVIIa was presented in the wells of microtitre plates, to HIV-inactivated human serum in a final dilution of 1:100. Any bound human immunoglobulin was detected

with an enzyme-labelled antihuman-Ig gamma chain conjugate. The value of pretreatment samples, analysed in the assay, were used to calculate the cut-off, which was defined as the mean value plus two standard deviations.

The global evaluation of efficacy was defined as follows. Response was rated as 'excellent' if one or more of the following clinical responses (as compared to the pretreatment assessment) occurred according to the investigator's clinical judgement ≤ 8 h following initiation of treatment: (1) a definite relief of pain/tenderness as reported by the patient, (2) a measurable decrease of the size of the haemorrhage and (3) arrest of bleeding.

Responses were rated 'effective' if one or more of the above clinical responses occurred between 8 and 14 h following start of treatment. Responses were rated as 'partially effective' if the same occurred *after* 14 h or if the patient had a slight but detectable relief of pain/tenderness, a slight but detectable decrease in size of the haemorrhage or if the bleeding had slowed. The response was rated as 'ineffective' if there was no relief or a worsening of pain or tenderness, no decrease or a worsening of the extent of the haemorrhage, or if the bleeding remained the same or worsened at 14 h.

Each bleeding episode was treated with a maximum of six doses of rFVIIa, and each patient was treated for a maximum of four bleeding episodes.

Study subjects

Over 150 subjects from 20 sites were screened for the study. To qualify for inclusion, persons had to have severe haemophilia A or B (defined here as $< 2\%$ FVIII or FIX), with or without inhibitors, and a signed informed consent. Haemophilic patients without inhibitors were included (a) in order to increase

the numbers of subjects and (b) since the presumed mechanism of action of rFVIIa made it seem likely that it would be equally effective in patients with or without inhibitors. All subjects were randomized to one of the two treatment dosages, irrespective of whether or not they ultimately received treatment. After enrolment, randomization and baseline assessment, patients with acute haemarthroses, peripheral intramuscular or mucocutaneous haemorrhages were eligible for treatment with rFVIIa.

Exclusion criteria were as follows: patients with severe hepatic failure were excluded from the study. Bleeding episodes excluded for treatment in enrolled patients were (1) serious bleeding episodes, such as compartment syndrome, gastrointestinal, retropharyngeal, sublingual, iliopsoas and central nervous system bleeding; (2) those in which the patient had been treated with clotting factor and/or antifibrinolytic agents within the previous 48 h, or with corticosteroids within the previous 4 weeks.

Of > 150 subjects screened, 116 came in for baseline assessments. Among the 116 who were randomized and had baseline assessments performed, 84 were treated on this protocol. Thirty-two were never treated in this study, in most cases because they never returned to the clinic with an eligible bleeding episode.

Observations

In this study, which began in December 1990, 179 bleeding episodes were treated in 78 patients (66 of whom had inhibitors) (see Table 1 for demographic characteristics for the evaluable population treated). Statistically, the dose groups were comparable with respect to baseline characteristics.

Joint bleeding

Of the 179 bleeding episodes treated, 145 (81%) were acute haemarthroses. The joints involved are shown in Table 2. The average number of joint

Table 1. Demographic characteristics for the population treated.

Characteristic	35 $\mu\text{g kg}^{-1}$	70 $\mu\text{g kg}^{-1}$	<i>P</i>
Mean age (years)	23.8	23.2	0.981
Mean body weight (kg)	62.6	56.4	0.283
Mean height (cm)	166.6	156.0	0.113
Haemophilia type:			
A/with inhibitor	27 (77%)	35 (81%)	
A/without inhibitor	6 (17%)	5 (12%)	
B/with inhibitor	1 (3%)	3 (7%)	
B/without inhibitor	1 (3%)	0	0.435

P values assess the significance of the difference between dose groups and were determined by an analysis of variance model adjusting for centre group, or by the Mantel-Haenszel test stratifying by centre group.

Table 2. Location of joint bleeds treated in this study.

Location of bleed	Treatment regimen	
	35 $\mu\text{g kg}^{-1}$	70 $\mu\text{g kg}^{-1}$
Knee	30 (51%)	39 (46%)
Elbow	11 (19%)	19 (22%)
Shoulder	3	10
Hip		1
Wrist	1	5
Ankle	16 (27%)	17 (20%)
Others (ex:metacarpalphalangeal)	1	3

bleeds per patient treated and the average time from onset of joint bleeding until first treatment are shown in Table 3A. While there was an approximate 7.8 h difference between dose groups with respect to average time from onset of bleed to start of treatment, there was only a 1.6 h difference with respect to the medians (10.0 h for the 70 µg kg⁻¹

group vs. 8.4 h for the 35 µg kg⁻¹ group). There was no statistically significant difference between dose groups in terms of baseline severity of pain assessments for 119 evaluable episodes of acute haemarthrosis. There was no statistically significant difference between dose groups. Similarly, there was no significant dose group difference between target and damaged joints and nontarget, nondamaged joints with respect to pain severity.

Table 3A. Characteristics of joint bleeds treated.

Characteristic	35 µg kg ⁻¹	70 µg kg ⁻¹	P
Number of bleeds per patient; mean (range)	2.0 (1-6)	2.2 (1-4)	0.321 *
Mean time (range) from onset of bleed to start of treatment (h)	13.2 (2-28)	20.7 (2-30)	0.147 †
Median time (h) from onset of bleed to start of treatment	8.4	10.0	

* P value assesses the significance of the difference between dosage groups and was determined by an analysis of variance model adjusting for centre group. † P value assesses the significance of the difference between dosage group and was determined using survey data linear regression with patient as the primary sampling unit and with an adjustment for centre group.

The global response (determined at 12 ± 2 h post-initial treatment or at the end of treatment, whichever came first) was essentially the same in the two treatment groups. As shown in Table 3B, overall, both treatments were efficacious, with 71% having an excellent (59% and 60%) or effective (12% and 11%) response. While the 70 µg kg⁻¹ group had slightly longer times between onset of bleeding and start of treatment than the 35 µg kg⁻¹ group (see Table 3C), the times were not significantly different.

For target and/or badly damaged joints, 69% of bleeds in the 70 µg kg⁻¹ group had an excellent response, as opposed to 53% in the 35 µg kg⁻¹ group. For joints not damaged and not target joints, 56% in the 70 µg kg⁻¹ and 64% in the 35 µg kg⁻¹ group achieved an excellent response.

Table 3B. Efficacy of rFVIIa in 144 evaluable episodes of acute hemiarthrosis.

Parameter	Value	35 µg kg ⁻¹ (n = 5)	70 µg kg ⁻¹ (n = 85)	P
Global response	Ineffective (0)	7 (12%)	8 (9%)	0.912*
	Partially effective (1)	10 (17%)	17 (20%)	
	Effective (2)	7 (12%)	9 (11%)	
	Excellent (3)	35 (59%)	51 (60%)	
Response per bleed‡	Mean	2.19	2.21	0.714†

* P value assesses dosage group difference and is based on the proportional odds test using survey data techniques with patient as the primary sampling unit. † P value assesses dosage group difference using survey data regression adjusting for centre group bleed severity, an indicator of target joint, an indicator of weight-bearing joint, type of haemophilia and an indicator of whether or not the patient had inhibitors. Patient is the primary sampling unit. ‡The mean 'response per bleed' is obtained by assigning the scores 0, 1, 2, 3 to the primary endpoint as shown in the table, and then calculating the mean score per dose group.

Table 3C. Efficacy of rFVIIa (primary endpoint*) for 126 joint bleeds by time from onset of bleed to start of treatment.

	≤ 4 h		> 4-9 h		9-18 h		> 18 h	
	35 µg kg ⁻¹ n = 13	70 µg kg ⁻¹ n = 17	35 µg kg ⁻¹ n = 16	70 µg kg ⁻¹ n = 19	35 µg kg ⁻¹ n = 19	70 µg kg ⁻¹ n = 16	35 µg kg ⁻¹ n = 7	70 µg kg ⁻¹ n = 25
Global response								
Ineffective	2(15%)	1(6%)	0	2(10%)	4(21%)	1(6%)	1(14%)	1(4)
Partially effective	1(8)	2(12)	2(13)	3(16)	3(16)	2(13)	2(29)	9(36)
Effective	2(15)	2(12)	2(13)	0	2(11)	0	0	6(24)
Excellent	8(62)	12(70)	12(74)	14(74)	10(52)	13(81)	4(57)	9(36)

n = number of patients per group. Percentage of total number in same time of onset to treatment group is shown in parentheses. * Primary endpoint is the investigator's global evaluation of the response to treatment at 12 ± 2 h post-initiation of treatment, or at the end of treatment, whichever came first.

Overall, the mean and median number of doses given per episode of joint bleeding were 3.1 and 2.0, respectively. The mean number of doses was 3.1 for the 70 µg kg⁻¹ group and 2.7 for the 35 µg kg⁻¹ group ($P = 0.142$). Among those having an excellent or effective response, the mean and median number of doses were 2.5 and 2.0; the median number was the same in both dosage groups. In those with a partially effective or ineffective response, the mean and median number of doses was 4.5 (range 2–6).

Table 3D shows efficacy of the two doses for episodes of joint bleeding which were 'first time' joint bleeds for a particular patient treated on this protocol. (This analysis helps remove bias caused by patients being treated more at one dose than the other, given that dose works better.) There were 31 and 23 such bleeds in the 70 µg kg⁻¹ and 35 µg kg⁻¹ groups, respectively. Both treatment dosages were effective and statistically equivalent.

Table 3E breaks down treatment responses by inhibitor status. No definite conclusions can be drawn from these data, however, since there were only 20 evaluable joint bleeds in patients without inhibitors.

Intramuscular haemorrhages

Among 29 episodes of peripheral intramuscular haemorrhages, there were 14 and 15 in the

Table 3D Efficacy of rFVIIa or joint bleeds treated for the first time in a particular patient.

Parameter	Value	35 µg kg ⁻¹ (<i>n</i> = 23)	70 µg kg ⁻¹ (<i>n</i> = 31)	<i>P</i>
Global response	Ineffective	1 (4%)	3 (10%)	0.181
	Partially effective	3 (13%)	8 (26%)	
	Effective	5 (22%)	2 (7%)	
	Excellent	14 (61%)	18 (57%)	

P value assesses dose group difference and is based on the proportional odds test.

Table 3E Efficacy of rFVIIa in 119 evaluable joint bleeds by inhibitor status.

Parameter	Value	With inhibitors		Without inhibitors	
		35 µg kg ⁻¹ (<i>n</i> = 37)	70 µg kg ⁻¹ (<i>n</i> = 62)	35 µg kg ⁻¹ (<i>n</i> = 8)	70 µg kg ⁻¹ (<i>n</i> = 12)
Global response	Ineffective (0)	3%	13%	25%	0
	Partially (1)	19%	19%	13%	8%
	Effective (2)	16%	11%	0	8%
	Excellent (3)	62%	57%	62%	84%
Response per bleed*	Mean	2.4	2.1	2.0	2.8

* The mean 'response per bleed' is obtained by assigning the scores 0, 1, 2 and 3 to the primary endpoint as shown in the table, and then calculating the mean score per dose group.

70 µg kg⁻¹ and 35 µg kg⁻¹ dosage groups, respectively. The average number of doses was 3.6 for the 70 µg kg⁻¹ dosage group and 3.5 for the 35 µg kg⁻¹ dosage group ($P = 0.429$). Both groups had an approximately equivalent number of excellent responses (50% vs. 47%). However, while numbers of episodes are small, the 35 µg kg⁻¹ group had more ineffective (20%) and partially effective (27%) results than the 70 µg kg⁻¹ group (14% and 14%).

Mucocutaneous haemorrhages

There were only five episodes of mucocutaneous haemorrhage, all in persons with haemophilia A without inhibitors. All of these were treated with the 35 µg kg⁻¹ dose. Three of five had an excellent response, while one was rated effective and one partially effective.

Adverse events

Nineteen of the 84 treated patients experienced at least one minor adverse event during the course of the study. Most adverse events reported were mild in nature and transient. There were no apparent differences between the two dosage groups in the occurrence of adverse events. During the course of the study, transient changes in blood pressure (BP) were observed in 13 patients. Six of these had a transient, very mild increase in systolic BP (maximum increase 10 mmHg), whereas the other seven had a slight decrease in systolic or diastolic BP (maximum decrease 10 mmHg). A slight increase in body temperature (<0.8 °C) was reported in three patients, two had headache, one had a rash, one reported burning at the injection site and one reportedly had 'tendonitis' the following day.

Three serious adverse events were reported. The first of these probably reflects treatment failure rather than a side-effect of treatment with rFVIIa. One subject, a 6-year-old child with haemophilia A and

high-level inhibitor, received rFVIIa, $35 \mu\text{g kg}^{-1}$, for a forearm bleed. Invasive compartment pressure measurement was performed following administration of one dose of rFVIIa. The pressure was found to be normal and administration of rFVIIa was continued until an 'effective' response had been obtained. A total of six doses of rFVIIa were given over a 12-h period. Six hours following the last dose of rFVIIa, swelling and paresthesia were evident in the distal part of the arm where the instrument to measure pressure had been inserted. A diagnosis of 'compartment syndrome' was then made, and fasciotomy was subsequently performed under coverage of porcine FVIII.

The remaining two serious adverse events reported do not appear to have resulted from treatment with rFVIIa. One was reported as 'progressive chronic active hepatitis' occurring in a 53-year-old man with severe haemophilia A who had a history of hepatitis B and non-A, non-B hepatitis with hepatomegaly and abnormal liver function tests. Three months after receiving three doses of rFVIIa, he complained of anorexia, jaundice and pruritis, and was noted to have ascites and ecchymoses on physical examination.

A 27-year-old man with severe haemophilia A, HIV infection and FVIII inhibitor died 15 months after receiving three doses of rFVIIa in the study. He fell down a flight of stairs at home and was found convulsing and unconscious; he died a short time later in a local hospital as a result of intracranial haemorrhage before rFVIIa or other treatment could be administered.

Laboratory parameters

The potential for the development of excessive intravascular coagulation or DIC during rFVIIa therapy was closely monitored throughout the treatment protocol. Platelet count, fibrinogen level, activated partial thromboplastin time (APTT) and prothrombin time (PT) were obtained before the initial injection of rFVIIa for each bleeding episode, and before each subsequent injection. There were four bleeding episodes (two in the $35 \mu\text{g kg}^{-1}$ and two in the $70 \mu\text{g kg}^{-1}$ dose group) in which normal baseline fibrinogen levels fell below the normal range during treatment with rFVIIa. Additionally, there were 10 bleeding episodes in which baseline fibrinogen levels were below the local laboratory's normal range; fibrinogen levels remained stable in these patients following treatment with rFVIIa. Throughout the study, all patients maintained fibrinogen levels of $\geq 135 \text{ mg dL}^{-1}$.

There were 10 bleeding episodes (six in the $35 \mu\text{g kg}^{-1}$ dose group and four in the $70 \mu\text{g kg}^{-1}$

dose group) in which platelet counts changed from normal to low following treatment with rFVIIa. In five of the 10, the change was $< 18\,000 \text{ mm}^{-3}$; in the others, decreases of $20\,000$ – $57\,000 \text{ mm}^{-3}$ were reported. All patients, however, maintained platelet count levels of $\geq 117\,000 \text{ mm}^{-3}$. Four subjects had a decrease in both fibrinogen and platelet count of 20%.

There were 23 bleeding episodes where baseline platelet counts were below the lower limit of normal prior to treatment with rFVIIa. (The majority of the 23 patients had laboratory evidence of liver disease; thus it seems possible that the low baseline platelet counts may have resulted from hypersplenism.) In two of these, baseline platelet counts were $54\,000$ and $58\,000 \text{ mm}^{-3}$ and they did not change significantly post-infusion. None of these patients, regardless of baseline platelet count, had evidence of clinical DIC at any time during the study.

The PT was normal at baseline in most patients and, as seen in previous studies with rFVIIa, the PT often shortened to below normal (to values as low as 7 s, as compared to control range of 11–12.5 s) during treatment. As expected, baseline APTT values were prolonged in all patients. While there was also a shortening of APTT in many patients during treatment with rFVIIa, in only two patients did the APTT normalize (e.g. from baseline of 70 s to 31 s).

Surveillance for antibody to rFVIIa, and for antibodies to contaminants in the rFVIIa preparation

Follow-up samples were obtained from 76 of the 84 subjects for antibody to rFVIIa. Six of the 76 had also been treated with rFVIIa under a compassionate use protocol. Before their last antibody determination, individual patients had been treated with rFVIIa for one bleeding episode (35 patients), 2–4 bleeding episodes (38 patients) or for more than four bleeding episodes (three patients).

All post-treatment samples showed values below the cut-off, indicating that no specific antibody formation against rFVIIa was demonstrated in any of the 76 patients.

Baseline and follow-up samples from the 76 subjects were also assayed for antibodies to BHK cell proteins and murine IgG. There was no evidence of new antibody formation to these trace contaminants.

Discussion

Treatment options for bleeding in patients with haemophilia and high-titre FVIII and FIX inhibitors are limited and often inadequate, and may cause

undesirable side-effects. Current therapies, including FIX complex concentrates (FIX CC, PCC), activated PCC and porcine FVIII may have some increased risk of infectious disease transmission [23], allergic reactions, anamnestic inhibitor responses [8, 9] and, with the use of PCC and APCC, some risk of inducing DIC, deep venous thrombosis and/or acute myocardial infarction [6, 7]. Additionally, PCC and APCC cannot be relied upon to stop bleeding [24–26].

This study demonstrates that rFVIIa in a dosage of 35 or 70 $\mu\text{g kg}^{-1}$ is both safe and reasonably effective in the treatment of joint or muscle haemorrhages in haemophilic patients with inhibitor antibodies to FVIII or FIX. While no direct comparisons can be made with responses to treatment with FIX CC, it should be noted that in each of three controlled trials a single dose of FIX CC was judged effective in controlling acute haemarthroses in 50% of episodes [24–26]. In this study, 71% of episodes of joint bleeding had an excellent or effective response to either dosage of rFVIIa at 12 h or less after institution of treatment. If one looks only at inhibitor patients, 68% and 78% had an excellent or effective response to the 70 $\mu\text{g kg}^{-1}$ and 35 $\mu\text{g kg}^{-1}$ dosages, respectively. It should be noted that all patients in this rFVIIa study had to travel to their treatment centre for infusion of rFVIIa. Thus, none were treated immediately when bleeding occurred. While the study designs in these trials are quite different, it appears that rFVIIa offers a definite treatment option for haemophiliacs with inhibitor antibodies.

While the porcine FVIII preparation, Hyate:C, has often proved life-saving in persons whose anti-FVIII inhibitors have low cross-reactivity to porcine FVIII, this treatment option has several limitations and potential complications, including thrombocytopenia, allergic reactions and anamnestic responses [27].

No conclusions can be drawn for primary mucocutaneous bleeds treated with rFVIIa due to the very small sample size involved. Overall, the two dose groups were clinically and statistically equivalent despite the fact that the 70 $\mu\text{g kg}^{-1}$ group had, on average, a longer (but not significantly longer) time between onset of bleeding and start of treatment than did the 35 $\mu\text{g kg}^{-1}$ group (≈ 7.5 h longer).

For all severe joint bleeds and for joint bleeding in target or damaged joints, the 70 $\mu\text{g kg}^{-1}$ group achieved more 'excellent' responses than the 35 $\mu\text{g kg}^{-1}$ group. For bleeding into weight-bearing, damaged joints, the two doses achieved the same percentages of excellent responses. For muscle bleeds, the 70 $\mu\text{g kg}^{-1}$ group achieved slightly more effective and excellent responses than the 35 $\mu\text{g kg}^{-1}$

group. Differences in excellent responses were not statistically significant, however.

Both dosage groups had excellent safety profiles and, overall, were approximately equivalent with responses to adverse events, changes in laboratory values and significant fluctuations in vital signs vs. pretreatment observations.

Based on the results from this study, in which there was no significant difference between the two dosage regimens, the appropriate dose for the treatment of joint and peripheral muscle bleeding in haemophilic patients with inhibitors would appear to be 35–70 $\mu\text{g kg}^{-1}$, given at intervals of 2–3 h until haemostasis is achieved. However, compassionate use experience (in which a high percentage of excellent results in serious bleeding situations were obtained with ≈ 90 $\mu\text{g kg}^{-1}$ dose, given every 2–3 h), suggests that a higher dose may be more effective [21, 28, 29]. To evaluate results with this higher dose, an open labelled home treatment trial was recently conducted in the US, employing a dosage of 90 $\mu\text{g kg}^{-1}$ every 2–3 h (maximum number of doses of four per bleeding episode). This dosage of rFVIIa produced effective haemostasis in 92% of bleeding episodes after 1–3 doses (mean 2.2) [30]. In view of the potential problems associated with other therapeutic modalities for treatment of bleeding in inhibitor patients, including a continued risk of transmission of blood-borne viral disease [23, 31], and their frequent lack of efficacy, rFVIIa offers an attractive management option. The safety profile of rFVIIa appears to be excellent, there is no risk of anamnestic response and infusion volumes are small (as compared with PCC). On the other hand, rFVIIa does not appear to be optimal treatment for noninhibitor patients, as rFVIII (and rFIX) preparations are available, have a longer half-life and treatment responses with these are excellent [32–34].

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Appendix

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