

REVIEW ARTICLE

Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal

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Summary. Acquired haemophilia is a rare bleeding disorder usually caused by the spontaneous formation of inhibitory antibodies to coagulation FVIII. The disease occurs most commonly in the elderly, and although acquired haemophilia may be associated with a variety of underlying conditions, up to 50% of reported cases are idiopathic. Treatment options have traditionally involved human FVIII or FIX replacement therapy (if the inhibitor titre allows), porcine FVIII or the use of activated prothrombin complex concentrates. Recombinant activated coagulation FVII (rFVIIa) was available on an emergency and compassionate use basis from 1988 to 1999 at sites in Europe and North America. It has been registered in Europe for use in treating acquired haemophilia since 1996 and has recently been licensed for this indication in the United States. By

directly activating FX on the surface of activated platelets at the site of injury (thereby bypassing FVIII and FIX), rFVIIa can circumvent the actions of inhibitory antibodies present in acquired haemophilia patients. This paper provides an overview of experiences with rFVIIa for the treatment of acquired haemophilia from the NovoSeven® compassionate and emergency use programmes (1989–1999), the Hemophilia and Thrombosis Research Society Registry, and independent published reports from January 1999 to September 2005. rFVIIa has been reported to provide safe and effective haemostasis as a first line therapy in patients of all ages for a variety of surgical and non-surgical bleeding situations.

Keywords: acquired haemophilia, bleeding disorder, NovoSeven®, recombinant FVIIa

Introduction

Acquired haemophilia is a rare and often severe bleeding disorder caused by the spontaneous development of inhibitory antibodies to coagulation FVIII or, more rarely, FIX in individuals with no bleeding history [1–8]. These auto-antibodies interfere with the factor's procoagulant activity and lead to a moderate to severe bleeding diathesis [4].

Treatment options for acute bleeding episodes in patients with low-titre inhibitors (≤ 5 BU) include human FVIII or FIX concentrates and 1-deamino-8-D-arginine vasopressin (DDAVP) [9–11]. Activated pro-thrombin complex concentrates (aPCCs) have

also been used to achieve haemostasis in patients with high-titre inhibitors (>5 BU) as has porcine FVIII, although this is currently unavailable. The management of acute bleeding episodes in acquired haemophilia patients has been hampered by the lack of prospective studies (due to the rare nature of the disease), the poor correlation between inhibitor titre and therapy response (i.e. bleeding severity doesn't correlate well with FVIII levels or inhibitor titre due to non-linear inhibitor reaction kinetics, unlike those characterizing alloantibody formation in congenital haemophilia), the side-effect profiles of the treatment options and the theoretical risk of infectious disease transmission with plasma-derived products [12–15].

Recombinant activated FVIIa (rFVIIa) offers an alternative treatment option for patients with acquired haemophilia. As a recombinant product, rFVIIa is not derived from human or animal plasma and is administered as a small volume bolus dose. Recombinant FVIIa activates FX directly on the surface of activated

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platelets at the site of injury [16], bypassing FVIII and FIX and thus circumventing the actions of inhibitory antibodies developed in these patients. Recombinant FVIIa also enhances the natural coagulation pathway by boosting local thrombin generation at sites of injury where tissue factor is exposed and activated platelets are localised, potentially reducing the risk for systemic thrombotic complications [16,17].

Recombinant FVIIa has been reported to be clinically effective in patients with acquired haemophilia participating in the NovoSeven compassionate and emergency use programmes [18] as well as in patients whose data are filed with the Hemophilia and Thrombosis Research Society Registry (HTRS). In addition, since the first availability of rFVIIa for the clinical treatment of haemophilia A or B patients with inhibitors, many published studies and case reports have emerged assessing the safety and efficacy of its use for treating bleeds in patients with acquired haemophilia. Recombinant FVIIa is approved for the treatment of bleeding episodes and for the prevention of bleeding in connection with surgery or invasive procedures in patients with acquired haemophilia in Europe, and has recently been licensed in the US for this indication.

The difficulty of performing prospective clinical trials in rare diseases such as acquired haemophilia necessitates the wider collection of data from available sources to increase overall understanding and improve patient treatment. This paper reviews the rFVIIa experience in patients with acquired haemophilia from the NovoSeven[®] compassionate and emergency use programmes, the HTRS registry, and independent published reports.

Methods

Recombinant FVIIa was available on an emergency and compassionate use basis from 1988 to 1999 for the open-label treatment of patients with haemophilia and inhibitors to FVIII or FIX, acquired antibodies to FVIII or FIX, or FVII-deficiency for life-threatening haemorrhage and haemostasis maintenance during surgery when alternative therapies were unavailable or had already failed to stop haemorrhage, or when complications were foreseen [18]. We examined the records of a total of 365 patients enrolled in compassionate use programmes (four studies) operating in North America, Europe and Asia between 1988 and 1999. Sixty-one patients (16.7%) were diagnosed with acquired haemophilia and are considered here.

The HTRS Registry was implemented in March 1999 as a United States national data repository for patients with coagulation disorders. Clinical, socio-demographic, and quality-of-life patient data are

collected from Hemophilia Treatment Centers in an effort to better understand the pathophysiology, current clinical management, and outcomes of patients with these disorders. Patients of any age with the following characteristics are eligible for enrolment into the HTRS database: congenital coagulation factor deficiencies, acquired inhibitors, platelet function disorders, von Willebrand disease (acquired or congenital), or treatment with rFVIIa, irrespective of the underlying coagulopathy. Physician-entered data are submitted to the HTRS registry online, and each centre has on-line access to both centre-specific summary data as well as aggregate data from all participating centres. We examined the records of the 196 patients with 1931 bleeding episodes that were entered into the HTRS database between March 1999 and July 2005. Nine patients with acquired haemophilia were treated with rFVIIa and are considered here.

For the independent publications assessed in this paper, a cross-database literature search (BIOSIS, Current Contents, EMBASE, and Medline) from January 1999 through September 2005 was used to identify independent reports of acquired haemophilia patients treated with rFVIIa. The search terms 'acquired and haemophilia' and 'acquired and inhibitor(s)' were used with each of the following: 'recombinant activated FVII' (without and without 'human'), 'rFVIIa', 'rhFVIIa' and 'NovoSeven.' Only English language literature was considered and publications included only those where patients had inhibitors to FVIII or FIX and were treated with rFVIIa. Published reports for patients included in the compassionate use programmes or HTRS registry were excluded. Forty-three publications, including scientific meeting abstracts and one electronic case publication, met inclusion criteria and describe the use of rFVIIa in 69 acquired haemophilia patients with 91 reported bleeding episodes [3,19–60].

The different sources examined in this manuscript assessed rFVIIa efficacy and safety similarly, but not identically. All efficacy and safety assessments examined here are those reported by the physicians/authors. For the compassionate use programmes, physicians documented clinical rFVIIa response at 8 and 24 h post-treatment initiation, and a final assessment was made upon therapy termination. For acute bleeding episodes, clinical response was assessed as: treatment effective, partially effective, ineffective, patient died, patient withdrew consent or patient suffered an adverse experience leading to discontinuation of rFVIIa treatment. For surgical procedures, patients were evaluated as: no bleeding or less than normal bleeding (effective), equivalent to normal bleeding

(partially effective), or greater than normal bleeding (ineffective). Post-operatively, bleeding was evaluated as: not visible or none (effective), minimal oozing (partially effective), overt oozing or frank bleeding (ineffective). Safety was assessed by adverse event reporting throughout the treatment period.

In the HTRS Registry, efficacy was reported after the last rFVIIa dose or 72 h after the first rFVIIa dose (prior to 31 December 2003; the first registry version). For both versions, bleeding outcome was assessed as: bleeding stopped, bleeding slowed but did not stop, or no improvement. Safety was again assessed by adverse event reporting throughout the treatment period.

For the published literature, episodes for which the treating physician described a successful outcome (i.e. 'bleeding stopped,' 'treatment was successful,' 'haemostasis was achieved,' 'treatment was effective,' and treatment was 'good' or 'excellent') were scored as effective. Partial efficacy was scored when the physician used the specific term 'partially effective' or when response was described as 'slow' or 'gradual.' Episodes for which the physician described the treatment as 'ineffective' or where bleeding continued were scored as ineffective. Safety assessments were those reported by the authors.

Results

Compassionate use programmes

Subject demographics for the 61 acquired haemophilia patients from the compassionate use programmes are summarized in Table 1. The mean patient age was 60 years (range 2–99), and the number of male (34) and female (27) patients was similar. Ethnic origin was unavailable for 64% of treated patients.

Table 1. Patient characteristics.

	Compassionate use	HTRS registry	Published literature	Total
Patients	61	9	69	139
Age (years)				
Mean	60	63	60	60
Range	2–99	31–81	2–92	2–99
Gender, <i>n</i> (%)				
Male	34 (56)	3 (33)	31 (45)	68 (49)
Female	27 (44)	2 (22)	36 (52)	64 (46)
Unknown	–	4 (44)	2 (3)	6 (4)
Ethnicity, <i>n</i> (%)				
Caucasian	10 (16)	2 (22)	4 (6)	16 (12)
African-American	8 (13)	1 (11)	2 (3)	11 (8)
Other	4 (7)	2 (22)	3 (4)	9 (7)
Unknown	39 (64)	4 (44)	60 (87)	103 (74)

Table 2. Number and type of bleeding episodes.

Bleeding type	Compassionate use	HTRS registry	Published literature	Total
Surgical	32	3	23	58
Non-surgical				
Spontaneous	62	6	62	130
Traumatic	6	2	2	10
Other	–	2*	–	2
Not reported	–	–	4	4
Total	100	13	91	204

*One patient had an unspecified type of bleed, and another had one bleeding episode that was both spontaneous and surgical at two locations with one efficacy assessment.

A total of 100 bleeding episodes (68 non-surgical, 32 surgical) were reported in these 61 patients (Table 2). Most patients (42/61, 68.9%) had a single bleeding episode treated with rFVIIa (range = 1–7), and most bleeding episodes occurred at sites categorized by the investigator as peripheral muscle (*n* = 23), abdominal cavity (*n* = 19) or 'other' (*n* = 41). 'Other' locations included surgical sites, gastrointestinal sites and muscle. Treatment regimens were similar for different types of bleeding episodes; the mean dose for non-surgical episodes was 88.3 $\mu\text{g kg}^{-1}$ (range = 65.6–124.9) while that for surgical episodes was 89.9 $\mu\text{g kg}^{-1}$ (range = 30.8–197.4). Treatment duration was also similar across bleeding types, with a mean duration of non-surgical bleeding episodes of 6.1 days (range = 1–33) and a mean duration of surgical bleeding episodes of 6.3 days (range = 1–33).

Forty-four bleeding episodes were treated using rFVIIa as a first line therapy (no prior haemostatic agents used). Of those episodes for which efficacy data were available, rFVIIa treatment was considered effective or partially effective in 95% (38/40). For those bleeding episodes treated unsuccessfully with other haemostatic agents prior to rFVIIa, treatment was considered effective or partially effective in 83% (39/47; Table 3).

Concomitant haemostatic medications were unreported for two of the four trials comprising the compassionate use programmes. In those trials for which data are available, 29 of 44 (66%) patients received concomitant haemostatic medications. Anti-fibrinolytic agents were the most commonly used, administered in 37 of those patients receiving concomitant medication, and some patients received more than one type of medication.

Overall, treatment with rFVIIa was determined to be effective or partially effective in 88.5% (77/87) of bleeding episodes for which efficacy data were available, and ineffective in 11.5% (10/87) of episodes (Table 4). Examined by bleeding type,

Data source use of rFVIIa	No. of bleeding episodes*	Effective <i>n</i> (%)**	Partially effective <i>n</i> (%)**	Ineffective <i>n</i> (%)**
All sources (total)	182	136 (74.7)	25 (13.7)	21 (11.5)
First-line treatment	103	86 (83)	12 (12)	5 (5)
Salvage treatment	73	48 (66)	10 (14)	15 (21)
Not reported	6	2 (33)	3 (50)	1 (17)
Comp. use (total)	87	62 (71.3)	15 (17.2)	10 (11.5)
First-line treatment	40	29 (73)	9 (23)	2 (5)
Salvage treatment	47	33 (70)	6 (13)	8 (17)
HTRS registry (total)	11***	5 (45.5)	5 (45.5)	1 (9)
First-line treatment	2	1 (50)	–	1 (50)
Salvage treatment	4	2 (50)	2 (50)	–
Not reported	5	2 (40)	3 (60)	–
Published lit. (total)	84	69 (82)	5 (6)	10 (12)
First-line treatment	63	57 (90)	3 (5)	3 (5)
Salvage treatment	21	12 (57)	2 (10)	7 (33)

*For which efficacy data are available.

**% of episodes for which efficacy data are available.

***One patient received rFVIIa for haemostasis maintenance only and was excluded from efficacy analyses.

Table 3. Treatment effectiveness by rFVIIa use.

Data source	No. episodes	Excellent/effective <i>n</i> (%)*	Partially effective <i>n</i> (%)*	Ineffective <i>n</i> (%)*
All data sources	182	136 (74.7)	25 (13.7)	21 (11.5)
Surgical	57	36 (63)	13 (23)	8 (14)
Non-surgical	124	99 (80)	12 (10)	13 (10)
[Spontaneous]	115	92 (80)	10 (9)	13 (11)
[Trauma]	9	7 (78)	2 (22)	–
Unspecified	1	1 (100)	–	–
Compassionate use	87	62 (71.3)	15 (17.2)	10 (11.5)
Surgical	31	17 (55)	10 (32)	4 (13)
Non-surgical	56	45 (80)	5 (9)	6 (11)
[Spontaneous]	50	40 (80)	4 (8)	6 (12)
[Trauma]	6	5 (83)	1 (17)	–
HTRS	11	5 (45.5)	5 (45.5)	1 (9)
Surgical	3	1 (33)	1 (33)	1 (33)
Non-surgical	7	3 (43)	4 (57)	–
[Spontaneous]	5	2 (40)	3 (60)	–
[Trauma]	2	1 (50)	1 (50)	–
Unspecified	1	1 (100)	–	–
Publications	84	69 (82)	5 (6)	10 (12)
Surgical	23	18 (78)	2 (9)	3 (13)
Non-surgical	61	51 (84)	3 (5)	7 (11)
[Spontaneous]	60	50 (83)	3 (5)	7 (12)
[Trauma]	1	1 (100)	–	–

*% of episodes for which efficacy data are available.

Table 4. rFVIIa efficacy by bleeding type.

rFVIIa treatment was rated effective or partially effective in 89% (50/56) of non-surgical and 87% (27/31) of surgical bleeding episodes for which efficacy data were available (Table 4).

The mean time to treatment from bleeding onset to first rFVIIa dose was determined in non-surgical bleeding episodes for each outcome (effective, partially effective, ineffective) in the compassionate use programmes but was not reported in the published

literature or the HTRS registry. The time to treatment ranged from 1 to 29 days for effective outcomes (mean = 7.09 days), to 1–67 days for ineffective outcomes (mean = 27.7 days).

Ninety-three adverse events (AE) were reported for 34 patients. Pyrexia (8.6%), vomiting (6.5%), and headache (3.2%) were the most commonly reported (each representing >3% of total recorded AE). Six thrombotic events were experienced by four patients:

cerebrovascular accident, pulmonary embolism and deep vein thrombosis (all experienced by a single patient with acquired inhibitors to FVIII), as well as cardiac arrest (one patient, one event), cerebral artery occlusion (one patient one event) and cerebrovascular accident (one patient one event). All four patients died. Sixteen total deaths were reported and most were attributed by the physicians to underlying disease or conditions (14/16, 88%).

The Hemophilia and Thrombosis Research Society Registry

Subject characteristics for the nine HTRS registry patients with acquired haemophilia treated with rFVIIa are summarized in Table 1. The mean patient age was 63 years (range: 31–81). Gender and ethnicity were unreported for 44.4% of patients.

Thirteen bleeds (nine patients) included three surgery-related, six spontaneous, two trauma-related, and two 'other' episodes (one was unspecified, and the other was both surgical and spontaneous at two locations with a single efficacy assessment; Table 2). Seven of nine (78%) patients were treated for a single bleeding episode. Bleeding locations included the head ($n = 1$), the muscle ($n = 5$), the leg and the arm ($n = 1$) and the mouth ($n = 1$). Locations for five bleeding episodes were unreported.

Recombinant FVIIa was used as a first line treatment for two bleeding episodes (two patients), and as salvage therapy for five bleeding episodes (five patients). Concomitant medication information was unknown for six episodes (three patients). Concomitant medications included FVIII and aPCCs (one patient, one bleeding episode), FFP (one patient, one bleeding episode), and porcine FVIII (three patients, three bleeding episodes).

Bolus doses from 60 to 160 $\mu\text{g kg}^{-1}$ rFVIIa were used for all bleeding episodes. Dose ranges/regimens were similar for spontaneous, surgery, trauma and 'other' bleeding episodes. One patient received rFVIIa to maintain haemostasis after a bleeding episode had been controlled using porcine FVIII, and was therefore excluded from rFVIIa efficacy analysis. rFVIIa treatment was deemed effective or partially effective in 90% of those bleeding episodes for which efficacy data were reported (Table 4). Examined by bleeding type, rFVIIa treatment was effective or partially effective in two-thirds of surgical and 100% of non-surgical bleeding episodes for which data were available (Table 4). A total of four AE (including two thrombotic) were reported by four patients. These include subdural haematoma ($n = 1$), coma

($n = 1$), extension of a thigh haematoma ($n = 1$) and acute cerebrovascular accident ($n = 1$). No deaths were reported.

Independent publications

Sixty-nine acquired haemophilia patients receiving rFVIIa for 91 reported bleeding episodes met inclusion criteria. The number of rFVIIa-treated bleeding episodes was unreported for three patients [40,47,55]. Subject characteristics for the 69 patients are summarized in Table 1. The mean patient age was 60 years (range: 2–92) and there were similar numbers of male ($n = 31$) and female ($n = 36$) patients. Patient ethnic background information was not provided in the majority (87%) of the publications. Sixty-seven patients were reported to have developed inhibitory antibodies to FVIII, one patient had developed FIX antibodies [46], and the type of inhibitory antibodies in one patient was not reported [40].

Approximately one-third of the patients ($n = 23$) had no underlying predisposition to acquired haemophilia (idiopathic). Neoplasia ($n = 13$) and immunological disorders ($n = 8$) were the most commonly reported underlying conditions. All other underlying conditions reported occurred in fewer than 10% of patients.

The most frequent use of rFVIIa was for the treatment of non-surgical bleeding episodes (spontaneous or trauma-associated; $n = 64$, 70%; Table 2). Such uses of rFVIIa included the treatment of mucosal (gastrointestinal, epistaxis), subcutaneous, intramuscular, soft tissue and retroperitoneal bleeding, and haematuria. Most patients experienced a combination of these types of bleeding episodes.

Recombinant FVIIa was also used to treat or prevent bleeding during/following a number of surgical procedures ($n = 23$, 25%; Table 2), including haemostatic coverage during venipuncture and subcutaneous port insertion, abscess drainage, craniotomy, fasciotomy, papillosphincterectomy, surgical haematoma decompression, lung resection, pacemaker insertion and mastectomy. Other surgical uses of rFVIIa included the management of postsurgical bleeding and incision site bleeding.

Recombinant FVIIa was used as first-line therapy for 63 bleeding episodes and was considered effective or partially effective in 95% ($n = 60$). For the 21 bleeding episodes for which rFVIIa was used as salvage therapy, treatment was considered effective or partially effective in 67% ($n = 14$; Table 3). Information on the timing of administration of other haemostatic agents used in treating a bleeding

episode in relation to rFVIIa treatment was unknown for seven bleeding episodes.

The use of concomitant haemostatic agents was reported for 44 patients [3,19–39,41–47,49,50,52–54,57–60]. The most commonly reported haemostatic agents were activated prothrombin complex concentrates (seven patients), FVIII concentrates (seven patients), porcine FVIII (seven patients), fresh frozen plasma (five patients) and tranexamic acid (four patients). FIX concentrate, desmopressin, epsilon-aminocaproic acid and fibrin sealant were each reported for one patient, and some patients were treated with more than one other haemostatic agent.

Recombinant FVIIa dose ranges/regimens were similar for both surgical and non-surgical bleeding episodes, administered either as bolus injection (46–150 $\mu\text{g kg}^{-1}$ at 2–24 h intervals) or continuous infusion (8–50 $\mu\text{g kg}^{-1} \text{h}^{-1}$). Treatment duration across bleeding types was also similar; most treatments lasted <7 days for both surgical and non-surgical episodes.

Recombinant FVIIa was determined to be effective or partially effective in 88% ($n = 74$) of those bleeding episodes for which efficacy data are available and ineffective in 12% ($n = 10$; Table 4). Percentages for surgical (87%, $n = 20$) and non-surgical bleeding episodes (89%, $n = 54$) were similar (Table 4).

Recombinant FVIIa treatment was reported 'safe', 'without side effects', 'no adverse events/effects observed', 'no deleterious side effects observed' or 'no side effects seen' in 26% ($n = 11$) of the publications. Twenty publications (47%) did not specify safety outcome, although no specific adverse events were reported in these publications. Seventeen adverse events were reported in seventeen patients. These include cerebral ischemia (one patient) [3], myocardial infarction (one patient) [38], cerebral infarction (two patients) [26,51], melena (one patient) [26], death (10 patients) [20,28,30,32,35,49], cardiac arrest (one patient) [60] and one case listed as alopecia, depression, weight gain and hirsutism [57]. Four of the 17 adverse events were thrombotic in nature (cerebral ischemia [3], myocardial infarction [38], and two cerebral infarctions [26,51]) and a total of 15 deaths (death as an outcome) were reported, three of which were associated with thrombotic adverse events [26,38,51]. Most deaths were attributed by the authors to underlying disease or other therapies (13/15) and 11/15 deaths occurred after rFVIIa treatment was discontinued (from 2 to 40 days later). The latency period was unspecified for one patient [26]. One

additional non-severe adverse event related to concomitant steroid treatment was reported [57].

Discussion

Acquired haemophilia is a rare bleeding disorder with a high potential for significant bleeding problems and an inhibitor-related mortality rate of 7.9–22% [2,5,20]. As bleeding severity does not correlate well with FVIII levels or inhibitor titre, patients remain at risk for life-threatening bleeds until inhibitors can be eradicated, thus making the effective treatment of actual bleeding episodes critically important.

Conducting controlled clinical trials in acquired haemophilia to assess haemostatic agents is difficult given the low incidence of the disease. We therefore looked to available data from the compassionate use programmes, the HTRS registry and published case reports to assess the treatment of acquired haemophilia with rFVIIa. A total of 139 patients treated with rFVIIa for 204 bleeding episodes are reviewed here. Ages ranged from 2 to 99 years, and both sexes were represented in approximately equal numbers (49% male and 46% female patients of those for whom gender data were reported). Ethnicity was unknown for the majority (74%) of patients considered here.

The most frequent use of rFVIIa across each data set was for the treatment of non-surgical bleeding episodes (spontaneous or trauma-associated; Table 2). Overall efficacy ratings of 'excellent' or 'effective' were reported in 67% (136/203) 'partially effective' in 12% (25/203), and 'ineffective' in 10% (21/203) of all bleeding episodes reviewed (combined data sources). Efficacy was unavailable for 10% of all bleeding episodes. When bleeding episodes without efficacy data are excluded, rFVIIa was rated effective or partially effective in 88% (161/182) of bleeding episodes (Table 4). Recombinant FVIIa efficacy was comparable across data sources when effective and partially effective bleeding episodes for which data were available are combined: 89% (77/87) in the compassionate use programmes, 90% (10/11) in the HTRS registry and 88% (74/84) in the publications (Table 4).

With regard to bleeding type, 80% (99/124) of combined non-surgical bleeding episodes treated with rFVIIa for which efficacy data were available had an effective outcome, as did 63% (36/57) of combined surgical bleeding episodes similarly treated (Table 4). When combining effective and partially effective outcomes, treatment efficacy was generally similar for non-surgical (90%, 111/124) and surgical

(86%, 49/57) types of bleeding episodes. Efficacy was also similar between surgical and non-surgical types of bleeding episodes within each of the three clinical data sources.

First-line treatment was effective overall (effective and partially effective episodes) in 95% of bleeding episodes for which efficacy data were available, compared with 80% efficacy when rFVIIa was used as salvage therapy (prior haemostatic agents failed to stop haemorrhage; Table 3). Within the compassionate use programmes, first-line therapy appeared to be more effective than salvage treatment particularly when effective and partially effective episodes were combined (95% for the first-line and 83% for the salvage treatment). Similar results were seen in the publications with 95% efficacy for first-line treatment and 67% for salvage treatments. The mean time to rFVIIa treatment data from the compassionate use programmes also suggest that earlier rFVIIa treatment results in more effective outcomes.

One hundred and fourteen AE were reported in 55 patients from the three data sources Appendix. Most safety data were provided in the compassionate use programmes and the HTRS registry; safety information in published literature was limited. The most commonly reported AE in the combined data sources were death, pyrexia and vomiting. Most death AE were reported in the published literature.

The incidence of thrombotic adverse events was low. A total of six thrombotic AE (four patients) were reported in the compassionate use programmes, two (two patients) in the HTRS registry and four (four patients) in the published medical literature. Of the 10 patients experiencing thrombotic events, there were two recoveries, one partial recovery and seven deaths. Many of the conditions for which rFVIIa was administered in the compassionate use programmes carried a high thrombotic risk (postoperative setting, postpartum period), and many patients receiving rFVIIa had a predisposition to thrombosis (underlying cardiovascular disease, malignancy, indwelling catheters, concomitant use of other haemostatic agents).

A total of 31 (31/139, 22%) deaths were reported in the compassionate use programmes and publications (no deaths were reported in the HTRS registry). Most deaths were judged attributable to a severe underlying clinical condition. The death rate in this study (22%) is comparable with the reported mortality rate of patients with acquired haemophilia (7.9–22%) [2,5,20]. Acquired haemophilia patients are often critically ill and present with severe life-threatening bleeding.

The potential for publication bias does exist, as independent case reports likely represent only a

fraction of rFVIIa treatment cases in acquired haemophilia, and successful treatments are more likely to be published/reported than failed ones. However, the similarity of the efficacy results to the other data sources suggests that this may not be the case. Overall safety information may be underestimated as adverse events are infrequently published in case reports. However, the overall incidence of 'death' as an adverse event may be overestimated as one of the most commonly reported AE within the published literature, as adverse event information in the literature was not coded as an AE according to the MedDRA dictionary. Finally, in the HTRS registry, adverse events are reported voluntarily and it is not always possible to estimate the exact frequency of AE in the patient population. In summary, the combined available data examined here provide supporting evidence for the efficacy and safety of rFVIIa as the first-line treatment for patients with acquired haemophilia in a wide range of both surgical and non-surgical bleeding situations.

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Appendix

Summary of all adverse events (all clinical data sources).

	Comp. use program, <i>n</i> (%)		HTRS, <i>n</i> (%)		Publications report, <i>n</i> (%)	
No. patients treated	61		9		69	
Pts. With TEAE	34		4		17	
	93		4		17	
No. TEAEs	<i>P</i>	E (%)	<i>P</i>	E (%)	<i>P</i>	E (%)
Blood & lymph system disorders	3	3 (3.2)	0	0	0	0
Anemia	1	1				
Cyst NOS	1	1				
Thrombocytopenia	1	1				
Cardiac disorders	5	6 (6.5)	0	0	2	2 (11.8)
Angina pectoris	1	1			0	0
Cardiac arrest	1	1			1	1
Cardiac failure	1	1			0	0
Fibrillation atrial	1	1			0	0
Left ventricle failure	1	1			1	1
Myocardial infarction	0	0			0	0
Supraventricular extrasystoles	1	1				
Eye disorders	1	1 (1.1)	0	0	0	0
Vision blurred	1	1				
Gastrointestinal disorders	7	11 (11.8)	0	0	0	0
Abdominal hematoma	1	1				
Constipation	1	1				
Diarrhea	1	1				
Nausea	2	2				
Vomiting	4	6 (6.5)				
General disorders and administration site conditions	12	17 (18.3)	0	0	10	10 (58.6)
Catheter site hematoma	1	1			0	0
Catheter site hemorrhage	2	2			0	0
Catheter site-related reaction	1	1			0	0
Death	2	2			10	10 (58.6)
Generalized oedema	1	2			0	0
Pyrexia	7	8 (8.6)			0	0
Therapeutic response decreased	1	1			0	0
Hepatobiliary disorders	1	1 (1-1)	0	0	0	0
Hepatic function abnormal	1	1				
Infections and infestations	3	5 (5.4)	0	0	0	0
Bacteremia	1	2				
Bronchopneumonia	1	1				
Sepsis	1	1				
Staphylococcal sepsis	1	1				
Injury, poisoning and procedural complications	3	3 (3.2)	2	2 (50)	0	0
Contusion	1	1	0	0		
Subcutaneous hematoma	1	1	0	0		
Subdural hematoma	0	0	1	1		
Hematoma extension (thigh)	0	0	1	1		
Vascular access complication	1	1	0	0		
Investigations	7 (11.5)	10 (10.8)	0	0	0	0
Blood bilirubin increased	1	1				
Blood fibrinogen decreased	2	2				
Cardiac murmur	1	1				
Fibrin D dimer increased decreased	1	1				
Fibrin degradation products	2	2				
Platelet count decreased	1	1				

Appendix (Continued).

	Comp. use program, <i>n</i> (%)		HTRS, <i>n</i> (%)		Publications re- port, <i>n</i> (%)	
No. patients treated	61		9		69	
Pts. With TEAE	34		4		17	
	93		4		17	
No. TEAEs	<i>P</i>	E (%)	<i>P</i>	E (%)	<i>P</i>	E (%)
Prothrombin time shorten	1	1				
Prothrombin time prolonged	1	1				
Musculoskeletal and connective tissue disorders	2	3 (3.2)	0	0	0	0
Hemarthrosis	1	1				
Joint swelling	1	1				
Muscle hemorrhage	1	1				
Nervous system disorders	9	11 (11.8)	2	2 (50)	3	3 (17.6)
Cerebral artery occlusion	1	1	0	0	0	0
Cerebral hemorrhage	2	2	0	0	0	0
Cerebral infarction	0	0	0	0	1	1
Cerebral ischemia	0	0	0	0	2	2
Cerebrovascular accident	2	2	1	1	0	0
Coma	0	0	1	1	0	0
Dizziness	1	1	0	0	0	0
Hemorrhagic stroke	1	1	0	0	0	0
Headache	3	3 (3.2)	0	0	0	0
Lethargy	1	1	0	0	0	0
Other	0	0	0	0	1	1 (5.9)
Steroid-related events ^a					1	1
Renal and urinary disorders	2	2 (2.2)	0	0	0	0
Renal impairment/acute failure	2	2				
Reproductive system	1	1 (1.1)	0	0	0	0
Pelvic hemorrhage	1	1				
Respiratory thoracic and mediastinal disorders	4	5 (5.4)	0	0	0	0
Epistaxis	1	1				
Embolism pulmonary	2	2				
Pleural effusion	1	1				
Pulmonary edema	1	1				
Skin and subcutaneous tissue disorders	6	7 (7.5)	0	0	0	0
Ecchymosis	1	1				
Hyperhidrosis	1	1				
Pruritus	2	2				
Rash/Rash erythematous	2	2				
Surgical and medical procedures	3	4 (4.3)				
Arterial repair	1	1				
Central venous catheterization	2	2	0	0	0	0
Hematoma evacuation	1	1				
Vascular disorders	2	3 (3.2)	0	0	1	1 (5.9)
Hematoma	1	1	0	0	0	0
Hemorrhage extension	0	0			1	1
Shock	1	1			0	0
Thrombosis deep vein	1	1			0	0

^aSteroid-related adverse events include weight gain, acne, hirsutism, hair loss, psychological changes, and joint pain. *P* = number of patients experiencing a TEAE *E* = (number of events/total number of TEAE)* 100 = %.