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The use of recombinant activated factor VII in patients with acquired haemophilia

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ABSTRACT

Acquired haemophilia (AH) is a rare, often severe bleeding disorder characterised by autoantibodies to coagulation factor VIII (FVIII). Observational studies offer crucial insight into the disease and its treatment. Recombinant activated factor VII (rFVIIa, eptacog alfa activated) was available on an emergency and compassionate use basis from 1988 to 1999 at sites in Europe and North America. In 1996, rFVIIa was approved in Europe for the treatment of AH; it was licensed for this indication in the United States in 2006. Recombinant activated FVII is approved for first-line treatment of bleeding episodes and prevention of bleeding in surgical/invasive procedures in patients with AH. This review provides an up-to-date summary of the haemostatic efficacy of rFVIIa in patients with AH, from the first emergency and compassionate use programmes, to patient registries and a post-marketing surveillance study. In acute bleeding episodes, rFVIIa provided high and consistent rates of control, and available data showed that acute bleed control rates were higher for first-line rFVIIa versus salvage rFVIIa. In surgical procedures, rFVIIa also provided high rates of control. In patients with AH, rFVIIa has a high rate of haemostatic efficacy in acute and surgical bleeding episodes.

1. Introduction

Acquired haemophilia (AH) is a rare, often severe bleeding disorder caused by the spontaneous development of autoantibodies to coagulation factor VIII (FVIII) [1]. These acquired autoantibodies inhibit the procoagulant activity of FVIII, leading to markedly reduced FVIII activity and a moderate to severe bleeding diathesis. Acquired haemophilia has an estimated incidence of approximately 1:1,000,000 per year [2,3]. The causes of AH are not yet understood; however, around half of cases are considered idiopathic and half are associated with a variety of pathological or physiological conditions (including connective tissue disease, malignant tumours, pregnancy, childbirth, drugs and ageing) [1,4].

Patients with AH experience bleeding episodes that are either spontaneous (68% of cases) or associated with a trauma or invasive procedure (32% of cases) [5]. In contrast with patients with congenital haemophilia, for whom intra-articular bleeding is common, patients with AH more frequently experience bleeding in the skin, mucous membranes, muscles and soft tissue [1,3]. Bleeding in AH is usually severe at presentation (in more than two-thirds of cases) [6]. The severity of bleeding does not appear to correlate with FVIII level or inhibitor titre at diagnosis [1,7,8]. The reported bleeding mortality rate was 3.2% in the European Acquired Haemophilia (EACH2) registry [9] (published in 2012), and ranged between 7.9% and 22% in earlier studies [9–12].

Treatments aim to control acute and surgical bleeding episodes (haemostatic therapy) and to eradicate autoantibodies (immunosuppressive therapy) [1]. First-line haemostatic therapy in patients with AH involves the use of bypassing agents, including recombinant activated factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (pd-aPCC) [4,13]. Recombinant activated FVII (eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) was available from 1988 to 1999 on an emergency and compassionate use basis at sites in Europe and North America. Registration for the use of rFVIIa was in 1996 (Europe) [14], 2000 (Japan) and 2006 (United States) for the treatment of bleeding episodes and prevention of bleeding in surgical interventions or invasive procedures in patients with AH. By directly activating coagulation FX on the surface of activated platelets at the site of injury and bypassing FVIII and

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1. **summary of the haemostatic efficacy of rFVIIa in patients with AH, from the first emergency and com...**
Anchor Name: Efficacy summary *[Agency UK becky.stirk@hansonzandi.co.uk]*

FIX, rFVIIa can circumvent the actions of inhibitory antibodies in patients with AH [15].

The rarity of AH makes it difficult to conduct controlled, prospective trials; wider data collection from other sources is therefore warranted. In 2007, Sumner et al. reviewed the rFVIIa experience in AH (139 patients with 204 bleeding episodes) from: the NovoSeven® emergency and compassionate use programmes (1988–1999); the Hemostasis and Thrombosis Research Society (HTRS) registry (March 1999–July 2005); and independent published reports (January 1999–September 2005) [16]. The combined data provided supporting evidence for the efficacy and safety of rFVIIa as first-line treatment for patients with AH in a range of both surgical and non-surgical bleeding situations [16]. The aim of this present review is to provide an updated compilation of available data on rFVIIa efficacy in patients with AH, from emergency and compassionate use programmes, recent patient registries and a post-marketing surveillance (PMS) study.

2. Methods

2.1. Data sources

This review summarises experience with rFVIIa efficacy in patients with AH with acute or surgical bleeding, using data from two emergency and compassionate use programmes [12,17], four patient registries – HTRS registry [18–21], EACH2 registry [6], Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise (SACHA) registry [22] and WIRK [23] registry – and a Japanese PMS study [24,25]. These are summarised in Table 1. Of note is that data from the HTRS registry [18–21] and acute bleeding data from the Japanese PMS study [24] were available in congress abstracts. Although four of the aforementioned studies (one emergency use programme [12], the WIRK registry, the HTRS registry, and the Japanese PMS study) included data for patients with other bleeding disorders, this present review concentrates on AH only.

Data collection was prospective in one emergency use programme [17], the EACH2 registry [6], the HTRS registry [18–21], the UK surveillance study [10], the SACHA registry [22], the WIRK registry [23] and the German, Austrian and Swiss Thrombosis and Hemostasis Society (GTH) AH registry [26]; it was retrospective in the remaining programmes/registries (Table 1). Patients were from several continents in the emergency and compassionate use programmes, and the patient registries included the following regions: the United States (HTRS); Europe (EACH2); France (SACHA); Germany (WIRK); and Japan (PMS study). The periods of data collection ranged from 20 months to 10 years.

As the UK surveillance study [10] and the GTH AH registry [26] did not report on the efficacy of rFVIIa treatment, further information from them is not presented.

2.2. Efficacy assessments

The rFVIIa efficacy assessments in the data sources used similar, but not identical, definitions of haemostatic efficacy (Table 2). In each study, efficacy assessments were reported by the investigators/physicians.

2.3. Safety assessments

Safety analyses focused on the incidence of thromboembolic events (TEs) and deaths that, in the opinion of the investigator, were related to bypassing therapy.

3. Results

3.1. Patients

Table 3 describes the characteristics and bleeding episodes reported for patients with AH treated with rFVIIa in the programmes/registries (the average age of the patients ranged from 59 to 78 years). An overview of the reported incidence of associated conditions (including that given in more recent studies) is provided in Fig. 1 [9–11,26,27].

3.2. Efficacy of rFVIIa in acute bleeds

The haemostatic efficacy of rFVIIa in treating acute bleeds in patients with AH is summarised in Table 4. The reported average dose of rFVIIa was approximately 90 μg/kg. Across the data sources, the rate of 'effective' bleeding control for rFVIIa ranged from 48% to 100%, and the overall bleeding control rate for rFVIIa, which combined data for 'effective' and 'partially effective', ranged from 81% to 100%. In the EACH2 registry, comparative efficacy data were reported for treatment with rFVIIa versus pd-aPCC. The proportion of bleeding episodes controlled was similar for rFVIIa versus pd-aPCC (unmatched samples: 91% [145/159] versus 93% [56/60], respectively, $P = 0.60$; propensity score-matched samples: 93% [53/57] for both, $P = 1$).

For the compassionate use programme by Hay et al. [12], haemostatic efficacy data were reported according to whether rFVIIa was given as first-line or salvage treatment. The proportion of bleeding episodes controlled was higher for first-line versus salvage rFVIIa (100% [14/14] versus 92% [55/60]; Table 4).

3.3. Efficacy of rFVIIa in surgical bleeds

In the HTRS registry, there were 24 surgical procedures, most of which were minor [18]. In the Japanese PMS study, there were five surgical procedures treated with rFVIIa; two were minor (dental, gastrointestinal), and three were major (gastrointestinal, obstetric, neurosurgical) [25]. Table 5 shows the efficacy results for rFVIIa in treating surgical bleeds in patients with AH. In total, efficacy data were available for 27 procedures (not reported for two procedures in the HTRS [18]), and rFVIIa provided an overall bleeding control rate of between 80% and 86% across the data sources [18,25].

3.4. Safety of rFVIIa

There were no rFVIIa-related TEs reported in the emergency and compassionate use programmes [12,17], in the HTRS, SACHA or WIRK registries [18,22,23], or among the surgical patients in the Japanese PMS study [25].

In the EACH2 registry, TEs were reported in five of 174 (2.9%) and three of 63 (4.8%) patients taking rFVIIa and pd-aPCC, respectively. It was not possible to draw conclusions about the causal relationship between haemostatic treatment and the TEs, except in one patient who suffered a myocardial infarction that was suspected of being related to rFVIIa treatment. TEs were significantly associated with mean age but not with underlying clinical conditions [6]. In the patients with acute bleeds in the Japanese PMS study, three patients had TEs, all of which were thought to be related to rFVIIa treatment. These were: disseminated intravascular coagulation (DIC) in two patients (an 87-year-old female with rheumatoid arthritis and an 81-year-old male with pneumonia); and bowel necrosis in one patient (a 70-year-old male with intracerebral haemorrhage, complicated with pneumonia) [24]. Thus, all three patients were elderly with significant comorbidities.

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Table 1
Summary of programmes/registries in acquired haemophilia

Study	Aim	Data collection method	Dates	Country/Region
Emergency and compassionate use programmes:				
Arkin et al., 2000 [17]	Evaluate the efficacy and safety of rFVIIa in treating limb-threatening joint or muscle bleeds in severe haemophilia A/B and AH	Prospective, open-label	NR	United States
Hay et al., 1997 [12]	Assess the use of rFVIIa in AH patients with serious acute/surgical bleeding after other treatments have failed	Retrospective	1990–1995	Europe, Canada, United States, Australia, Malaysia
Registries:				
HTRS [18–21]	Post-marketing surveillance of all patients with AH irrespective of treatment	Prospective, using an IRB-monitored, web-based platform	2006–2011	United States
EACH2 [6]	Assess the control of first acute bleeding episodes treated with bypassing agents (rFVIIa or pd-aPCC), FVIII or desmopressin in AH	Prospective, longitudinal, using a web-based database	2003–2008	13 European countries
UK surveillance study [10]	Identify all patients presenting with AH in the UK, describe outcomes in a consecutive cohort unaffected by referral or reporting bias	Prospective	2001–2003	United Kingdom
SACHA [22]	Establish clinical course, disease associations and outcomes at 1 year for haemostatic treatment of acute bleeding (rFVIIa or pd-aPCC) and autoantibody eradication in AH	Prospective, controlled	2001–2006	France
WIRK [23]	Assess the efficacy and safety of rFVIIa during acute bleeding and invasive procedures in congenital haemophilia with inhibitors, AH, congenital FVII deficiency and Glanzmann's thrombasthenia	Prospective, post-marketing surveillance	20 months	Germany
GTH AH 01/2010 [26]	To establish clinically useful predictors of remission for patients with AH treated by immunosuppressive therapy according to the German, Austrian and Swiss Thrombosis and Hemostasis Society (GTH) consensus protocol	Prospective	2010–2013	Austria and Germany
Japanese PMS study:				
Seita et al., 2013 [24]	Investigate the safety and efficacy of rFVIIa in AH patients with acute bleeding	Retrospective, post-marketing surveillance	2000–2010	Japan
Takedani et al., 2014 [25]	Evaluate the safety and efficacy of rFVIIa in congenital haemophilia patients with inhibitors or AH patients undergoing surgery	Retrospective, post-marketing surveillance	2000–2010	Japan

AH, acquired haemophilia; rFVIIa, recombinant activated factor VII; NR, not reported; IRB, institutional review board; pd-aPCC, plasma-derived activated prothrombin complex concentrate; FVIII, coagulation factor VIII; HTRS, Hemostasis and Thrombosis Research Society; EACH2, European Acquired Haemophilia; SACHA, Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise.

Table 2
Summary of physician-reported haemostatic efficacy assessments

Study	Acute bleeds	Surgical bleeds
Emergency and compassionate use programmes:		
Arkin et al., 2000 [17]	'Effective' (complete or substantial decrease in bleeding), 'partially effective' (some decrease in bleeding) or 'ineffective' (no improvement in bleeding)	–
Hay et al., 1997 [12]	'Effective', 'partially effective' or 'ineffective' at 8 hours and 24 hours after treatment initiation	'Effective', 'partially effective' or 'ineffective'
Registries:		
HTRS [18–21]	'Bleeding stopped', 'bleeding slowed' or 'no improvement' for each specific product regimen or regimen change	Four-point scale and adequacy of haemostasis on the 'planned regimen' immediately and at 24 hours and 72 hours 'Excellent'/'good', 'fair'/'partially effective', 'poor/ineffective'
EACH2 [6]	'Bleeding resolved' or 'bleeding not resolved'	–
SACHA [22]	'No bleeding' (absence of new or active bleeding) or 'improvement' at 1 month	–
WIRK [23]	'Effective' (a stop or a significant reduction in bleeding at 9 hours after initiating treatment)	–
Japanese PMS study:		
Seita et al., 2013 [24]	'Markedly effective' (clinical improvement within 8 hours), 'effective' (clinical improvement within 8–12 hours), 'moderately effective' (clinical improvement in >12 hours) or 'ineffective'	–
Takedani et al., 2014 [25]	–	After surgery (up to 3 days): 'effective' (bleeding stopped or considerably reduced), 'slightly effective' (bleeding slightly reduced) or 'not effective' (bleeding not reduced) Maintenance of haemostasis of the surgical wound (until suture removal) classified as 'yes' or 'no'

HTRS, Hemostasis and Thrombosis Research Society; EACH2, European Acquired Haemophilia; SACHA, Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise; –, no data.

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Table 3
Summary of characteristics of patients with acquired haemophilia treated with recombinant activated factor VII (where available)

	Emergency and compassionate use programmes		Registries						
			HTRS[a]		EACH2[b]	SACHA	WIRK	Japanese PMS study	
	Arkin et al., 2000 [17]	Hay et al., 1997 [12]	Ma et al., 2012 [21]	Al-Mondhiry et al., 2012 [18]	Baudo et al., 2012 [6]	Borg et al., 2013 [22]	Birschmann et al., 2013 [23]	Seita et al., 2013 [24]	Takedani et al., 2014 [25]
All patients	23	38	166	166	501	82	64	132	37
Patients with AH, n	6	38	166	166	501	82	7	132	6
Patients treated with haemostatic agent (rFVIIa, pd-aPCC, FVIII or desmopressin), n	6	38	NR	NR	307	38	7	132	6
Patients with AH treated with rFVIIa, n	6	38	NR	NR	159[c]	28	7	132	6
Gender, n (%)									
Male	NR	19 (50)	NR	NR (29)	86 (54)	NR	5 (71)	75 (57)	NR
Female	NR	19 (50)	NR	NR (71)	73 (46)	NR	2 (29)	57 (43)	NR
Age, mean (range), years	NR	59[d] (2–89)	67 (NR)	78 (28–89)	73[d] (IQR 15–91)	NR	59 (15–87)	68	62[a] (39–79)
Bleeding type, n									
Acute	NR	67	125	–	158	NR	12	371	–
Spontaneous	NR	NR	95	–	120	NR	7	NR	–
Traumatic	NR	NR	30	–	38	NR	5	NR	–
Surgical/dental	–	3	9	24	–	–	–	–	5
Other	–	–	4	–	–	–	–	–	–
Not reported/unknown	–	8	1	–	1	–	2	–	–

HTRS, Hemostasis and Thrombosis Research Society; EACH2, European Acquired Haemophilia; SACHA, Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise; PMS, post-marketing surveillance; AH, acquired haemophilia; rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; FVIII, coagulation factor VIII; NR, not reported; IQR, interquartile range; –, no data.
[a] Data were analysed on a per episode basis.
[b] Data are for first-line treatment of first bleeding episode.
[c] 174 patients were treated first line with rFVIIa, but only 159 had a reported outcome.
[d] Values are median.

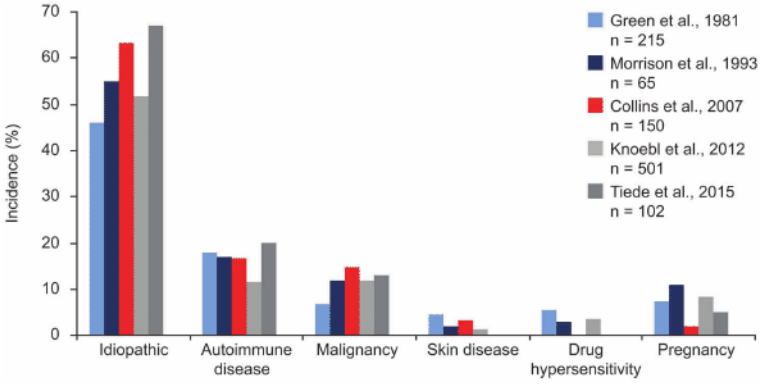

Fig. 1. Incidence of associated conditions reported in acquired haemophilia [9–11,26,27]

In the recent studies, death due to fatal bleeding in AH has decreased in occurrence compared with earlier surveys. In 1981, in a survey of 215 AH patients, Green et al. reported death in 22% of patients attributed directly or indirectly to the presence of the inhibitor [11] versus 4.5% from the EACH2 registry [6]. The UK surveillance study [10] and the most recent GTH study [26] reported cause of death by fatal bleeding in 9.1% and 2.9% of patients, respectively, and the SACHA registry [22] reported fatal bleeding in 3.5% of patients. Death from infection or side-effects of immunosuppressive therapy was reported in 4.2% of patients from the EACH2 registry (many deaths [38%] were of unknown cause) [6] and in 11%, 16% and 12% of patients from the UK surveillance study [10], the GTH study [26] and the SACHA registry [22], respectively (not reported by Green et al.). Death from cardiovascular events was reported as 6% in the GTH study [26] and 7.3% in the SACHA registry [22] (not reported by Green et al., or from the UK surveillance study or EACH2 registry; both the SACHA and EACH2 registries reported no deaths associated with recent use of bypassing agents in this category) [6,10,11,22,26].

4. Discussion

AH is associated with high rates of morbidity and mortality, and the paucity and random occurrence of new cases hinders the development of high-level clinical trial evidence for the determination of its optimal management – no randomised

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Table 4
Efficacy of recombinant activated factor VII and plasma-derived activated prothrombin complex concentrate in acute bleeds in patients with acquired haemophilia (where available)

	rFVIIa treatment information	Haemostatic treatment	Patients treated, n	Episodes treated, n	Haemostatic efficacy, n (%) bleeding episodes[a]		Overall bleeding control, %
					Effective	Partially effective	
Emergency and compassionate use programmes:							
Arkin et al., 2000 [17]	NR	rFVIIa	6	NR[b]	NR	NR	100
Hay et al., 1997 [12]	Median initial dose: 90.4 μg/kg						
First-line	(range 45–181)	rFVIIa	6	14	14 (100)	0	100
Salvage		rFVIIa	29	60	45 (75)	10 (17)	92
Total		rFVIIa	35	74[c]	59 (80)	10 (14)	94
Registries:							
HTRS [21]	Median initial dose: 90 μg/kg (range 88–100)	rFVIIa	NR	139	117 (84)	15 (11)	95
EACH2 [6][d]	Median initial dose: 90 μg/kg	rFVIIa	159	159	145 (91)	–	91
(unmatched samples)	(IQR 84.71–102.86)	pd-aPCC	60	60	56 (93)	–	93
EACH2 [6][d] (propensity score-matched samples)	NR	rFVIIa	57	57	53 (93)	–	93
		pd-aPCC	57	57	53 (93)	–	93
SACHA [22][e]	Total dose for initial bleeding episode: 0.8 mg/kg (SD 0.8; range 0.01–3.0)	rFVIIa	28	NR	13 (48)	9 (33)	81
		pd-aPCC	6	NR	2 (33)	4 (67)	100
Japanese PMS study:							
Seita et al., 2013 [24]	Median (mean) dose: 93.2 μg/kg (99.5)	rFVIIa	132	371	189 (51)	152 (41)	92

rFVIIa, recombinant activated factor VII; HTRS, Hemostasis and Thrombosis Research Society; NR, not reported; EACH2, European Acquired Haemophilia; IQR, interquartile range; pd-aPCC, plasma-derived activated prothrombin complex concentrate; SACHA, Surveillance des Auto antiCorps au cours de l'Hémophilie Acquise; SD, standard deviation; PMS, post-marketing surveillance; –, no data.
[a] Data presented are n (%) patients.
[b] Number of episodes is not included because data reported are not specific to AH patients.
[c] Efficacy was not reported for four bleeds.
[d] Data are for first-line treatment of first bleeding episode.
[e] One patient died; there are no data on bleeding outcomes in three (11%) patients; there was a similar subcutaneous bleed with no other bleeds in two (7%) patients.
Notes:
WIRK is not included in this table because there was no subgroup analysis for patients with AH.
'Effective' combines data for 'effective', 'bleeding stopped', 'bleeding resolved', 'no bleeding' and 'markedly effective'/'effective'. 'Partially effective' combines data for 'partially effective', 'bleeding slowed', 'improvement' and 'moderately effective'.

clinical trials of haemostatic therapies for patients with AH were found in a Cochrane Systematic Review [28]. Despite this, international recommendations on the diagnosis and treatment of patients with AH have been published, based on clinical experience of specialists in the field [4]. The first priority in diagnosed patients is to control acute bleeding, and first-line therapy is with bypassing agents: rFVIIa (90 μg/kg every 2–3 hours) or pd-aPCC (50–100 IU/kg every 8–12 hours). Other haemostatic agents (e.g., recombinant or plasma-derived human FVIII concentrates, or desmopressin) should only be used when bypassing therapy is unavailable [4]. The EACH2 registry has confirmed that bypassing agents are more efficacious than either FVIII or desmopressin, and that they should be the first-line agents of choice [6]. If first-line haemostatic treatment fails, an alternative option is the acute reduction, or removal, of the acquired inhibitor by immunoadsorption and/or plasmapheresis [4]. Patients with AH undergoing minor or major invasive procedures should receive prophylactic therapy with a bypassing agent.

Published treatment guidelines recommend immunosuppressive therapy to eradicate the inhibitor as soon as the diagnosis of AH is made, because patients remain at risk of severe and fatal haemorrhage until the inhibitor is removed [4]. First-line treatment is with corticosteroids alone or with cyclophosphamide, and second-line treatment is with rituximab [4]. It is noteworthy that baseline FVIII activity was recently reported to have a strong impact on time to achieve remission, and it was concluded that the presenting FVIII activity and inhibitor concentration were potentially useful prognostic factors to tailor immunosuppressive therapy for patients with AH [26].

The growing number of observational studies and registries of patients with AH offers crucial insight into this rare bleeding disorder – such insight may serve as the basis for evidence-based treatment [4]. Recombinant activated FVII is recommended as first-line treatment of bleeding episodes and for the prevention of bleeding in surgical interventions or invasive procedures in patients with AH [14]. This present review provides an up-to-date summary of data on the haemostatic efficacy of rFVIIa in patients with AH from emergency and compassionate use programmes, patient registries and a PMS study. The review by Sumner et al. included rFVIIa data in patients with AH from the NovoSeven® emergency and compassionate use programmes (1988–1999), the HTRS registry (March 1999–July 2005) and independent published reports (January 1999–September 2005) [16]. The rFVIIa-treated patients in the emergency and compassionate use programmes in Sumner et al. (n = 44) [16] are captured in the present review by the earlier data sources of Hay et al. (n = 38) [12] and Arkin et al. (n = 6) [17]. From the HTRS registry, the review by Sumner et al. included 13 rFVIIa-treated patients with AH [16]; this present review includes these

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Table 5
Efficacy of recombinant activated factor VII in surgical bleeds in patients with acquired haemophilia (where available).

	Haemostatic treatment	Treatment regimen	Adjunctive treatments	Number of infusions	Procedures, n	Haemostatic efficacy, n (%) of bleeding episodes		Overall bleeding control, %
						Effective	Partially effective	
HTRS registry [18][a]	rFVIIa	Median initial dose: 96.1 μg/kg (range 44–270)	Used in 12 procedures: pd-aPCC (n = 5); desmopressin (n = 2); rFVIII (n = 3); blood products (n = 2)	Median: 4 (range 1–77)	24	17 (77)	2 (9)	86
Japanese PMS study [25]	rFVIIa	Mean dose: 90.4 μg/kg (range 96–128)	Used in four procedures: pd-aPCC (n = 1); tranexamic acid (n = 3)	Median: 3 (range 1–51)	5	4 (80)	0	80

HTRS, Hemostasis and Thrombosis Research Society; rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; FVIII, coagulation factor VIII; PMS, post-marketing surveillance.
[a] Efficacy data were not available for two patients.

patients as well as those recruited later and published in Ma et al. and Al-Mondhiry et al. (total n = 166) [18,21]. In the present review, high rates of control in acute bleeding episodes and surgical procedures were provided by rFVIIa treatment, and the high haemostatic efficacy with rFVIIa was consistent across all data sources. For acute bleeding episodes, the range of efficacy with rFVIIa across the data sources was fairly wide, and the data for pd-aPCC also showed a wide range of efficacy between data sources. This may be due to methodological differences between the studies, including the methods of assessing haemostatic efficacy: the definitions of haemostatic efficacy were similar, but not identical (e.g., physician-reported efficacy definitions in different data sources included 'effective', 'bleeding stopped' and 'bleeding resolved'). Available data on acute bleeding episodes showed that haemostatic control rates were higher for first-line versus salvage rFVIIa (100% versus 92%) [12].

Prospective randomised trials comparing the efficacy of rFVIIa versus pd-aPCC in patients with AH have not been conducted to date and it is very unlikely that an adequately powered study would be feasible in the future. Of the currently available data sources, the EACH2 registry reported comparative haemostatic efficacy in patients with AH treated with rFVIIa versus pd-aPCC; 307 patients were treated with a first-line haemostatic agent, 174 (56.7%) received rFVIIa, 63 (20.5%) pd-aPCC, 56 (18.2%) FVIII, and 14 (4.6%) desmopressin. Bleeding was controlled in 269 of 338 (79.6%) patients treated with a first-line haemostatic agent or ancillary therapy alone. Propensity score matching was applied to allow unbiased comparison between treatment groups. Bleeding control was significantly higher in patients treated with bypassing agents versus FVIII/desmopressin (93.3% versus 68.3%; $P = 0.003$). Bleeding control was similar between rFVIIa and pd-aPCC (93.0%; $P = 1$) [6].

The SACHA registry also reported haemostatic efficacy in patients with AH treated with rFVIIa versus pd-aPCC. The response rate was high for rFVIIa and pd-aPCC (81% and 100%, respectively); however, the pd-aPCC group only included six patients whereas 28 were treated with rFVIIa, thus a direct comparison cannot be made [22].

The potential risk for thrombotic complications is an important consideration in the haemostatic treatment of patients with AH; this is because these patients tend to be elderly and have existing underlying conditions with intrinsic high risk of thrombosis. Thrombotic risk factors in patients with AH include smoking, hypertension, cardiovascular disease and type 2 diabetes mellitus [4]. The safety profile of rFVIIa treatment in patients with AH is summarised in detail by Neufeld et al. in this supplement [29]. Briefly, in post-marketing sources (up to 31 December 2013), 13% of the events reported in rFVIIa-treated patients with AH were TEs: 50 patients had a total of 54 TEs; 19 of the 50 patients (38%) had a fatal outcome [29]. Clinical trials have reported three TEs associated with rFVIIa in patients with AH (fatal cerebrovascular thrombosis in a 55-year-old male; cerebrovascular accident, bilateral deep vein thrombosis and pulmonary embolism in an 81-year-old male; and DIC in a 56-year-old female) [30]. All cases of cerebrovascular thrombosis or DIC in the clinical trials are thought to have resulted from various combinations of age, comorbid conditions and concomitant treatment with factor concentrates or pd-aPCC. This present review shows that rFVIIa was associated with a low rate of reported TEs across the data sources – all but two reported no rFVIIa-related TEs. In the EACH2 registry, TEs were reported in five of 174 (2.9%) and three of 63 (4.8%) patients taking rFVIIa and pd-aPCC, respectively [6]. However, it is not possible to draw any definite conclusions about the causal relationship between the haemostatic treatment and the TEs from the data available in the registry, except for one case in which the local investigator reported that the TE (myocardial infarction) was suspected to be related to rFVIIa treatment. Furthermore, TEs were significantly associated with mean age but not with underlying clinical conditions.

Three patients in the Japanese PMS study by Seita et al. had TEs that may have been related to rFVIIa treatment; all three were elderly and had significant comorbidities [24]. Two of the patients had concurrent infection with pneumonia, suggesting that patients with infection may have a higher risk of TEs, and should be carefully monitored for these events [24]. Overall, this review provides further evidence for the low risk of TEs associated with rFVIIa treatment in patients with AH [31].

There are a number of limitations with this review. Firstly, as mentioned above, a single method for assessing haemostatic efficacy has not been established or validated. Secondly, there may be overlap in the patients included in the registries (e.g., between the French SACHA registry and the European EACH2 registry). Thirdly, the lack of randomisation in observational data sources can result in selection bias; however, their findings are important because they reflect real-life practice.

Further work in the collection and analysis of patient data for AH is essential to continue to improve understanding of this rare disease, avoid any delays in diagnosis and create optimal evidence-based treatment strategies. Physicians who treat patients with AH should be encouraged to contribute cases to registries that collect patient data on clinical characteristics, management and outcomes [4].

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To increase the usefulness of AH patient registries, standardised treatment protocols would be valuable, and there needs to be consensus on the definitions of factors such as bleeding severity, haemostatic treatment success and AH remission. This would improve the collection of data on aspects such as protocol for autoantibody eradication, haemostatic treatment dosing regimens, surgical procedures, peripartum AH cases and subsequent pregnancies after AH has occurred. Data with longer follow-up would be useful, especially in peripartum women with AH. It may also help to advance our understanding of this syndrome and its treatment if subgroup analyses of registry data were conducted, including analyses of patients responding better to certain treatment options, and of patients with particular underlying conditions (e.g., cancer). Finally, it would be useful to analyse risk factors for recurrence of bleeding or poor treatment outcome.

In conclusion, combined data from emergency and compassionate use programmes, patient registries and a post-marketing study show that rFVIIa has been the most rigorously reported haemostatic agent used to control bleeding in patients with AH, and that it provides a high and consistent rate of haemostatic efficacy. The data provide supporting evidence for the efficacy and safety of rFVIIa as the first-line treatment for patients with AH in a wide range of both surgical and non-surgical bleeding situations.

Conflict of interest statement

A Tiede has received research support, lecture fees and/or honoraria for consultancy from Bayer, Baxter, Biotest, Biogen Idec, CSL Behring, Novo Nordisk, Pfizer and SOBI. K Amano has received lecture fees and/or honoraria for consultancy from Bayer, Baxter, Biogen Idec, Novo Nordisk, Pfizer, Kaketsuken and Chugai Pharmaceutical. A Ma has been on advisory boards for Novo Nordisk, Kedrion, Biogen Idec and Bayer. P Arkhammar and A Rosholm are employees of Novo Nordisk A/S, Denmark. S Benchikh El Fegoun is an employee of Novo Nordisk Health Care AG, Switzerland. S Seremetis is an employee of Novo Nordisk Inc., USA. F Baudo has received honoraria directly from Bayer, Baxter, Grifols and Novo Nordisk.

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References

[1] Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost 2013;110:1114-20.
[2] Collins P, Macartney N, Davies R, Lees S, Giddings J, Majer R. A population based, unselected, consecutive cohort of patients with acquired haemophilia A. Br J Haematol 2004;124:86-90.
[3] Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: a concise review. Am J Hematol 2005;80:55-63.
[4] Huth-Kühne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Lévesque H, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009;94:566-75.
[5] Baudo F, Mostarda G, de Cataldo F. Acquired factor VIII and factor IX inhibitors: survey of Italian Hemophilia Centers (AICE). Haematologica 2003;88:93-9.
[6] Baudo F, Collins P, Huth-Kühne A, Lévesque H, Marco P, Nemes L, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012;120:39-46.
[7] Franchini M, Targher G, Montagnana M, Lippi G. Laboratory, clinical and therapeutic aspects of acquired hemophilia A. Clin Chim Acta 2008;395:14-8.
[8] Toschi V, Baudo F. Diagnosis, laboratory aspects and management of acquired hemophilia A. Intern Emerg Med 2010;5:325-33.
[9] Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 2012;10:622-31.
[10] Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007;109:1870-7.
[11] Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. Thromb Haemost 1981;45:200-3.
[12] Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. Thromb Haemost 1997;78:1463-7.
[13] Collins PW. Management of acquired haemophilia A. J Thromb Haemost 2011;9(Suppl. 1):226-35.
[14] NovoSeven® Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000074/WC500030873.pdf. [Accessed March 3, 2015].
[15] Von Depka M. NovoSeven: mode of action and use in acquired haemophilia. Intensive Care Med 2002;28(Suppl. 2):S222-7.
[16] Sumner MJ, Geldziler BD, Pedersen M, Seremetis S. Treatment of acquired haemophilia with recombinant activated FVII: a critical appraisal. Haemophilia 2007;13:451-61.
[17] Arkin S, Blei F, Fetten J, Foulke R, Gilchrist GS, Heisel MA, et al. Human coagulation factor FVIIa (recombinant) in the management of limb-threatening bleeds unresponsive to alternative therapies: results from the NovoSeven emergency-use programme in patients with severe haemophilia or with acquired inhibitors. Blood Coagul Fibrinolysis 2000;11:255-9.
[18] Al-Mondhiry HAB, Ma A, Kessler CM, Fisher M, Gut RZ, Cooper DL. US experience with recombinant factor VIIa (rFVIIa) for surgery in acquired hemophilia (AH): analysis from the Hemostasis and Thrombosis Research Society (HTRS) registry. Blood 2012;120:3372.
[19] Ma A, Kessler CM, Gut RZ, Cooper DL. Recombinant factor VIIa (rFVIIa) use for surgery in acquired haemophilia (AH): Analysis from the Hemostasis and Thrombosis Research Society (HTRS) registry. J Thromb Haemost 2011;9(Suppl. 2):228.
[20] Ma A, Kessler CM, Gut RZ, Cooper DL. Recombinant factor VIIa (rFVIIa) is safe and effective when used to treat acute bleeding episodes and to prevent bleeding during surgery in patients with acquired hemophilia: updated assessment from the Hemostasis and Trhombosis Research Society (HTRS) registry AH database. Blood 2011;118:3374.
[21] Ma AD, Kessler C, Al-Mondhiry HAB, Fisher M, Gut RZ, Cooper DL. Use of recombinant factor VIIa (rFVIIa) for acute bleeding episodes in acquired haemophilia: final anaylsis from the Hemostasis and Thrombosis Research Society (HTRS) registry AH study. Blood 2012;120:4264.
[22] Borg JY, Guillet B, Le Cam-Duchez V, Goudemand J, Lévesque H. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hemophilie Acquise) registry. Haemophilia 2013;19:564-70.
[23] Birschmann I, Klamroth R, Eichler H, Schenk J, Kirchmaier CM, Halimeh S. Results of the WIRK prospective, non-interventional observational study of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors and other bleeding disorders. Haemophilia 2013;19:679-85.
[24] Seita I, Amano K, Higasa S, Sawada A, Kuwahara M, Shima M. Treatment of acute bleeding episodes in acquired haemophilia with recombinant activated factor VII (rFVIIa): analysis from 10-year Japanese post-marketing surveillance. J Thromb Haemost 2013;11(Suppl. 2):119.
[25] Takedani H, Shima M, Horikoshi Y, Koyama T, Fukutake K, Kuwahara M, et al. Ten-year experience of recombinant activated factor VII use in surgical patients with congenital haemophilia with inhibitors or acquired haemophilia in Japan. Haemophilia 2014 Dec 18 [Epub ahead of print].
[26] Tiede A, Klamroth R, Scharf RE, Trappe RU, Holstein K, Huth-Kühne A, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. Blood 2015;125:1091-7.
[27] Morrison AE, Ludlam CA, Kessler C. Use of porcine factor VIII in the treatment of patients with acquired hemophilia. Blood 1993;81:1513-20.
[28] Zeng Y, Zhou R, Duan X, Long D, Yang S. Interventions for treating acute bleeding episodes in people with acquired hemophilia A. Cochrane Database Syst Rev 2014;8:CD010761.
[29] Neufeld EJ, Négrier C, Arkhammar P, Benchikh el Fegoun S, Simonsen MD, Rosholm A, et al. Safety update on the use of recombinant activated factor VII in approved indications. Blood Reviews 2015;29(Suppl. 1):S34-41.
[30] Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. J Thromb Haemost 2004;2:899-909.
[31] Abshire T. Safety update on recombinant factor VIIa in the treatment of congenital and acquired hemophilia. Semin Hematol 2008;45(2 Suppl. 1):S3-6.

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