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Treatment of acute bleeding in acquired haemophilia A with recombinant activated factor VII: analysis of 10-year Japanese postmarketing surveillance data

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Introduction: Patients with acquired haemophilia A (AHA) have autoantibodies against factor VIII (FVIII), and may develop spontaneous bleeding that requires treatment with FVIII inhibitor bypassing agents such as recombinant activated FVII (rFVIIa, NovoSeven®). However, data regarding the use of rFVIIa are limited. **Aim:** To investigate the use, efficacy and safety of rFVIIa for the treatment of AHA by analysis of 10-year multicentre Japanese postmarketing surveillance data. **Methods:** Treatment regimens, haemostatic efficacy and adverse events were recorded for rFVIIa therapy of AHA patients with bleeding episodes. Treatment was evaluated as markedly effective, effective, moderate or ineffective. **Results:** Data were collected for 371 bleeding episodes in 132 patients. Bleeding improved after rFVIIa therapy in 92% of episodes (markedly effective in 41%, effective in 10%, moderate in 41%). The response rate was significantly better in patients who received an initial dose of ≥90 μg kg^{-1} than in those who received an initial dose of <90 μg kg^{-1}. The response rate was also significantly better when rFVIIa was administered earlier after the onset of bleeding. Twelve serious adverse events were recorded in six patients, including five serious thromboembolic events in three patients who were all elderly with significant comorbidities. **Conclusion:** This is the largest, single-country study of rFVIIa therapy in AHA patients reported to date. The Japanese surveillance data show comparable efficacy and safety to prior multinational studies. Doses of 90–120 μg kg^{-1} and prompt initiation of treatment may be important to achieve good bleeding control.

Keywords: acquired, haemophilia A, haemorrhage, recombinant activated factor VII, safety, treatment efficacy

Introduction

Acquired haemophilia A (AHA) is a rare autoimmune disorder characterized by formation of autoantibodies against blood coagulation factor VIII (FVIII). AHA may occur in association with conditions such as connective tissue disease, malignant tumours, childbirth and ageing [1]. A 2-year national surveillance study conducted in the United Kingdom by the UK Haemophilia Centre Doctors' Organization reported an incidence rate of AHA of 1.48 per million per year, with 85% of patients aged ≥65 years [2]. In Japan, a retrospective survey conducted by the Japanese Society on Thrombosis and Haemostasis (JSTH) reported 58 cases of AHA [3]. A subsequent 3-year Japanese survey by the JSTH included 55 cases of AHA, resulting in an estimated incidence rate similar to that reported in other countries [2,4]. Reports from Japan and elsewhere show that age of onset is ≥50 years in nearly 90% of patients. There is a bimodal age distribution, with the first peak at age 20–40 years (predominantly in females), and a second at an older age [3–5].

The acquired inhibitors against FVIII result in markedly reduced FVIII activity and spontaneous bleeding. The most common site of bleeding in AHA is subcutaneous, followed by intramuscular. Unlike patients with congenital haemophilia, AHA patients often experience simultaneous bleeds in more than one anatomical location; additionally, intra-articular bleeding, which is the most common site in congenital haemophilia, is less common in AHA [1,4]. The basic management strategies for patients with AHA include immunosuppressive therapy to reduce the risk of bleeding by reducing the anti-FVIII autoantibody

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(inhibitor) level and haemostatic therapy to control bleeding episodes. Bleeding is often more serious in AHA than in congenital haemophilia and potentially life-threatening bleeding requires immediate haemostatic therapy [1].

Bypassing agents used as first-line haemostatic therapy in AHA patients include recombinant activated FVII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsværd, Denmark) and plasma-derived activated prothrombin complex concentrate (pd-aPCC, FEIBA; Baxalta, Bannockburn, IL, USA) [1].

rFVIIa was available on an emergency and compassionate basis between 1988 and 1999 in various regions (the European Union, Canada, USA, Australia and Malaysia) [6]. In AHA patients, FVIII dysfunction results in inadequate generation of thrombin. Administration of 90 μg kg^{-1} rFVIIa results in a plasma concentration of 25 nM (250-fold higher than the basal FVIIa level), leading to direct activation of FX on the activated platelet membrane, even in the absence of tissue factor [7–10]. This causes generation of activated FX, even in the absence of FVIII function, resulting in generation of thrombin from prothrombin, and fibrin clot formation leading to haemostasis.

When rFVIIa was approved for the treatment in Japan in 2000, data regarding its use were limited. A 10-year re-examination period was therefore designated and postmarketing surveillance was initiated. Here, we report the accumulated data regarding the use, efficacy and safety of rFVIIa for the treatment of bleeding episodes in AHA patients during the 10-year surveillance period. To date, this is the largest, single-country study of the use of rFVIIa in AHA patients [6,11–13].

Subjects and methods

Study subjects and data collection

This study included 371 bleeding episodes in 132 AHA patients at 94 institutions (see Appendix) for whom case report forms were completed between May 2000 and March 2010. The use of rFVIIa to control surgery-related bleeding was not included. The study was conducted in accordance with the principles of the Ordinance on Standards for Conducting Post-Marketing Surveillance and Studies on Drugs [14]. The Japanese label recommends initial administration of rFVIIa at 90 μg kg^{-1} every 2–3 h (60–120 μg kg^{-1} after initial dose) until haemostasis is achieved. The dosing interval can be prolonged for further administration of rFVIIa if necessary. [Correction added on 13 October 2016, after initial online publication: In the preceding sentence, the initial administration of rFVIIa was initially incorrect and has been amended in this version.]

The following were recorded for each bleeding episode: date and time of bleeding; site of bleeding; dates and times of rFVIIa administration; doses of rFVIIa administered; symptoms at time of rFVIIa administration; haemostatic efficacy of rFVIIa therapy. Laboratory data were reviewed including activated partial thromboplastin time, prothrombin time (PT), thrombin-antithrombin complex level, D-dimer level, fibrin degradation product level and fibrinogen level. Adverse events were recorded, including laboratory abnormalities, date of onset, seriousness, treatment, causal relationship and outcome. Adverse events where a causal relationship with rFVIIa therapy could not be clearly ruled out were included in the analyses. Serious adverse events were defined as medical events that were life-threatening or resulted in hospitalization or prolongation of hospitalization, persisting or significant disability/incapacity, congenital anomaly/birth defects or other important medical events.

Assessment of the haemostatic efficacy of rFVIIa

As an observational study, treatment was based on local practice and there were no set treatment protocols. The haemostatic efficacy of rFVIIa was assessed using the haemostasis assessment criteria used in the clinical trials that supported the approval of rFVIIa use in Japan [15]. For each bleeding episode, the investigators rated treatment as markedly effective (a haemostatic effect was observed <8 h after administration of the first dose of rFVIIa), effective (a haemostatic effect was observed after 8–12 h), moderate (a haemostatic effect was observed after >12 h) or ineffective (no haemostatic effect was observed or bleeding worsened). Haemostatic response was defined as the proportion of patients with either a markedly effective or effective response. As haemostatic efficacy of rFVIIa may be influenced by concomitant treatment (either before, after or simultaneous with rFVIIa), the data were analysed in two groups of patients: a group who received rFVIIa in combination with aPCC/FVIII and a rFVIIa monotherapy group.

Statistical analysis

The chi-square test was used to compare the haemostatic efficacy between the rFVIIa monotherapy and rFVIIa + aPCC/FVIII groups. The Wilcoxon test was used to compare rFVIIa therapy between different bleeding sites and the response rate between different time intervals from the onset of bleeding to the first rFVIIa dose. Logistic regression analysis was used to compare the response rate between different initial doses (≥90 μg kg^{-1} vs. <90 μg kg^{-1}) and different intervals between the first and second doses [≤3 h vs. >3 h (as recommended by the manufacturer)]. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and bleeding sites

Of the 132 AHA patients who received rFVIIa, 57 (43%) were female and 75 (57%) male. As previously reported [3–5], a bimodal age distribution was observed; a small peak occurred between 30 and 39 years ($n = 8$) with the main larger peak being observed between 70 and 79 years ($n = 52$). The median patient age and other characteristics are provided in Table 1.

The most common underlying conditions were autoimmune disease in 35 patients [including rheumatoid arthritis ($n = 13$), hypothyroidism ($n = 5$), pemphigoid/pemphigus ($n = 4$), systemic lupus erythematosus ($n = 3$) and idiopathic thrombocytopenic purpura ($n = 2$)], as well as malignant tumours in 16 patients [including gastrointestinal tumours ($n = 8$) and urological tumours ($n = 4$)]. No patients were pregnant at the time of treatment.

The most common bleeding site was intramuscular (40%), followed by subcutaneous (14%), intra-articular (9%), genitourinary (5%) and gastrointestinal (4%). Of the 371 bleeding episodes, 302 (81%) were treated with rFVIIa monotherapy and 69 (19%) were treated with rFVIIa + aPCC/FVIII.

rFVIIa dosing regimens

Table 2a shows details of rFVIIa use in the 302 bleeding episodes in the rFVIIa monotherapy group. Overall, the median (mean) values are as follows: each dose was 93.2 (99.5) μg kg^{-1}, the number of doses was 3.0 (11.6), the interval between the first and second doses was 3.0 (4.6) h and the duration of rFVIIa therapy was 2.0 (2.9) days. For intramuscular bleeding, the median (mean) number of doses was 5.0 (14.8), which was significantly higher than for other sites of bleeding ($P < 0.001$); the median (mean) duration of treatment was 2.0 (3.4) days, which was significantly longer than for other sites of bleeding ($P = 0.003$).

Table 2b shows details of rFVIIa use in bleeding episodes in the rFVIIa + aPCC/FVIII group. The interval between the first and second doses was 3.0 (4.3) h. These values were not significantly different between the two groups.

Efficacy

In the overall cohort, haemostasis was judged as markedly effective in 41.2% of bleeding episodes, effective in 9.7%, moderate in 41.0% and ineffective in 8.1%. There was no significant difference between the two groups (Table 3).

For anatomical locations where ≥10 bleeding episodes occurred, the 0–12 h response rate (the proportion of patients with either a markedly effective or effective response) was 59% for subcutaneous bleeding, 55% for intra-articular bleeding, 38% for intramuscular bleeding, 36% for gastrointestinal bleeding and 23% for genitourinary bleeding in the rFVIIa monotherapy group; and 53% for subcutaneous bleeding and 39% for intramuscular bleeding in the rFVIIa + aPCC/FVIII group.

The response rate was significantly better in patients who received an initial dose of ≥90 μg kg^{-1} than in those who received an initial dose of <90 μg kg^{-1}. The response rate tended to be better in patients with an interval between the first and second doses of ≤3 h than in those with an interval of >3 h, but this difference was not significant (Table 4). [Correction added on 13 October 2016, after initial online publication: In the preceding sentence, the expressions for the 3h interval were initially reversed and have been corrected.]

Analysis of the relationship between haemostatic efficacy and the interval from onset of bleeding to the first dose of rFVIIa showed a significantly higher response rate if rFVIIa was administered earlier after the onset of bleeding ($P < 0.0001$) (Fig. 1).

Adverse events

A total of 36 adverse events were recorded in 19 of the 132 patients, including 12 serious adverse events in six patients, four of whom died. Nineteen of the adverse events were laboratory abnormalities. The

Table 1. Characteristics of patients with acquired haemophilia A.

	Age <18 years ($n = 3$)		Age ≥18 years ($n = 129$)		All ($n = 132$)	
	Median	Range	Median	Range	Median	Range
Age (years)	10	(2–12)	74	(21–89)	73	(2–89)
Coagulation factor activity (%)	2	(1–4)	1	(0.1–92)	1	(0.1–92)
Inhibitor level (BU mL^{-1})*	7	(2–11.5)	30.6	(0–2400)	30	(0–2400)

*Due to the limited sensitivity of the Bethesda assay for values <0.6 BU, inhibitor values of 0 were obtained for patients who met diagnostic criteria for acquired haemophilia; please note that, during the recovery period, while inhibitor levels decreased below detectable levels, factor VIII activity had not yet recovered; BU, Bethesda Units.

Table 2. rFVIIa use in the (a) rFVIIa monotherapy group and (b) rFVIIa + aPCC/FVIII group.

		Dose (μg kg^{-1})			Number of doses				Duration of rFVIIa therapy (days)			
Site of bleeding	*n*	Median	Mean	IQR	Median	Mean	IQR	Max	Median	Mean	IQR	Max
(a)												
Intramuscular	110	94.1	97	(88.9–106.7)	5	14.8	(3.0–13.0)	315	2	3.4	(1.0–4.0)	45
Subcutaneous	33	100	104.1	(90.6–110.5)	3	8.4	(3.0–7.0)	64	1	2.3	(1.0–2.0)	14
Intra-articular	27	106.7	125.9	(106.7–126.3)	3	14.7	(2.0–12.0)	64	1	3.3	(1.0–3.0)	11
Genitourinary	11	90.6	99.6	(85.7–120.0)	8	15.9	(3.0–24.0)	60	2	4.2	(2.0–6.0)	14
Gastrointestinal	9	82.8	88.8	(82.8–86.8)	4	10.5	(3.5–15.0)	57	2	2.7	(1.0–3.0)	10
Intracranial	4	96.5	96.1	(91.5–100.7)	4.5	19.0	(2.0–34.5)	64	2	4.3	(2.0–6.5)	11
Oral	3	96.0	107.2	(96.0–129.7)	4	11.3	(3.5–20.5)	36	2.5	3	(1.5–4.5)	6
Intraperitoneal	2	87.8	87.8	(85.1–90.6)	19.5	19.5	(3.0–36.0)	36	4	4	(2.0–6.0)	6
Total*	280	93.2	99.5	(84.1–106.7)	3	11.6	(2.0–9.0)	315	2	2.9	(1.0–3.0)	45
(b)												
Intramuscular	31	96.0	106.1	(85.6–120.6)	6	16.3	(3.0–27.0)	56	2	3.6	(1.0–6.0)	12
Subcutaneous	17	89.1	99.9	(88.9–120.6)	4	9.2	(3.0–13.0)	32	2	3.3	(1.0–4.0)	13
Genitourinary	5	73.8	86.1	(73.8–85.6)	4	8.4	(4.0–4.0)	27	2	2.6	(1.0–2.0)	7
Gastrointestinal	4	90.8	87.9	(79.7–96.0)	4	9.8	(4.0–15.5)	27	2	3	(1.5–4.5)	7
Oral	1	96.0	96.0	(96.0–96.0)	3	3.0	(3.0–3.0)	3	1	1	(1.0–1.0)	1
Total†	66	89.6	100.8	(85.0–120.6)	5	13.4	(3.0–27.0)	56	2	3.5	(1.0–5.0)	13

*Includes 81 bleeding episodes at other sites. Twenty-two bleeding episodes with insufficient dosage information are not included.
†Includes eight bleeding episodes at other sites; information on rFVIIa dose was not available for three bleeding episodes.
IQR, interquartile range; rFVIIa, recombinant activated factor VII; aPCC, activated prothrombin complex concentrate.

Table 3. Comparison of haemostatic efficacy between the rFVIIa monotherapy and rFVIIa + aPCC/FVIII groups.

	Markedly effective <8 h	Effective 8–12 h	Moderate ≥12 h	Ineffective	Total	Response rate	*P* value chi-square
rFVIIa monotherapy, *n* (%)	129 (42.7)	26 (8.6)	120 (39.7)	27 (8.9)	302 (100.0)	155/302 (51.3)	0.8621
rFVIIa + aPCC/FVIII, *n* (%)	24 (34.8)	10 (14.5)	32 (46.4)	3 (4.3)	69 (100.0)	34/69 (49.3)	
Total, *n* (%)	153 (41.2)	36 (9.7)	152 (41.0)	30 (8.1)	371 (100.0)	189/371 (50.9)	

Response rate = (markedly effective + effective)/total.
aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

Table 4. Odds ratios (OR) for the response rate (300 bleeding episodes).

		OR	95% CI	*P* value
Initial dose (μg kg^{-1})	≥90	2.3	(1.4–3.9)	0.001
	<90			
Dosing interval (h)	≤3	1.5	(0.9–2.6)	0.136
	>3			

Response rate = (markedly effective + effective)/total. Bleeding episodes with insufficient dosage information are not included in this analysis.
CI, confidence interval.

adverse events involving abnormalities in at least one of the markers of disseminated intravascular coagulation (DIC) were decreased platelet count (n = 2), increased D-dimer level (n = 2), increased fibrin degradation product level (n = 1) and increased thrombin-antithrombin complex level (n = 1).

Twelve serious adverse events were reported in six patients, including investigator-reported pre-DIC – defined as the condition at least 1 week before the onset of DIC [16] – and acute cholecystitis in one patient; hepatic dysfunction and renal failure in one patient; investigator-reported DIC (two episodes) and sepsis in one patient; intestinal ischaemia, intestinal necrosis and hydrocephalus in one patient; interstitial pneumonia in one patient; and hypotension in one patient. The serious adverse events resulted in death in four patients (two with investigator-reported thromboembolic events and two without thromboembolic events).

Five serious thromboembolic events occurred in three patients (pre-DIC in one patient, two episodes of DIC in one patient and intestinal ischaemia and

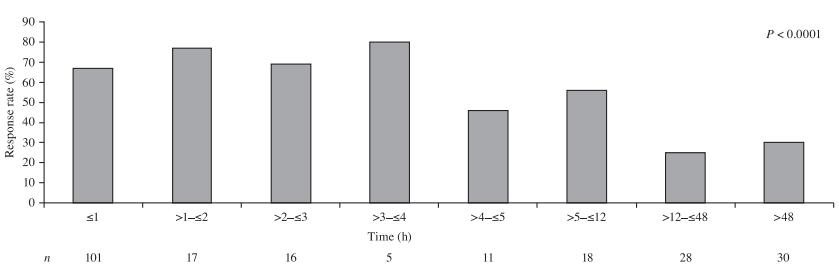

Fig. 1. Response rate according to the time from the onset of bleeding to the first dose of rFVIIa. Response rate = (markedly effective + effective)/total. rFVIIa, recombinant activated factor VII.

intestinal necrosis in one patient). The details of these events are described below.

Case 1. Two serious adverse events (pre-DIC and acute cholecystitis) occurred in an 87-year-old female with underlying cholelithiasis and chronic rheumatoid arthritis. The day after administration of one dose of rFVIIa for intramuscular bleeding in her upper arm, she developed acute cholecystitis. Her PT and activated partial thromboplastin time were prolonged at 15.2 and 80.2 s, respectively, and she had an investigator-reported diagnosis of pre-DIC. Her platelet count decreased from 424×10^3 to 331×10^3 μL^{-1}. Although the acute cholecystitis was considered to be associated with cholelithiasis, it was judged that a causal relationship between rFVIIa therapy and cholecystitis, with progression to pre-DIC, could not be ruled out.

Case 2. Three serious adverse events (sepsis and two episodes of DIC) occurred in an 81-year-old male who underwent lithotomy for underlying choledocholithiasis. After the lithotomy procedure, there was ongoing bleeding from the insertion site of the drainage tube, leading to a diagnosis of AHA. His postoperative course was complicated by aspiration pneumonia. rFVIIa was administered for more than 2 weeks. The platelet count decreased to 30×10^3 μL^{-1}, and DIC was diagnosed by the Investigator 16 days after the last dose of rFVIIa (however, no prolongation in PT or decrease in fibrinogen level was observed at that time). Although the DIC improved, according to the investigator, aspiration pneumonia recurred 45 days after the last dose of rFVIIa, at which time the platelet count decreased to 8×10^3 μL^{-1} and the fibrinogen level decreased to 45 mg dL^{-1} (recorded as the second episode of DIC). He died from what was reported as DIC and septic shock. The aspiration pneumonia was considered to have occurred because of reduced immunity due to long-term steroid therapy, leading to the development of sepsis and DIC. However, it was judged that a causal relationship between rFVIIa therapy and DIC could not be ruled out.

Case 3. Three serious adverse events (intestinal ischaemia, intestinal necrosis and hydrocephalus) occurred in a 70-year-old male on oral steroid medication with underlying suspected Hashimoto's encephalopathy, who developed subcutaneous bleeding that resulted in a diagnosis of AHA. He developed a pontine haemorrhage, and received only one dose of rFVIIa. His obstructive hydrocephalus, which resulted from the bleed obstructing the flow of cerebrospinal fluid, progressed and he developed aspiration pneumonia because of his decreased level of consciousness. Six days after the pontine haemorrhage, a lumbar spinal catheter was inserted for cerebrospinal fluid drainage, and three doses of rFVIIa were administered. The drainage catheter was removed after 10 days because it was occluded. At the time of removal, two intravenous doses of rFVIIa were administered. Six days after the last dose of rFVIIa, he developed serious intestinal ischaemia and necrosis and died the following day. The Investigator judged that a causal relationship between rFVIIa therapy and intestinal ischaemia/necrosis could not be ruled out; no other factors were identified that could have caused these events.

Death occurred in two other patients with serious non-thromboembolic adverse events; details are described below.

Case 4. One serious adverse event (hypotension) occurred in a 76-year-old male with underlying prostate cancer who developed intramuscular bleeding in the left thigh, subcutaneous bleeding and gingival bleeding. He was treated with red blood cell and FVIII transfusions and there was a transient decrease in his haemoglobin level to 3.8 g dL^{-1}. After three doses of rFVIIa, his condition stabilized. Four days after the last dose of rFVIIa, he developed sudden hypotension. He was treated with blood transfusion, fluid infusion and vasopressor therapy, but his hypotension did not improve and he died 2 days later. It was judged that a causal relationship between rFVIIa therapy and the patient's death could not be ruled out.

Case 5. Two serious adverse events (hepatic dysfunction and acute renal failure) occurred in a 75-year-old male with underlying pemphigus and pneumonia who received four doses of rFVIIa over a 2-month period for bronchoscopy, arterial puncture and central venous catheterization. He also received multiple drug therapy for his pneumonia. Twenty-four days after the last dose of rFVIIa, he developed hepatic dysfunction. During the following month, he received a total of six doses of rFVIIa for melena, intra-oral bleeding and bleeding from an arterial puncture. On the day of his last dose of rFVIIa, he developed acute renal failure and died, despite ongoing treatment. Although multiple drugs may have contributed to his deterioration, it was judged that a causal relationship between rFVIIa therapy and the patient's death could not be ruled out.

Discussion

These Japanese AHA patient surveillance data show that bleeding was controlled (haemostatic effect judged as markedly effective, effective or moderate) in 92% of bleeding episodes, similar to previously reported results (Table 5) [6,11,12]. Our analysis of the relationship between haemostatic efficacy and the interval from the onset of bleeding to the first dose of rFVIIa shows that there was a significantly higher

response rate when rFVIIa was administered earlier after the onset of bleeding. Overall, a 0–12 h ('markedly effective' or 'effective') treatment response to rFVIIa occurred in 50.9% of bleeding episodes (189/371); however, the 0–12 h response rate was 67–80% in patients who received the first dose of rFVIIa <4 h after the onset of bleeding, vs. 25–56% in patients who received the first dose of rFVIIa ≥4 h after the onset of bleeding (Fig. 1). These data suggest that prompt initiation of treatment is important to haemostatic efficacy.

The Japanese surveillance data included 69 bleeding episodes in 34 patients who received rFVIIa in combination with aPCC or FVIII. As concomitant therapy (either before, after or simultaneous with rFVIIa) may affect the assessment of rFVIIa effectiveness, haemostatic efficacy was assessed separately in the rFVIIa monotherapy and rFVIIa + aPCC/FVIII groups. No significant difference in haemostatic efficacy was found between these two groups, indicating that our analysis did not demonstrate any improvement in haemostasis following the addition of aPCC/FVIII. However, as additional therapy is more likely to be used in cases of severe or refractory bleeding, the ability to compare efficacy retrospectively between rFVIIa + aPCC/FVIII therapy and rFVIIa monotherapy is limited.

While a difference was observed between the mean and median number of doses, this is due to the data being skewed (with some patients requiring a higher number of doses); the median number of rFVIIa doses reported in the Japanese surveillance cohort appears to be lower than that in previous reports (Table 5) [6,12].

Hay *et al.* [6] retrospectively evaluated the haemostatic efficacy of rFVIIa in 78 bleeding episodes in 38 AHA patients enrolled in compassionate and emergency use programmes at 32 institutions in the European Union, Canada, USA, Australia and Malaysia from 1990 to 1995. Of these, rFVIIa was used as first-line treatment for 14 bleeds in six patients, with a response rate (haemostatic effect judged to be markedly effective, effective or moderate) of 100% within 24 h of initiation of treatment. Sumner *et al.* [11] analysed data regarding the haemostatic efficacy of rFVIIa from the above-mentioned compassionate use programmes (100 bleeding episodes in 61 patients in the European Union, USA and Asia from 1988 to 1999), the Haemophilia and Thrombosis Research Society Registry in the USA (13 bleeding episodes in nine patients from 1999 to 2005) and published reports (91 bleeding episodes in 69 patients from 1999 to 2005). These combined data showed a response rate to first-line treatment with rFVIIa of 95%. Baudo *et al.* [12] analysed data collected by the European Acquired Haemophilia Registry (EACH2) from 117 institutions in 13 European Union countries

Table 5. Summary of key findings from the Japanese postmarketing surveillance study and published data on haemostatic efficacy of rFVIIa in AHA patients.

	Number of patients	Number of episodes analysed	Dose, median (μg kg^{-1})	Total number of doses per patient, median	Bleeding control response rate following rFVIIa used as first-line treatment (%)*
Japanese postmarketing surveillance study‡	132	371 bleeds	rFVIIa monotherapy: 93.2; +aPCC/FVIII, 89.6	rFVIIa monotherapy: 3; +aPCC/FVIII, 5	91 (rFVIIa monotherapy)
Hay *et al.* [6]	38†	78 bleeds†	90.4† (range: 45–181)	28† (range: 1–541)	100
Sumner *et al.* [11]	139	204 bleeds†	NR	NR	95
Baudo *et al.* [12]‡ EACH2	174	NR	90 (IQR: 84.71–102.86)	12 (IQR: 3–35)	91.2
Ma *et al.* [17]	68	139 bleeds	90† (IQR: 87.6–100)	3 (IQR: 2–14)	87
Ma *et al.* [18]	17	30	399 (range: 44–6229)	4 (range: 1–77)	91
Lentz *et al.* [13]‡ AHS§	65	NR	NR	NR	NR

*Note: definition of response rate differs between studies.
†Data are for bleeds treated with rFVIIa as first- or second-line treatment.
‡All data provided are for bleeds treated with rFVIIa as first-line treatment.
§AHS was a passive-surveillance website in the USA, designed to support the postmarketing commitment by obtaining data on rFVIIa-exposed patients and the presence/absence of thrombotic events. No specific treatment data were captured.
AHA, acquired haemophilia A; AHS, Acquired Haemophilia Surveillance project; aPCC, activated prothrombin complex concentrate; EACH2, European Acquired Haemophilia Registry; FVIII, factor VIII; IQR, interquartile range; NR, not reported; rFVIIa, recombinant activated FVII.

from 2003 to 2008 [5], and found that rFVIIa was used as first-line treatment in 174 patients. Bleeding was considered to be controllable after rFVIIa therapy in 91% of the patients.

Data were recently reported on 139 rFVIIa-treated bleeding episodes in 68 acquired haemophilia patients from the Haemostasis and Thrombosis Research Society (HTRS) Registry [17]. Haemostasis was achieved in 135 episodes (97%), while only four bleeding episodes (3%) required change to another haemostatic agent. Bleeding stopped in 87% of episodes treated with first-line rFVIIa and in 67% of episodes when rFVIIa was the second line of treatment. Dosing of rFVIIa in the HTRS Registry was similar to the current data, with fewer outliers. Furthermore, data on rFVIIa use in the perioperative management of AHA patients from the HTRS Registry were recently reported for the first time [18]. In total, 17 patients were treated for 30 surgeries (22 with efficacy evaluations, 24 with dosing information), including six procedures performed in two patients during ongoing postoperative management of prior procedures. Overall, efficacy was reported as excellent/good, or no other haemostatic medications needed, in 20 of 22 procedures (91%) with a reported haemostatic outcome.

While the median interval between the first and second doses was 3.0 h in both the Japanese surveillance data and the EACH2 Registry data, the total number of doses was lower in the Japanese surveillance data [median: 3; interquartile range (IQR): 2–9 vs. median 12; IQR 3–35; EACH2 Registry data; 12]. However, bleeding was classified as severe in 90% of episodes in the EACH2 Registry data, but in only 47% of episodes in the Japanese surveillance data, which may explain the lower number of doses in these data.

In the Japanese surveillance data, a total of 36 adverse events were reported in 19/132 patients (14.4%). There were five serious thromboembolic events in three patients (2.3%), including three episodes of DIC in two patients and intestinal ischaemia and intestinal necrosis in one patient. This is similar to the incidence of thrombotic events reported in the EACH2 Registry data [12]. All three patients in this study with thromboembolic events were ≥70 years old and had concurrent infection (acute cholecystitis in one patient and pneumonia in two patients), suggesting that elderly patients and/or those with infection may have a higher risk of thromboembolic events. In the EACH2 Registry, thrombotic events related to haemostatic therapy were reported in 11/307 patients (3.6%), including thrombotic events related to rFVIIa therapy in 5/174 patients (2.9%) [12]. Six cases were myocardial infarction, one was a stroke and four were venous thromboembolism. In the HTRS Registry, only one thromboembolic event was reported among 139 rFVIIa-treated bleeds: a transient ischaemic attack occurred in a 31-year-old postpartum woman with eclampsia and cerebral vasculitis who was treated with 110 doses at 2-h intervals; this event was reported as unrelated to rFVIIa treatment by the investigator [17]. No thromboses were reported during 30 rFVIIa-treated surgical procedures reported in the HTRS Registry [18].

The Acquired Haemophilia Surveillance (AHS) project was designed as a passive-surveillance website in the USA to augment data on rFVIIa-exposed patients and the presence/absence of thrombotic adverse events. The AHS adds to the body of data recorded in the HTRS registry without burdens of registry ethics approvals, but the limited reporting was only safety-focused (the report identified 65 cases of AHA treated with rFVIIa between 2008 and 2011, none of which were associated with thrombotic adverse events) [13].

In conclusion, our analysis of the use, efficacy and safety of rFVIIa for the treatment of bleeding episodes in AHA patients in Japan found that the rates of haemostatic efficacy and adverse events were comparable to those previously reported in multinational studies in other countries. Most AHA patients were elderly and had comorbidities that increased the risk of adverse events. Physicians should therefore closely monitor patients for thromboembolic and other events, particularly patients with infection. This is the largest single-country study of rFVIIa therapy in AHA patients reported to date. The results suggest that doses of 90–120 μg kg^{-1} and prompt initiation of treatment may be important to achieve good bleeding control.

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Appendix

Institutions involved in the postmarketing surveillance

- NTT Osaka Hospital
- Iwaki Kyouritsu Hospital
- Toyota Memorial Hospital
- Oji General Hospital
- Kaizuka Hospital
- Midori Hospital
- Teine Keijinkai Hospital
- Ogikubo Hospital
- Azusawa Hospital
- Kobari General Hospital
- Otowa Hospital
- Marutacho Hospital
- Tokorozawa Central Hospital
- Shinyukai Watanabe Hospital
- Seijinkai Shimizu Hospital
- Fukuoka Tokushukai Medical Center
- Kisogawa Hospital
- Gamagori City Hospital
- Kansai Medical University Takii Hospital
- Nishimino Hospital
- Gifu Municipal Hospital
- Kinan Hospital Kumiai Kinan Hospital
- Tenri Hospital
- Nara Medical University Hospital
- Ehime University Hospital
- Okayama University Hospital
- Gifu University Hospital
- Kanazawa University Hospital
- Hiroshima University Hospital
- Hirosaki University School of Medicine & Hospital
- Saga University Hospital
- Mie University Hospital
- Yamaguchi University Hospital
- Nagasaki University Hospital
- Nagoya University Hospital
- Sanyudo Hospital
- Aiiku Hospital
- Kurashiki Central Hospital
- Saitama Medical Center
- Miura City Hospital
- University of Occupational and Environmental Health
- Asahikawa City Hospital
- Yokkaichi Municipal Hospital

- Steel Memorial Muroran Hospital
- Nagoya Memorial Hospital
- Tomigusu Hospital
- Saiseikai Karatsu Hospital
- Saiseikai Matsusaka General Hospital
- Mito Saiseikai General Hospital
- Chibaken Saiseikai Narashino Hospital
- Seirei Hamamatsu General Hospital
- Social Insurance Kyoto Hospital
- Yamanashi Hospital of Social Insurance
- Kasugai Municipal Hospital
- Surugadai Nihon University Hospital
- Juntendo University Shizuoka Hospital
- Showa University Hospital
- St. Marianna University School of Medicine Hospital
- Okayama Citizen's Hospital
- Odate Municipal General Hospital
- Otsu Municipal Hospital
- Kobe City Medical Center West Hospital
- Kakogawa City Hospital Organization
- Saga-ken Medical Centre Koseikan
- Tokyo Medical University Hospital
- Jikei University Hospital
- National Hospital Organization Matsumoto Medical Center
- National Hospital Organization Okayama Medical Center
- National Hospital Organization Kanazawa Medical Center
- National Hospital Organization Kumamoto Medical Center
- National Hospital Organization Hiroshima-Nishi Medical Center
- National Hospital Organization Takasaki General Medical Center
- National Hospital Organization Miyakonojo Medical Center
- National Hospital Organization Toyohashi Medical Center
- Wakayama Rosai Hospital
- Japanese Red Cross Society Saitama Red Cross Hospital
- Japanese Red Cross Kyoto Daini Hospital
- Japanese Red Cross Ogawa Hospital
- Japanese Red Cross Society Onoda Hospital
- Matsue Red Cross Hospital
- Matsuyama Red Cross Hospital
- Japanese Red Cross Narita Hospital
- Japanese Red Cross Shizuoka Hospital
- Date Red Cross Hospital
- Japanese Red Cross Society Osaka Red Cross Hospital
- Japanese Red Cross Society Wakayama Medical Center
- Himeji Medical Co-Op Kyoritsu Hospital
- Toyama Prefectural Central Hospital
- Toyama City Hospital
- Hyogo College of Medicine Hospital
- Hyogo Prefectural Awaji Medical Center
- Hyogo Prefectural Amagasaki Hospital
- Toyohashi Municipal Hospital
- Hokkaido Social Insurance Hospital

