

ORIGINAL ARTICLE *Inhibitors*

Effect of rFVIIa dose and time to treatment on patients with haemophilia and inhibitors: analysis of HemoRec registry data from the Czech Republic

P. SALAJ,* P. BRABEC,† M. PENKA,‡ V. POHLREICOVA,* P. SMEJKAL,‡ P. CETKOVSKY,* L. DUSEK† and U. HEDNER§

*Institute of Hematology and Blood Transfusion, Prague, Czech Republic; †Institute of Biostatistics and Analyses at Masaryk University in Brno, Czech Republic; ‡Department of Clinical Hematology at Faculty Hospital Brno, Czech Republic; and §University of Lund, Sweden and Novo Nordisk A/S, Research & Development, Maaloev, Denmark

Summary. Identifying haemophilia patients with inhibitors for clinical trials is difficult due to the limited number of patients available. Registries are therefore being established as an additional means of data collection. The aim of this study was to investigate the effect of different recombinant activated factor VII (rFVIIa; NovoSeven®) dose ranges and dosing schedules on the incidence of re-bleeding in haemophilia patients with inhibitors. In this retrospective, uncontrolled study, data on the bleeding patterns of adult haemophilia patients with high responding inhibitors were analysed. Only data from the Czech Republic, obtained by the HemoRec registry, were used. This study analysed 'real-life' clinical data and focused on the collection of the same parameters in different patients: time from bleeding onset to first injection, effect of first injection, number of re-bleedings, total number of injections and total

amount of haemostatic drug used. Fifteen patients met the inclusion criteria and were included into the study (128 bleeding episodes). Patients treated within 2 h of bleeding onset experienced less re-bleeding than patients treated after 2 h of bleeding onset (5.2% vs. 13.7%, respectively). In addition, patients who were treated after 2 h of bleeding onset experienced fewer re-bleedings when high-dose rFVIIa was used (15.8% and 0%; $<120 \mu\text{g kg}^{-1}$ and $>250 \mu\text{g kg}^{-1}$, respectively). Initial high-dose rFVIIa was also associated with a decline in total rFVIIa consumption. This registry has provided a unique insight into the bleeding patterns of inhibitor patients, highlighting the importance of early treatment initiation and appropriate starting dose.

Keywords: bleeding, dose, haemophilia, inhibitors, registry, rFVIIa

Introduction

The development of inhibitors to factor VIII (FVIII) and factor IX (FIX) is one of the most challenging complications in haemophilia. Inhibitor development occurs in approximately 21–33% of severe haemophilia A patients [1] and 2–5% of haemophilia B patients [2]. Due to suboptimal treatment (especially of joint bleeds) and lack of prophylactic regimens,

chronic haemophilia arthropathy is common in these patients, and results in reduced mobility and quality of life [3].

Although complicated procedures, such as the extracorporeal adsorption of inhibitors, can be attempted to make treatment with factor concentrates feasible in inhibitor patients, they are not used in the treatment of mild to moderate bleeding episodes. Such bleeding episodes in inhibitor patients are currently treated with FVIII bypassing agents like recombinant activated factor VII (rFVIIa; NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark) and activated prothrombin complex concentrate (aPCC; FEIBA®; Baxter, Vienna, Austria). Controlled studies have shown rFVIIa to have an efficacy rate of approximately 80–90% [4–6], whilst controlled studies of

Correspondence: Dr Peter Salaj, Institute of Hematology and Blood Transfusion, U Nemocnice 1, 128 20 Prague 2, Czech Republic.

Tel.: +420 221 977284; fax: +420 221 977249; e-mail: peter.salaj@uhkt.cz

Accepted after revision 21 January 2009

aPCC have reported efficacy rates of approximately 60–80% [6–8]. rFVIIa has been used extensively over the last two decades in haemophilia patients with inhibitors and has established a good safety profile [9].

Since rFVIIa is not a substitution therapy like FVIII/FIX, but represents a completely new concept of treatment (the administration of supra-physiological dose of rFVIIa that effectively induces haemostasis at the site of injury), finding the optimal dose has been a major challenge [10]. The primary goal of bypassing agents like rFVIIa is to make the treatment of inhibitor patients similar to that offered to non-inhibitor patients – effective treatment of mild-to-moderate joint bleeds in one single injection. Individual adjustment of dosing due to biological variation has been found to help achieve this goal [6,11,12]. Recently, a dosing regimen of rFVIIa 270 $\mu\text{g kg}^{-1}$ (given as one single injection) has been shown to have comparable efficacy to the rFVIIa $3 \times 90 \mu\text{g kg}^{-1}$ standard regimen. The single-dose regimen was approved for use in the European Union (EU) in 2007 [6,12,13]. Nevertheless, issues regarding optimal dosing remain and need to be addressed to enable the benefits experienced by non-inhibitor patients to be achieved by inhibitor patients.

Since the number of haemophilia patients with inhibitors is low, the opportunities for clinical studies in this patient population are limited. Consequently, establishing registries for compiling experience in haemophilia care is being explored as an alternative means of collecting clinical data. HemoRec is a prospective, observational registry established in 2005, for the collection of haemophilia data in the Central European region including the Czech Republic, Poland, Slovakia, Hungary and Slovenia [14]. By 2008, 2060 patient records had been entered into the registry. It is hoped that by assessing data from this registry, useful information on the practices and treatment schedules, including optimal patient care, improved patient outcomes and improved use of valuable resources and therapies can be identified.

This manuscript describes the analysis and results from ‘real-life’ clinical treatment of inhibitor patients in the Czech Republic using rFVIIa. We investigated the effect of different rFVIIa dose ranges, and the effect the timing of their administration had on the incidence of re-bleeding in inhibitor patients. The overall consumption of the haemostatic product required per bleeding episode was also assessed.

Materials and methods

This was a retrospective, uncontrolled study based on analyses of descriptive data from haemophilia

patients with inhibitors in the Czech Republic, which were collected and analysed by the HemoRec registry.

Data collection

HemoRec is a web-based application designed to easily capture a broad array of data on haemophilia patients including demographic information, medical history, physical examinations and laboratory results. Detailed information on the primary diagnosis, symptoms and manifestations, treatments and potential complications were recorded. The software provides rapid access to data on haemophilia patients entered into the system, detailing graphs and reports on specific patients or patient groups. The software offers a multilingual and customized system set-up that allows individual user preferences. HemoRec is provided by the Institute of Biostatistics and Analysis at the Masaryk University in Brno, Czech Republic, and is maintained in accordance with patient data privacy regulations in the EU, US and Canada.

Patient eligibility

For the purposes of the present study, only adult haemophilia patients (adults ≥ 18 years of age) with high responding inhibitors (historic inhibitor peak ≥ 10 Bethesda Units mL^{-1}) from the Czech Republic were eligible for inclusion in the study and analyses. Only data from bleeding episodes treated with rFVIIa have been used. Additional criteria included previous treatment with at least one treatment course of rFVIIa. All haemorrhages, either spontaneous or trauma treated with rFVIIa, in both hospital and home-treatment settings, were included in our analysis.

Endpoints

In contrast to published prospective trials with rFVIIa where treatment protocols with strict fixed doses and efficacy parameters have been used, we retrospectively analysed ‘real-life’ clinical data from different centres without preliminary set-up of primary or secondary objectives. We therefore aimed to be as objective as possible by focusing on the collection of the same parameters for all patients and bleeding episodes. The time between the onset of bleeding and the first injection, and the effect of rFVIIa dose (of the first injection) was analysed and compared with the incidence of re-bleedings, total number of injections per bleed and total amount of

haemostatic drug per bleeding episode. Re-bleeding was defined as bleeding in the same location as the original bleed within 48 h.

Safety

Treatment safety was evaluated according to investigator-determined adverse events (AEs) reported in the registry. AEs were qualified to be related or unrelated to the used haemostatic drug.

Statistical analysis

Descriptive statistical analyses were used for continuous clinical parameters (mean, median and range) whereas categorical variables were summarized using frequency tables. Non-parametric tests (Mann–Whitney test, Kruskal–Wallis test) were applied to assess the difference in continuous variables. Standard level of statistical significance $P \leq 0.05$ was used.

Results

Of the 99 patients with haemophilia and inhibitors registered in the HemoRec registry, 15 patients from the Czech Republic met the inclusion criteria and were included in the study. Demographic data for the eligible cohort are provided in Table 1. The resulting group had registry data for the 128 bleeding episodes treated with rFVIIa (Table 2). The majority of bleeding episodes were into joints and accounted for 75% (96 of 128) of recorded bleeds, 7.0% (9 of 128) of bleeding episodes were characterized as muscle bleedings and 11.7% (15 of 128) occurred in either the head, trunk, genitals or other locations. Eight of 128 (6.3%) bleeding episodes included bleeds at more than one anatomical site concurrently (Table 3). Of the 96 joint bleeds, 36 (37.5%) were bleeds into target joints and 60 (62.5%) were bleeds into non-target joints (Table 4).

Table 1. Demographic characteristics of patients ($n = 15$) and their bleeding episodes. All patients considered in the analyses were Caucasian.

	Mean	Median	Range
Age	31.6	29.0	19–53
Level of FVIII inhibitor (BU mL ⁻¹)	17.3	7.1	0.7–332.8
Mean no. of bleedings per year	5.0	2.5	1–17
	<i>n</i> positive	<i>n</i> all	%
Patients with HCV in anamnesis	6	15	40
Patients with HIV in anamnesis	0	15	0

HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Table 2. Time from the onset of bleeding to the beginning of treatment, number of injections per treatment course, re-bleedings and used amounts of rFVIIa in 128 bleeding episodes.

	Average	Median	Range	%
Hours between the onset of bleeding and the first injection	4.1	2.0	0–42	
No. of rFVIIa injections	1.9	1.0	1–11	
Amount of first injection rFVIIa ($\mu\text{g kg}^{-1}$)	141.0	116.1	70–348	
Amount of rFVIIa per bleeding episode ($\mu\text{g kg}^{-1}$)	232.1	193.5	70–967	
Re-bleedings (%) of total no. of bleedings				8.6

Table 3. Location and distribution of bleeding episodes ($n = 128$).

Location of bleed	Distribution of bleeding episodes (%)
Joints	75
Muscles	7.0
Head	3.9
Trunk	3.1
Genitals	1.6
Other locations	3.1
More than one location	6.3

Table 4. Incidence of re-bleeding according to target/non-target joints.

	No. of bleeding episodes	No. of bleeding episodes with re-bleeding	Bleeding episodes with re-bleeding (%)
All joint bleedings	96	8	8.3
Target joints	36	3	8.3
Non-target joints	60	5	8.3

No significant differences ($P > 0.05$) for target vs. non-target joints.

The time between the onset of bleeding and the first injection varied greatly across the study population (0–42 h); however, the average time to first infusion was 4.1 h with a median of 2 h (Table 2). The average time to first infusion was due to the fact that 80% of bleeding episodes were treated at home. Seventy-seven of the 128 bleedings (60.2%) were treated within the first 2 h of bleeding onset, while 51 of 128 (39.8%) received treatment after 2 h. The majority of bleeding episodes treated within 2 h after onset of bleeding received treatment within the first hour of the start of bleeding (50 of 77; 64.9%). The influence of early initiation of rFVIIa treatment on re-bleeding rate is shown in Fig. 1. Early treatment with rFVIIa appears to be more effective compared with delayed treatment in controlling bleeding. The incidence of re-bleeding is more than twice as high

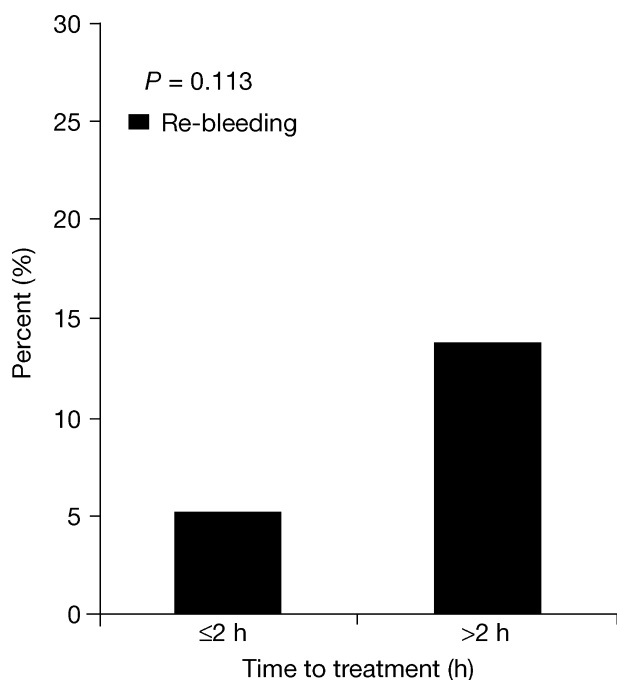


Fig. 1. Incidence of re-bleeding in relation to time to treatment.

in patients treated after 2 h (5.2% vs. 13.7% re-bleedings; $P = 0.113$).

The haemostatic efficacy of rFVIIa for control of joint bleeds, as determined by re-bleeding rates, did

not differ ($P > 0.05$) according to whether bleeding was at target or non-target joints (Table 4). There was also no apparent difference between the efficacy of rFVIIa at target and non-target joints when data were analysed for administration within 2 h of bleeding onset or administration after 2 h from bleeding onset (Table 5). However, there were only a small number of bleeding episodes per category.

The effect of the first rFVIIa dose and the time to treatment is shown in Fig. 2. The group treated within 2 h of bleeding onset showed no significant difference with varying dose of rFVIIa and the incidence of re-bleeding (<120 $\mu\text{g kg}^{-1}$ [5.7%], 120–250 $\mu\text{g kg}^{-1}$ [4%], >250 $\mu\text{g kg}^{-1}$ [5.9%]; <120 $\mu\text{g kg}^{-1}$ vs. >250 $\mu\text{g kg}^{-1}$, $P = 0.947$). In contrast, the dose received by patients treated after 2 h of bleeding onset had a much greater impact on the incidence of re-bleeding (<120 $\mu\text{g kg}^{-1}$ [15.8%], 120–250 $\mu\text{g kg}^{-1}$ [9.1%], >250 $\mu\text{g kg}^{-1}$ [0%]; <120 $\mu\text{g kg}^{-1}$ vs. >250 $\mu\text{g kg}^{-1}$, $P = 0.721$).

Seventy-nine of 128 (62%) bleeding episodes were managed with one injection of rFVIIa (mean rFVIIa dose 153.1 $\mu\text{g kg}^{-1}$). Fewer re-bleeding episodes were observed when single-dose rFVIIa was administered compared with multiple dose rFVIIa infusions (6.3% vs. 12.2%; $P = 0.332$; Fig. 3a). The total amount of rFVIIa required per

Table 5. Incidence of re-bleeding in target/non-target joints according to the time to treatment.

	Time to treatment	No. of bleeding episodes	No. of bleeding episodes with re-bleeding	Bleeding episodes with re-bleeding (%)
Target joints*	Up to 2 h	24	1	4.2
	More than 2 h	12	2	16.7
Non-target joints†	Up to 2 h	38	2	5.3
	More than 2 h	22	3	13.6

* $P = 0.210$; † $P = 0.267$.

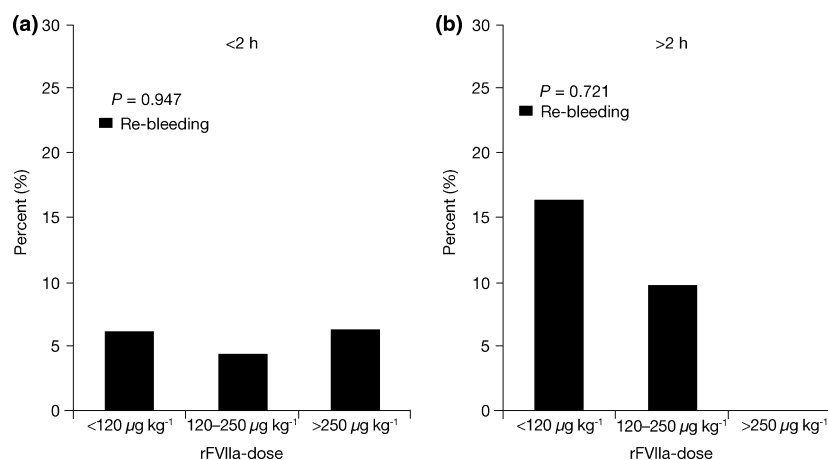


Fig. 2. Incidence of re-bleeding in relation to time to treatment and first rFVIIa dose (a: <2 h; b: ≥ 2 h). P -values compare rFVIIa <120 $\mu\text{g kg}^{-1}$ vs. >250 $\mu\text{g kg}^{-1}$. $P = 0.721$ for 'b' is due to only two bleeding episodes in >250 $\mu\text{g kg}^{-1}$ group.

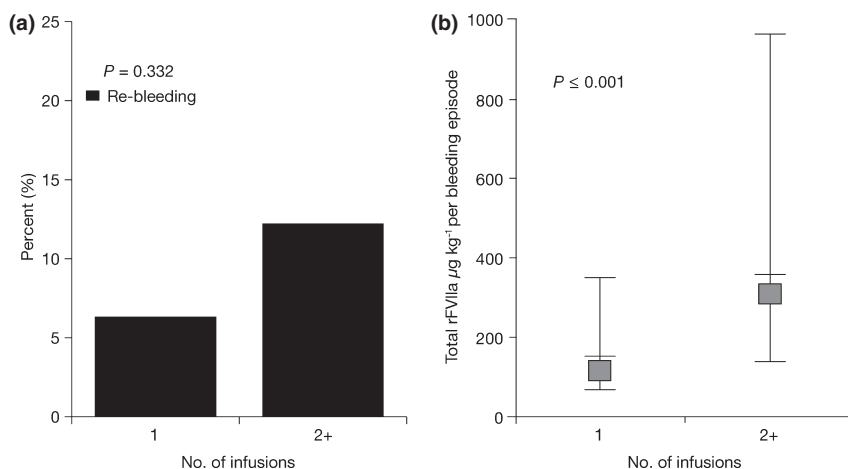


Fig. 3. Incidence of re-bleeding (a) and total rFVIIa consumption (b) in relation to the number of infusions.

Table 6. Number of rFVIIa injections, the amount of first injection and total rFVIIa consumption per bleeding episode.

No. of injections	No. of bleeding episodes	Bleeding episodes (%)	Mean first dose rFVIIa ($\mu\text{g kg}^{-1}$)	Mean total dose rFVIIa ($\mu\text{g kg}^{-1}$) per bleed
1	79	61.7	153.1	153.1
2	22	17.2	134.3	259.4
3	11	8.6	126.9	355.6
4	9	7.0	102.3	372.6
5 and more	7	5.5	99.2	663.6
Total	128	100	141.1	232.1

bleeding episode was significantly greater for patients treated with multiple doses of rFVIIa compared with one single dose of rFVIIa ($P < 0.001$; Fig. 3b). The correlation between the mean dose at first injection, number of injections per bleeding episode and the mean total amount of rFVIIa per bleeding episode are shown in Table 6. Our results show that the administration of higher initial doses of rFVIIa lead to a decline in the total number of injections required per bleeding episode and decrease in mean total dose.

There were no apparent treatment-dependent patterns in number or types of AEs reported into the registry by participating centres. No thromboembolic AEs were reported.

Discussion

In this paper, data from 15 adult haemophilia A patients with inhibitors from the Czech Republic were compiled by the HemoRec registry with special emphasis on the use of rFVIIa. Among the 128 bleeding episodes, 77 of 128 (60.2%) were treated

within 2 h of bleeding onset, whilst 51 of 128 (39.8%) received treatment later than 2 h after the start of the bleeding episode. The majority of the bleeding episodes treated within 2 h of bleeding onset were within the first hour (50 of 77; 64.9%). It has been reported that in haemophilia patients without inhibitors, early treatment of bleeding episodes is associated with the most effective outcome in terms of a lower incidence of re-bleeding and a reduction in the amount of haemostatic product required [15]. The same trend was observed in this series of bleeding episodes in inhibitor patients treated with rFVIIa. The percentage of re-bleeds in patients treated within 2 h of bleeding onset was 5.2% compared with 13.7% in those treated after 2 h of bleeding onset.

As home treatment is associated with faster 'time to treatment' [5], these findings emphasize the importance of establishing home treatment in both non-inhibitor and inhibitor patients. Interestingly, in this study, the use of a higher dose of rFVIIa ($>250 \mu\text{g kg}^{-1}$) appeared to be extremely important in decreasing the number of re-bleeds in the group of patients treated after 2 h of bleeding onset. No re-bleeds were observed for patients receiving rFVIIa $>250 \mu\text{g kg}^{-1}$, while the percentage of re-bleeds in the patients receiving rFVIIa $<120 \mu\text{g kg}^{-1}$ was 15.8%. For patients receiving rFVIIa $120\text{--}250 \mu\text{g kg}^{-1}$ the percentage of patients experiencing re-bleeds was 9.1%, suggesting, on the basis of our limited results, that a correlation between rFVIIa initial dose and the incidence of re-bleeding may exist.

Thromboelastography studies indicate that higher doses of rFVIIa lead to sustained haemostatic effects [16], probably by increasing the activation of platelets and the initial thrombin burst at the

site of injury. It has been hypothesized that even if thrombin generation is not completely normalized, it is substantially enhanced in the presence of rFVIIa concentrations of up to 100 nM L^{-1} and above (roughly corresponding to an injected dose of approximately $180\text{--}200 \mu\text{g kg}^{-1}$) [17]. In addition, with higher doses of rFVIIa, time to start of thrombin generation is substantially shortened and the rate of thrombin generation is increased. The rate of thrombin generation is important for the fibrin structure of the haemostatic plug [18] and fibrin clots formed in the presence of high amounts of rFVIIa are more resistant to proteolysis [19,20], which may be of great importance in the context of joint inflammation, e.g. synovitis, where elevated enzyme levels exacerbate proteolysis and destruction of synovium, cartilage and bone [21]. The striking effect of high-dose rFVIIa on bleeding episodes treated 2 or more hours after bleeding onset could be explained by the increasing presence of inflammation. As the time between bleeding onset and the start of treatment lengthens, more inflammation develops. In an inflamed environment, intra-articular vessels show a greater tendency for bleeding [22]. Thus, higher doses of rFVIIa may be required to provide a greater and more rapid thrombin burst, formation of a firm fibrin plug and sustained haemostasis.

Clinical evaluation of a $300 \mu\text{g kg}^{-1}$ dose of rFVIIa showed that 95 of 114 (83.3%) bleeding episodes responded to a single dose of rFVIIa treatment [23]. Studies comparing the effect of one single dose of rFVIIa $270 \mu\text{g kg}^{-1}$ with rFVIIa $3 \times 90 \mu\text{g kg}^{-1}$ showed equivalence between the two dosing regimens [6,12,13]. In the study by Santagostino *et al.*, both rFVIIa $270 \mu\text{g kg}^{-1}$ and rFVIIa $3 \times 90 \mu\text{g kg}^{-1}$ dosing schedules were equally effective in controlling bleeding at 48 h when treatment was initiated within 6 h of bleeding onset [13]. However, none of these studies assessed the rate of re-bleeding. Re-bleeding and haemostatic product consumption was the focus of a case report by Cooper *et al.* [11]. The use of high-dose rFVIIa ($320 \mu\text{g kg}^{-1}$) to control bleeding was not only effective where other haemostatic regimens had failed, but also led to a lowered frequency of bleeding episodes per month and an overall reduction in rFVIIa consumption [11]. In the present series of patients, a significantly lower amount of rFVIIa was consumed by patients treated with a higher dose of rFVIIa, confirming the findings of previously published studies [23,24].

The results detailed in this paper indicate that doses of <120 to $>250 \mu\text{g kg}^{-1}$ rFVIIa provide

comparable efficacy if treatment is administered within 2 h of the initiation of bleeding (Fig. 2a). However, this study has also identified that when treatment cannot be given within 2 h, the most effective course of action is to initiate therapy with high-dose rFVIIa. In this study, high-dose rFVIIa provided the most effective control of bleeding and reduced the need for multiple injections (Fig. 2b).

The data presented also show HemoRec registry data to fully confirm earlier reports, including those of the similar Haemophilia & Thrombosis Research Society (HTRS) registry, that use of rFVIIa in a home treatment setting is safe, feasible and effective at inducing and maintaining haemostasis with a small number of doses [25,26]. The HTRS reported that doses of rFVIIa up to $346 \mu\text{g kg}^{-1}$ were well tolerated and that doses of $>200 \mu\text{g kg}^{-1}$ significantly increased the efficacy of rFVIIa to 97% compared with 84% efficacy for lower doses [25].

The analyses and results from the HemoRec registry also show that no thromboembolic events were associated with the use of rFVIIa at any dose. Recent literature supports the good safety profile of rFVIIa for the management of bleeding episodes in haemophilia patients with inhibitors using a single dose of rFVIIa $270 \mu\text{g kg}^{-1}$ [6,12]. rFVIIa has also been shown to be safe, well tolerated and effective for patients undergoing orthopaedic surgery [9,27] and in patients treated prophylactically [28].

This paper underlines the important role a registry can play in data collection, particularly in rare diseases where patient numbers are limited. Registry data have been extremely valuable in the management of other rare bleeding disorders [29,30]. This paper also demonstrates the value of a registry for mapping the quality of treatment in a specific region.

In conclusion, analysis of these registry data has provided a unique insight into the bleeding patterns of haemophilia patients with inhibitors treated with rFVIIa; highlighting the importance of early treatment initiation and the use of an appropriate starting dose.

Acknowledgements

The authors wish to thank Jennifer Powell of PAREXEL MMS for medical writing services in the preparation of this manuscript. Preparation of the manuscript was financially supported by Novo Nordisk.

Disclosures

P. Salaj and M. Penka have acted as paid speakers during scientific events organized by Novo Nordisk and have received a reimbursement for attending the scientific symposiums. P. Brabec and L. Dusek have received unrestricted education grant from Novo Nordisk focused on providing data collection system of international data collection of hemophilia patients in years 2006, 2007 and 2008. P. Smejkal has received a reimbursement for attending the scientific symposium. U. Hedner is employed by Novo Nordisk, the manufacturer of rFVIIa (NovoSeven®) since 1983. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- Haya S, Moret A, Cid AR *et al.* Inhibitors in haemophilia A: current management and open issues. *Haemophilia* 2007; **13**: 52–60.
- Rodriguez-Merchan EC, Wiedel JD, Wallny T *et al.* Elective orthopaedic surgery for inhibitor patients. *Haemophilia* 2003; **9**: 625–31.
- Morfini M, Haya G, Tagariello G *et al.* European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia* 2007; **13**: 606–12.
- Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *J Thromb Haemost* 1998; **80**: 773–8.
- Key NS, Aledort LM, Beardsley D *et al.* Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *J Thromb Haemost* 1998; **80**: 912–8.
- 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.
- Lusher JM, Shapiro SS, Palascak JE, Rao AV, Levine PH, Blatt PM. Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to factor VIII: a multicenter therapeutic trial. *N Engl J Med* 1980; **21**: 421–5.
- Sjamsedin LJ, Heijnen L, Mauser-Bunschoten EP *et al.* The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. *N Engl J Med* 1981; **24**: 717–21.
- 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.
- Hedner U. Treatment of patients with factor VIII and factor IX inhibitors with special focus on the use of recombinant factor VIIa. *J Thromb Haemost* 1999; **82**: 531–9.
- Cooper HA, Jones CP, Campion E, Roberts HR, Hedner U. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. *Haemophilia* 2001; **7**: 517–22.
- Kavakli K, Makris M, Zulfikar B *et al.* 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.
- 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.
- HemoRec registry web site. Available at: <http://www.hemorec.com> (last accessed on 3 October 2008).
- Furie B, Limentani SA, Rosenfield CG. A practical guide to the evaluation and treatment of hemophilia. *Blood* 1994; **84**: 3–9.
- Young G, Blain R, Nakagawa P, Nugent DJ. Individualization of bypassing treatment for haemophilia patients with inhibitors using thromboelastography. *Haemophilia* 2006; **12**: 598–604.
- Abshire TC. Dose optimisation of recombinant activated factor VII for control of mild to moderate bleeds in inhibitor patients: improved efficacy with higher dosing. *Semin Hematol* 2004; **41**: 3–7.
- Blombäck B, Carlsson K, Fatah K, Hessel B, Procyk R. Fibrin in human plasma: gel architectures governed by rate and nature of fibrinogen activation. *Thromb Res* 1994; **75**: 521–38.
- Hedner U. Mechanism of action, development and clinical experience of recombinant FVIIa. *J Biotechnol* 2006; **124**: 747–57.
- Wolberg AS, Allen GA, Monroe DM, Hedner U, Roberts HR, Hoffman M. High dose factor VIIa improves clot structure and stability in a model of haemophilia B. *Br J Haematol* 2005; **131**: 645–55.
- Roosendaal G, Vianen ME, Marx JJ, van den Berg HM, Lafeber FP, Bijlsma JW. Blood-induced joint damage: a human in vitro study. *Arthritis Rheum* 1999; **42**: 1025–32.
- Sherry DD. Avoiding the impact of musculoskeletal pain on quality of life in children with hemophilia. *Orthop Nurs* 2008; **27**: 103–8.
- Kenet G, Lubetsky A, Luboshitz J, Martinowitz U. A new approach to treatment of bleeding episodes in young haemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven®). *J Thromb Haemost* 2003; **1**: 450–5.

- 24 Kenet G, Lubetsky A, Luboshitz J, Gitel S, Varon D, Martinowitz U. Treatment of inhibitor patients with rFVIIa: continuous infusion protocols as compared to single, large dose. *Haemophilia* 2000; **6**: 279.
- 25 Parameswaran R, Shapiro AD, Gill JC, Kessler CM, HTRS Registry Investigators. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005; **11**: 100–6.
- 26 Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. *Br J Haematol* 1999; **104**: 22–6.
- 27 Oberfell A, Auvinen MK, Mathew P. Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 2007; **14**: 233–41.
- 28 Konkle BA, Ebbesen LS, Erhardtsen E *et al.* Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost* 2007; **5**: 1904–13.
- 29 Poon MC, d'Oiron R. Recombinant activated factor VII (NovoSeven®) treatment of platelet-related bleeding disorders. International Registry on Recombinant Factor VIIa and Congenital Platelet Disorders Group. *Blood Coagul Fibrinolysis* 2000; **11**(Suppl. 1): S55–68.
- 30 Acharya SS, Coughlin A, Dimichele DM; North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorders Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost* 2004; **2**: 248–56.