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ORIGINAL ARTICLE

Use of the UKHCDO Database for a postmarketing surveillance study of different doses of recombinant factor VIIa in haemophilia

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Introduction: Recombinant factor VIIa (rFVIIa) is recommended in Europe at standard (3×90 μg kg^{-1}) or high (1×270 μg kg^{-1}) doses. When granting the license for the high dose, the European Medicines Agency (EMA) requested postmarketing surveillance for thrombosis. This was conducted by the United Kingdom National Haemophilia Database (NHD) on behalf of Novo Nordisk and the EMA. **Aim:** To assess the use and safety of rFVIIa utilizing prospective data collected by the NHD (1 January 2008 to 30 June 2011). **Results:** Data were obtained from 67 haemophilia A/B patients with inhibitors treated for 1057 bleeds and 31 acquired haemophilia patients treated for 70 bleeds. Initial rFVIIa dose was categorized *post hoc* as low (<90 μg kg^{-1}), intermediate (≥90–<180 μg kg^{-1}) or high (≥180–<270 or ≥270 μg kg^{-1}). For haemophilia A/B, high and lower initial rFVIIa dose was used for 38.4% and 51.4% of episodes, respectively, while for acquired haemophilia, the values were 11.4% and 77.1% respectively. Median initial doses were higher for haemophilia A/B (146.3 μg kg^{-1}) than acquired haemophilia (90.5 μg kg^{-1}). A single administration of rFVIIa was the most frequently used regimen for haemophilia A/B, in contrast with standard recommendations and previous reports. For acquired haemophilia, most episodes were treated with multiple doses. No adverse drug reactions or thromboembolic events were reported for any rFVIIa dose. **Conclusion:** The novel use of a national database for postmarketing surveillance has demonstrated acceptable safety for all recommended doses of rFVIIa.

Keywords: National Haemophilia Database, real-world use, rFVIIa

Introduction

Activated recombinant Factor VII (rFVIIa, NovoSeven®, Novo Nordisk, Denmark) is an established and well-tolerated bypassing agent for the treatment of acute bleeding episodes in patients with haemophilia and inhibitors. Reported efficacy in randomized controlled clinical trials is 81–91% [1,2]. In Europe, rFVIIa is recommended at standard (3×90 μg kg^{-1}) or high (1×270 μg kg^{-1}) doses [3]. High-dose rFVIIa provides rapid control with reduced number of infusions required to achieve haemostasis [3–6]. This may improve patient outcome by providing faster pain relief and enhanced quality of life, and reducing emergency admissions [7,8].

In clinical trials, rFVIIa provides the same level of safety at all doses up to 270 μg kg^{-1} [3–6]. Importantly, the reported risk of thromboembolic events with rFVIIa is low [2,9–11]. When licensing the higher dose of rFVIIa, however, the European Medicines Agency (EMA) requested postmarketing surveillance for thrombosis in patients receiving high-dose regimens. Unusually, this postmarketing surveillance exercise was conducted on behalf of Novo Nordisk and the EMA by the United Kingdom (UK) National Haemophilia Database (NHD) between 1 January 2008 and 30 June 2011, concluding when the EMA were satisfied, there was no unacceptable risk of thrombosis associated with the higher dose.

In the UK, haemophilia centres are required by the Department of Health to report individual patient treatment and safety data quarterly to the NHD. The NHD therefore provides a comprehensive registry of patients with bleeding disorders from all UK

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haemophilia centres. The database has a key role in pharmacosurveillance, disease surveillance, audit, research and commissioning in haemophilia care within the UK.

Here, we report a postmarketing surveillance study conducted by the UK NHD to assess the real-world use and safety of standard and high initial rFVIIa doses in patients with congenital and acquired haemophilia A/B with inhibitors. The study not only focused on surveillance for thrombosis but also evaluated rFVIIa dosing regimens used by UK haemophilia centres in normal clinical practice, since these are likely to differ from clinical trials and even standard recommendations.

Design and methods

This prospective, postmarketing observational study of patients with bleeding disorders treated with rFVIIa used anonymized data reported to the UK NHD. The study was mandated by EMA primarily to monitor the relative safety of the higher (270 μg kg^{-1}) dose of NovoSeven, when the license was extended to include it. Patients were treated according to local treatment practices in accordance with the patients' usual care.

Data collection and extraction

All UK Haemophilia Centres are networked to the UK National Haemophilia Database (NHD). Treatment data were collected prospectively on all patients with haemophilia and in all centres and were collated and reported electronically to NHD quarterly. Haemophilia centres have a contractual requirement to report this data. NHD collects regular data on more than 25 000 UK patients with bleeding disorders including 7700 with haemophilia A and 1707 with haemophilia B.

Adverse events are reported using a secure, encrypted link, as they occur. Centres are also issued with monthly adverse event reminders with a tick box list of each reportable category of adverse event (harmonized with EUHASS) and have to make a 'negative report', to document when no adverse events have occurred. These events included adverse drug reactions, thromboembolic events (arterial and venous), disseminated intravascular coagulation and transfusion reactions judged by the managing clinician as probably or possibly related to rFVIIa treatment. Adverse event reports are investigated further and reported to the manufacturer, if product related.

Since this study required some data points not routinely collected by NHD, centres were asked to volunteer for this study and 16 larger Haemophilia Centres participated and are listed in the acknowledgement. Data from all eligible patients from participating centres are included in the report. The data collected included patient demographics, rFVIIa dosing regimens and details of any adverse events considered by the managing clinician to be possibly or probably related to use of rFVIIa treatment.

The NHD provided anonymized, quarterly electronic data extractions to Novo Nordisk from all patients with bleeding episodes treated with rFVIIa at the participating centres for onward transmission to the EMA. The study was terminated on 30 June 2011, when the EMA was satisfied.

The fileservers of both NHD and haemophilia centres are within the 'NHS net' protected from the worldwide web by a firewall and an array of further data security devices and protocols. The NHD is managed in accordance with the Data Protection Act of 1998 [12], Caldicott legislation [13], the Declaration of Helsinki [14] and the Guidelines for Good Pharmaco-epidemiology Practices [15].

Statistical analysis

Only descriptive statistics were used. There was no replacement of missing data values. Statistical programming was performed using UNIX SAS version 9.1 SAS (SAS Institute North Carolina, USA).

Patients were divided for analysis into three groups: haemophilia A with inhibitors, haemophilia B with inhibitors and acquired haemophilia. A treatment episode was defined as all rFVIIa treatments administered in the same patient with 26 h or less between administrations. A single-dose administration was defined as a dose spaced more than 26 h from any previous and following doses on the assumption that more than one treatment within that time span was probably for the same bleed. The duration of treatment of a single dose of rFVIIa was set to 2.5 h, based on the recommended dose interval for rFVIIa of 2 to 3 h. The initial rFVIIa dose was categorized as low (<90 μg kg^{-1}), intermediate (≥90–<180 μg kg^{-1}) or high (≥180 μg kg^{-1}). Prophylaxis (intermittent or periodic) was defined as a treatment regimen with a duration of >10 days (>240 h); data were reviewed prior to analysis in order to identify treatment regimens administered for the prevention of bleeds.

Results

Between 1 January 2008 and 30 June 2011, data from 98 patients with congenital and acquired haemophilia A and haemophilia B with inhibitors were collected by the NHD (Table 1). Data collection ceased when the EMA indicated that the safety objectives of the postmarketing surveillance had been satisfied.

A total of 60 patients with haemophilia A, seven with haemophilia B and 31 with acquired haemophilia were treated for 1127 bleeding episodes (Table 2). For both haemophilia A/B and acquired haemophilia, most treatment episodes were for non-surgical bleeds

Table 1. Patient demographics.

	Haemophilia A	Haemophilia B	Acquired haemophilia
N (patients treated with rFVIIa)	60	7	31
Age at time of treatment, years			
Mean, median (range)	27.7, 23.8 (0.8–80.1)	20.6, 18.2 (4.3–38.3)	65.6, 69.3 (27.6–94.0)
Age group (years), number of patients (episodes)[†]			
0–6	19 (191)	1 (1)	0 (0)
6–12	7 (171)	1 (12)	0 (0)
12–18	9 (49)	1 (20)	0 (0)
18–40	8 (236)	5 (48)	4 (14)
40–65	17 (250)	0 (0)	6 (13)
≥65	5 (79)	0 (0)	21 (43)

[†]The sum of the number of patients in each age group is more than the total number of patients with haemophilia A or B as patients may be counted more than once if they moved into an older age cohort during their time in the registry.

Table 2. Summary of treatment episodes and rFVIIa dosing regimens in patients with haemophilia A, haemophilia B and acquired haemophilia.

	Haemophilia A	Haemophilia B	Acquired haemophilia
Number of treatment episodes	976	81	70
Number of treatment episodes per patient			
Mean, median (range)	16.27, 7.5 (1–124)	11.57, 3.0 (1–47)	2.26, 2.0 (1–6)
Indication, number of episodes (%)			
Acute non-surgical bleeds	933 (95.6)	76 (93.8)	61 (87.1)
Surgery	11 (1.1)	3 (3.7)	8 (11.4)
Prophylaxis	32 (3.3)	2 (2.5)	1 (1.4)
Initial dose, μg kg^{-1}			
Mean, median (range)	180.7, 148.1 (11.0–491.8)	139.5, 119.0 (23.6–291.6)	103.6, 90.5 (13.8–360)
Initial dose group, number of episodes (%)			
<90 μg kg^{-1}	161 (16.5)	12 (14.8)	30 (42.9)
≥90–<180 μg kg^{-1}	338 (34.6)	32 (39.5)	24 (34.3)
≥180–<270 μg kg^{-1}	210 (21.5)	7 (8.6)	5 (7.1)
≥270 μg kg^{-1}	185 (19.0)	4 (6.5)	3 (4.3)
Missing data	82 (8.4)	26 (32.1)	8 (11.4)
Number of doses			
Mean, median (range)	4.5, 1.0 (1.0–131.0)	5.2, 1.0 (1.0–48.0)	5.6, 2.0 (1.0–54.0)
Duration of treatment, h			
Mean, median (range)	41.6, 2.5 (2.5–2834.5)	47.0, 2.5 (2.5–1442.5)	36.0, 6.0 (2.5–660.0)
Single-dose treatment			
Number of episodes (%)	510 (52.3)	29 (35.8)	22 (31.4)
Concomitant medication use, number of episodes (%)[†]	145 (14.9)	12 (14.8)	32 (45.7)
FVIII replacement products	60 (6.1)	0 (0)	3 (4.3)
pd-aPCC[‡]	33 (3.4)	11 (13.5)	21 (30.0)
Tranexamic acid	26 (2.7)	1 (1.2)	6 (8.6)
Desmopressin	7 (0.7)	0 (0)	1 (1.4)
No information	19 (2.0)	0 (0)	1 (1.4)

[†]Some treatment episodes involved more than one concomitant medication.
[‡]pd-aPCC, plasma-derived activated prothrombin complex concentrate.

treated on-demand (haemophilia A/B: 1009 [96%]; acquired haemophilia: 61 [87.1%]). Concomitant medication was used during 157 (14.9%) rFVIIa treatment episodes in patients with haemophilia A/B, and 32 (45.7%) rFVIIa treatment episodes in acquired haemophilia patients (Table 2). For haemophilia A/B, concomitant medication was most commonly FVIII replacement products (60 episodes), followed by plasma-derived activated prothrombin complex concentrate (pd-aPCC; 44 episodes). For patients with acquired haemophilia, pd-aPCC was the most frequently used concomitant medication (21 episodes), as many patients switched to rFVIIa after failing to respond to pd-aPCC.

A high initial rFVIIa dose (≥180 μg kg^{-1}) was used for 38.4% of episodes in patients with haemophilia A or B, while 51.4% of episodes were treated with lower rFVIIa doses (Table 2, Fig. 1). Initial doses tended to be considerably higher in patients with haemophilia A or B than in acquired haemophilia (Table 2, Fig. 1); a high initial rFVIIa dose (≥180 μg kg^{-1}) was used for only 11.4% of episodes in patients with acquired haemophilia, with 77.1% of episodes treated with lower rFVIIa doses (Table 2, Fig. 1).

In patients with haemophilia A and B, the mean (median) number of rFVIIa doses per treatment episode was 4.5 (1.0) and 5.2 (1.0) respectively; the mean (median) duration of treatment was 41.6 h (2.5 h) and 47.0 h (2.5 h) for haemophilia A and B respectively (Table 2). For patients with acquired haemophilia, the mean (median) number of rFVIIa

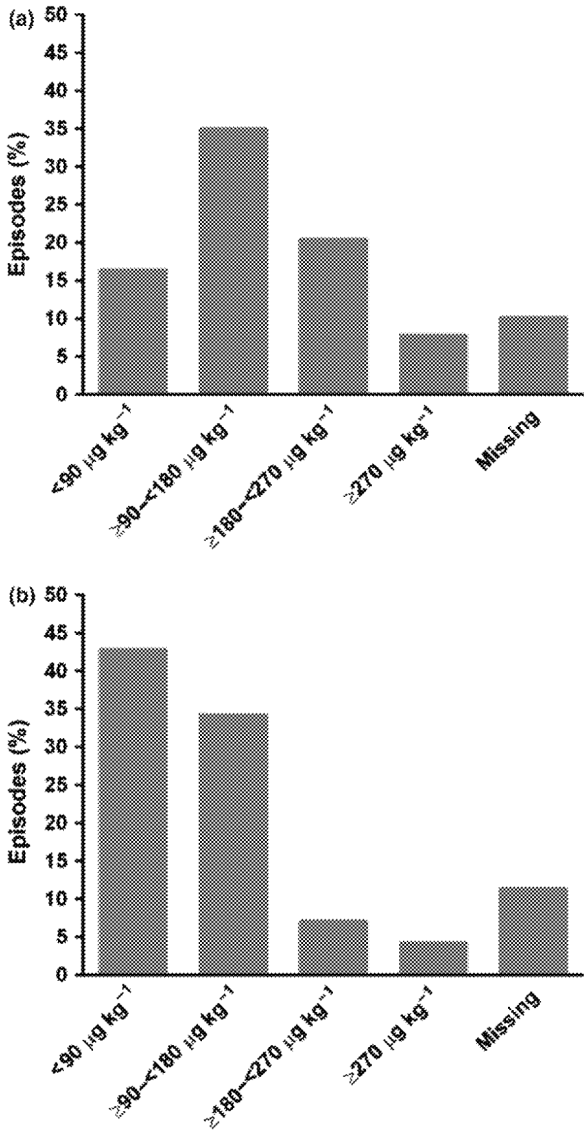

Fig. 1. Proportion of bleeds treated by rFVIIa dose category in patients with haemophilia A or B (a) and acquired haemophilia (b).

doses per treatment was 5.6 (2.0), and patients received treatment for a mean (median) of 36.0 h (6.0 h).

For patients with haemophilia A and B, a single-dose administration was used in 52.3% and 35.8% of treatment episodes, respectively, while for acquired haemophilia, this value was 31.4% (Table 2). High initial rFVIIa doses (≥180 μg kg^{-1}) were associated with a higher proportion of single-dose administrations than lower doses (Fig. 2), suggesting a reduced need for repeat dosing when an initial high dose is used. Table 3 summarizes rFVIIa dosing regimens in patients with haemophilia A or B (Table 3); high-dose rFVIIa (≥180 μg kg^{-1}) was also associated with a lower number of required doses vs. rFVIIa 90–180 μg kg^{-1} (median 1 vs. 2) and shorter treatment duration (median 2.5 vs. 6.5 h).

Table 4 summarizes rFVIIa dosing regimens in patients with haemophilia A or B receiving on-demand treatment for acute non-surgical bleeds, prophylaxis or treatment of surgical bleeding. Overall, the highest initial doses were administered in the on-demand group.

No adverse drug reactions or obvious anti-rFVIIa antibody formation were reported in any patient (patients were not routinely screened for anti-VIIa antibodies). There were no reports of thromboembolic events or disseminated intravascular coagulation, even in the 44 treatment episodes in patients with haemophilia A/B, and 21 treatment episodes in acquired haemophilia patients, for which rFVIIa was prescribed concomitantly with pd-aPCC.

Discussion

This report presents the results of a postmarketing study mandated by the regulator and conducted independently by the UK NHD. This is a novel use for such a database, which has many advantages over the more usual commercial approach to such studies. Although, in general, databases cannot collect data to Good Clinical Practice standards (at least not yet), they have access to a far larger number of subjects than are directly available to industry, enjoy a degree of independence, and already collect safety data. Pharmacovigilance is one of their more important functions. Since postmarketing studies are expensive to conduct and often fail to recruit adequately, these features may be attractive to both regulators and manufacturers. Indeed, national databases may be the only organizations with the capacity to conduct large-scale postmarketing pharmacovigilance in a statistically meaningful sample of patients. Directors of national databases have a duty to extract maximum scientific value from the data that they collect and, as patient safety is of paramount importance to all of us, pharmacovigilance and postmarketing surveillance should become an increasingly important function of disease databases. It would benefit the entire haemophilia community if national databases fostered an increasingly collaborative working relationship with manufacturers and the regulators.

As is often the case, our 'real-world' data revealed differences between normal clinical practice and standard dosage recommendations and usage, as reflected in clinical trials.

Data from 1057 treatment episodes were available from 67 patients with haemophilia A or B and inhibitors attending 16 centres. Data showed that, although it is normally recommended to use at least two infusions of rFVIIa even for haemarthrosis, a single rFVIIa administration was the most frequently used regimen

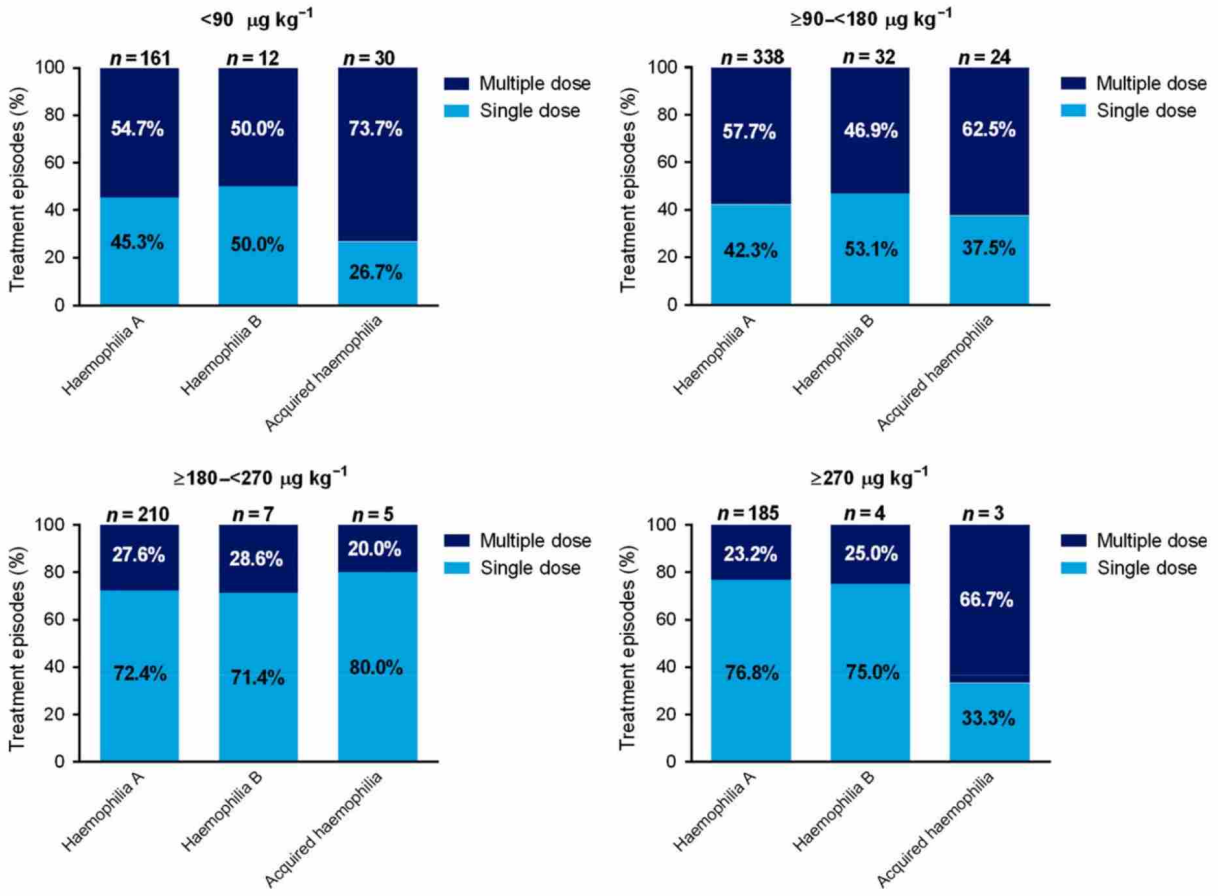

Fig. 2. Proportion of treatment episodes that utilized single-dose vs. multiple-dose rFVIIa regimens according to initial dose category.

Table 3. Dosing regimens by initial rFVIIa dose group in haemophilia A or B patients.

	Initial rFVIIa dose group			
	<90 μg kg^{-1}	≥90–<180 μg kg^{-1}	≥180–<270 μg kg^{-1}	≥270 μg kg^{-1}
Total number of treatment episodes[†]	173	370	217	189
Single-dose regimen				
N	79	158	157	145
Number of doses per treatment episode				
Mean	4.6	7.0	3.0	1.4
Median	2.0	2.0	1.0	1.0
Range	1.0–56.0	1.0–131.0	1.0–88.0	1.0–9.0
Duration of treatment, h				
Mean	48.9	64.4	27.4	9.7
Median	2.5	6.5	2.5	2.5
Range	2.5–2834.5	2.5–2498.7	2.5–1616.5	2.5–99.5

[†]Data missing for 108 treatment episodes.

in normal clinical practice. Single-dose usage was common when higher initial doses were used but widely used at all doses reported. Higher initial doses were also associated with a shorter duration of treatment and fewer infusions.

We observed no thrombotic events even at high (≥180 μg kg^{-1}) dosage and in all indications (i.e. haemophilia A/B, acquired haemophilia), including 44 treatment episodes in haemophilia A/B and 21 in acquired haemophilia in which off-label concomitant pd-aPCC treatment was also used. These findings are consistent with the very low risk of thrombosis associated with rFVIIa treatment in clinical trials, spontaneous and solicited reports and other observational studies [10]. In contrast, higher than recommended doses of pd-aPCC have been associated with

Table 4. Recombinant FVIIa dosing regimens by indication (acute non-surgical bleeds, prophylaxis and surgical episodes) in haemophilia A, haemophilia B and acquired haemophilia patients.

	Treatment of bleeding episodes			Prophylaxis			Treatment for surgical episodes		
	Haemophilia A	Haemophilia B	Acquired haemophilia	Haemophilia A	Haemophilia B	Acquired haemophilia	Haemophilia A	Haemophilia B	Acquired haemophilia
Number of episodes (%)	933 (95.6)[†]	76 (93.8)[†]	61 (87.1)[§]	32 (3.3)[†]	2 (2.5)[†]	1 (1.4)[§]	11 (1.1)[†]	3 (3.7)[†]	8 (11.4)[§]
Initial dose, μg kg^{-1}	183.6, 148.1 (11.0–491.8)	139.3, 117.6 (23.6–291.6)	104.2, 91.7 (13.8–360.0)	121.6, 104.1 (71.4–263.2)	175.1, 175.1 (175.1–175.1)	78.0, 78.0 (78.0–78.0)	113.5, 94.4 (40.4–220.6)	130.8, 146.3 (67.3–178.9)	103.1, 90.1 (78.1–189.0)
Number of doses per treatment episode	2.9, 1.0 (1.0–70.0)	4.5, 1.0 (1.0–35.0)	5.1, 2.0 (1.0–27.0)	47.7, 43.5 (22.0–131.0)	48.0, 48.0 (48.0–48.0)	54.0, 54.0 (54.0–54.0)	7.4, 3.0 (1.0–27.0)	3.3, 1.0 (1.0–8.0)	2.8, 2.0 (1.0–7.0)
Duration of treatment, h	14.2, 2.5 (2.5–226.6)	18.7, 2.5 (2.5–114.7)	26.4, 5.2 (2.5–160.9)	807.4, 510.9 (270.8–2834.5)	1443.0, 1443.0 (1443.0–1443.0)	660.0, 660.0 (660.0–660.0)	28.6, 25.0 (2.5–74.5)	25.2, 2.5 (2.5–70.5)	14.8, 4.8 (2.5–45.5)

Data are mean, median (range) unless otherwise stated. Percentages represent proportions of total treatment episodes for all indications in [†]haemophilia A, [‡]haemophilia B and [§]acquired haemophilia.

thromboembolic events [16]. Consequently, the labelling of pd-aPCC was revised to include a maximum dose of 100 IU kg^{-1} and a daily maximum dose of 200 IU kg^{-1} [17]. Recombinant FVIIa has no upper maximum daily dose [18].

It is noteworthy that patients with acquired haemophilia, and to a lesser extent haemophilia B, were treated with significantly lower doses of rFVIIa than those with haemophilia A, despite these three conditions having similar bleeding severity. The European Acquired Haemophilia (EACH2) registry reported similar treatment trends, in that for 174 acquired haemophilia patients who received first-line rFVIIa, the median initial dose was 90 μg kg^{-1} (interquartile range, 84.71–102.86 μg kg^{-1}) [19]. Patients with acquired haemophilia are usually elderly, and we suspect that they may be treated conservatively because they are perceived to have a greater risk of thrombosis. Our data and other registry data suggest that this concern may be largely unjustified, and the balance of risk may favour more aggressive initial treatment with high-dose rFVIIa.

High-dose rFVIIa has been reported to provide more rapid and effective bleeding control than standard doses, and to decrease the number of infusions required to achieve and maintain haemostasis [3–6]. A reduced need for repeated venipuncture is more convenient, may improve compliance and quality of life and reduce the need for indwelling catheters with their associated complications.

In this study, a single infusion of rFVIIa was the most frequent treatment regimen in haemophilia A. This was especially observed in patients taking high-dose rFVIIa, which was associated with a shorter duration of treatment. This analysis also demonstrated that patients treated with rFVIIa on-demand received the highest initial dose. Taken together, these findings suggest that a single high dose of rFVIIa is sufficient to provide haemostasis for most bleeds. A similar finding was reported in the international, observational ONE Registry [20]. In our study, while 31% of bleeds were treated with an initial low dose of rFVIIa (≤120 μg kg^{-1}), 26% with an intermediate dose (>120–<250 μg kg^{-1}) 43% with a high dose (≥250 μg kg^{-1}) and all rFVIIa dose groups achieved effective haemostasis [20], high-dose rFVIIa (≥250 μg kg^{-1}) was associated with a lower number of required doses (median 1) compared with the lower dose groups (both median 2).

While the safety and efficacy of rFVIIa in patients with haemophilia have previously been established in randomized controlled trials, our data provide valuable real-world data suggesting that repeated dosing is not usually required for most bleeds treated on-demand. A limitation, however, is that the study did not include information on treatment outcomes, which were of less interest to EMA than the relative safety

of higher dose NovoSeven. Our data also reflect UK clinical practice, which may differ from that found elsewhere.

We have shown that, National Databases may be used for regulatory postmarketing surveillance (PMS) studies, extending their current pharmacovigilance role. This has the advantage over traditional PMS studies in that a larger sample of patients may be studied over a relatively short period of time, independently of industry and at significantly lower cost. This is an approach that should be explored and used more widely.

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Author contributions

The study was conceived and designed by CRMH and GD in collaboration with Novo Nordisk to satisfy their regulatory obligation to EMA. CRMH and TS oversaw the data collection and cleaning, and managed the study from its beginning until it was closed in 2011. TS collated the data, and communicated with the centres and Novo Nordisk during the course of the study. The manuscript was written and edited by all of the contributing authors; writing assistance to the authors during the preparation of this manuscript was provided by Sharon Eastwood (medical writer, PAREXEL) and was financially supported by Novo Nordisk in compliance with international guidelines for good publication practice.

Disclosures

TS has no conflicts of interest to declare. CRMH has been on the speaker bureau for Novo Nordisk-sponsored symposia and has acted as an occasional advisor to Novo Nordisk. CRMH has no pharmaceutical shareholdings and has no financial interest in this study. GD has been on the speaker bureau for Novo Nordisk-sponsored symposia. GD has no pharmaceutical shareholdings and has no financial interest in this study.

References

1 Knight C, Dano AM, Kennedy-Martin T. Systematic review of efficacy of rFVIIa and aPCC treatment for hemophilia patients with inhibitors. *Adv Ther* 2009; **26**: 68–88.
2 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.
3 Kavakli K, Makris M, Zulfikar B, Erhardtsen E, Abrams ZS, Kenet G. Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors. A multi-centre, randomised, double-blind, cross-over trial. *Thromb Haemost* 2006; **95**: 600–5.
4 Pan-Petesch B, Laguna P, Mital A *et al.* Single-dose (270 μg kg^{-1}) recombinant activated factor VII for the treatment and prevention of bleeds in haemophilia A patients with inhibitors: experience from seven European haemophilia centres. *Haemophilia* 2009; **15**: 760–5.
5 Santagostino E, Mancuso ME, Rocino A, Mancuso G, Scaraggi F, Mannucci PM. A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. *J Thromb Haemost* 2006; **4**: 367–71.
6 Young G, Shafer FE, Rojas P, Seremetis S. Single 270 μg kg^{-1}-dose rFVIIa vs. standard 90 μg kg^{-1}-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. *Haemophilia* 2008; **14**: 287–94.
7 Oyesiku JO. Home treatment of haemophilia patients with inhibitors. *Haemophilia* 2011; **17**: 173–8.
8 Salek SZ, Benson GM, Elezovic I *et al.* The need for speed in the management of haemophilia patients with inhibitors. *Haemophilia* 2011; **17**: 95–102.
9 Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. *Haemophilia* 2008; **14**: 898–902.
10 Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004; **2**: 1700–8.
11 Sallah S, Isaksen M, Seremetis S, Payne RL. Comparative thrombotic event incidence after infusion of recombinant factor VIIa vs. factor VIII inhibitor bypass activity – a rebuttal. *J Thromb Haemost* 2005; **3**: 820–2.
12 Her Majesty's Government. Data Protection Act 1998. Available at http://www.legislation.gov.uk/ukpga/1998/29/contents. Accessed 29 October 2015.
13 Department of Health. The Caldicott Guardian Manual 2010. Available at http://systems.hscic.gov.uk/infogov/links/2010cgmanual.pdf. Accessed 29 October 2015.
14 WMA. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at www.wma.net/en/30publications/10policies/b3/. Accessed 8 December 2015.
15 International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). Available at https://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 9 November 2015.>
16 Gomperts ED. FEIBA safety and tolerability profile. *Haemophilia* 2006; **12**: 14–9.
17 FEIBA. VH/NF US Package Insert. Available at http://www.feiba.com/us/forms/feiba_nf_pi.pdf. Accessed 10 October 2014.
18 EMEA. European Medicines Evaluation Agency (EMEA). European Public Assessment Report (EPAR) summary for NovoSeven. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000074/human_med_000936.jsp&mid=WC0b01ac058001d124. Accessed 10 October 2014.
19 Baudo F, Collins P, Huth-Kuhne A *et al.* Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood* 2012; **120**: 39–46.
20 Chambost H, Santagostino E, Laffan M, Kavakli K, ONE Registry Steering Committee on behalf of the Investigators.. Real-world outcomes with recombinant factor VIIa treatment of acute bleeds in haemophilia patients with inhibitors: results from the international ONE registry. *Haemophilia* 2013; **19**: 571–7.