

ORIGINAL ARTICLE

Single-dose (270 $\mu\text{g kg}^{-1}$) recombinant activated factor VII for the treatment and prevention of bleeds in haemophilia A patients with inhibitors: experience from seven European haemophilia centres

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Summary. Several studies have suggested that recombinant factor VIIa (rFVIIa) is effective and safe at doses $>90 \mu\text{g kg}^{-1}$. In March 2007, the European Medicines Agency approved the use of single-dose rFVIIa 270 $\mu\text{g kg}^{-1}$ for the treatment of mild-to-moderate bleeds in haemophilia patients with inhibitors. The aim of this study was to describe the use of single-dose rFVIIa in a real-life setting. In November 2007, seven haemophilia specialists from five European countries convened to share and discuss their experiences with the single-dose rFVIIa regimen within haemophilia A. Case histories of eight patients were discussed in this retrospective study. Six adult and two paediatric patients (age range, 19 months–40 years) were treated with single-dose rFVIIa for a variety of target-joint bleeding, other bleeds and bleeding prevention. Treatment was successful in all the eight cases, with most patients requiring one dose to achieve

bleeding resolution. No thrombotic or other safety concerns were raised by single-dose rFVIIa treatment. All patients and physicians preferred single-dose rFVIIa treatment to multiple injections; key benefits of single-dose rFVIIa treatment reported by patients and physicians included improved quality of life, greater convenience and ease of administration, improved compliance, faster control of bleeding, less injection-related pain and faster pain relief. In the patients reported here, single-dose rFVIIa 270 $\mu\text{g kg}^{-1}$ appears to be an effective and safe haemostatic treatment that improves the quality of life and convenience of treatment for patients. Such treatment might be of particular benefit for patients with difficult venous access or needle phobia.

Keywords: haemophilia, haemorrhage, inhibitors, NovoSeven[®], rFVIIa, single dose

Introduction

The introduction of recombinant activated factor VII (rFVIIa, NovoSeven[®]; Novo Nordisk A/S, Bagsværd, Denmark) represented a significant development in the management of haemophilia

patients with inhibitors to factor VIII or IX. European approval for rFVIIa use as a treatment for spontaneous or surgical bleeds in these patients was granted in 1996, with a recommended dosing schedule of rFVIIa 90 $\mu\text{g kg}^{-1}$ every 2–3 h until haemostasis is achieved [1]. This regimen has proved to be effective and well tolerated for the inhibitor population, controlling up to 92% of mild-to-moderate bleeds with an average of 2.2 injections [2]. However, in the interest of optimizing treatment for haemophilia patients with inhibitors, there is now a growing belief that treatment with a single high dose might help to improve patients' quality of life

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and could potentially lead to a faster treatment response.

Several studies over recent years have suggested that not only single high dose rFVIIa is effective in producing haemostasis in inhibitor patients, but also it has a safety profile comparable with that of the standard multiple-dose schedule [3–6]. It has also been suggested that higher doses of rFVIIa produce a ‘more normal’ fibrin clot network with thinner fibrin fibres and tightly packed fibrin strands, leading to stronger clot formation [7]. The single-dose rFVIIa 270 µg kg⁻¹ regimen was approved by the European Union in March 2007 for the treatment of mild-to-moderate bleeding episodes in haemophilia patients with inhibitors.

Approval of this new dosing regimen has allowed physicians to expand the therapeutic armamentarium for inhibitor management. A key advantage of a single-dose rFVIIa regimen is the improved convenience of treatment, which might be particularly significant in patients with restricted venous access or frequent target-joint bleeds [4,6,8], and those who fear or reject multiple injections. Single-dose rFVIIa treatment may, therefore, improve patient compliance, minimize interruption to daily activities and increase the feasibility of home treatment.

In this study, we report case data from eight inhibitor patients who were treated with single-dose rFVIIa at seven haemophilia centres in five European countries.

Methods

In November 2007, a group of European haemophilia specialists shared and discussed examples of their experiences with the single-dose rFVIIa regimen. The aims of the meeting were (i) to share the experience in the use of single-dose rFVIIa outside the clinical trial setting; (ii) to determine patients’ and physicians’ perceptions of this new dosing schedule; and (iii) to evaluate the impact of single-dose rFVIIa treatment on the patients’ quality of life. Seven physicians from haemophilia centres in five European countries (two from France, two from Poland, and one each from Croatia, the Czech Republic and the United Kingdom) provided retrospective case history details of eight inhibitor patients’ bleeding episodes treated with the single-dose rFVIIa regimen.

Results

Patient demographics and clinical characteristics

The demographics and clinical characteristics of the eight case studies are summarized in Table 1. There

were six adult cases and two paediatric cases (age range, 19 months–40 years); all patients had haemophilia A, and there was wide variation in both historical inhibitor titre peaks and bleed frequencies (Table 1). With the exception of case 5 (19-month-old child), all patients had previously received treatment with the rFVIIa 3 × 90 µg kg⁻¹ dosing regimen and/or other haemostatic agents. Five patients had developed bleeds in target joints (cases 1, 2, 3, 6 and 8). Co-morbidity was reported for just one patient (case 7; hepatitis C) who had a 14-year history of drug abuse and a 6-year history of methadone treatment.

Physicians’ reasons for using single-dose rFVIIa

Ease of use and poor venous access/presence of damaged veins were cited as reasons for administering single-dose rFVIIa (cases 1, 2, 3, 5, 6 and 8; Table 2). In one patient with damaged veins (case 2), administration of the single-dose rFVIIa regimen was associated with faster bleed resolution and was more convenient than repeated injections. Other reasons for using single-dose rFVIIa rather than the rFVIIa 3 × 90 µg kg⁻¹ treatment included needle phobia (case 1), pain reduction (case 6), rescue therapy following inefficacy of multiple doses of activated prothrombin complex concentrate (APCC) (case 7), prevention of post-traumatic intracerebral haemorrhage following the fall of a young child on his face (case 5), avoidance of hospitalization (case 5) and desire to achieve a faster treatment response than would be afforded by the 3 × 90 µg kg⁻¹ dosing regimen (cases 4 and 6). Single-dose rFVIIa therapy was also administered to treat a muscle bleed following the development of an adverse reaction (body rash) to APCC therapy (case 4).

Single-dose rFVIIa was used to treat target-joint bleeds in four patients (elbow [cases 1 and 3] and knee [cases 6 and 8]) (Table 2). Case 4 received single-dose rFVIIa treatment to resolve a calf muscle bleed, while case 7 had a large haematoma of the forearm following surgery to repair a fractured radius bone of the same arm. Case 7 also presented with elements of compartment syndrome. One patient (case 2) received single-dose rFVIIa to treat multiple traumatic injuries resulting from a fall (muscle haematoma, joint bleeds and head laceration), and a 19-month-old child (case 5) was treated with single-dose rFVIIa to control his first ever bleed following a traumatic blow to the forehead.

Home vs. hospital administration

Five of the eight patients detailed in the case studies received single-dose rFVIIa in the home setting (cases

Table 1. Patient demographics and clinical characteristics.

Case no. (Centre, City)	Patient age	Haemophilia type	Historical inhibitor titre peak (BU/ml)	Previous treatment	Historical average no. of rFVIIa doses required per bleed (90 µg kg ⁻¹ /dose)	Target joint	No. of bleeds per year
1 Centre Régional de Traitement de l'Hémophilie et des Maladies Hémorragiques, Brest.	40 years	A	– (No previous inhibitor titre available)	APCC rFVIIa 3 × 90 µg kg ⁻¹ rFVIIa 270 µg kg ⁻¹ (single dose)	2–3	Elbow	30
2 Medical University of Gdansk, Gdansk.	29 years	A	7000	APCC FVIII rFVIIa 3 × 90 µg kg ⁻¹	2–4	Knee, elbow, ankle	50
3 Medical University, Warsaw.	12 years	A	40	APCC FVIII rFVIIa 3 × 90 µg kg ⁻¹	2–3	Elbow	25
4 St Thomas Hospital, London.	28 years	A	112	APCC FVIII rFVIIa 3 × 90 µg kg ⁻¹	2	None	35
5 Necker Hospital, Paris.	19 months	A	1.5	None	N/A	None	First bleed
6 University Hospital Centre-Rebro, Zagreb.	33 years	A	80.7	APCC FVIII rFVIIa 3 × 90 µg kg ⁻¹	2–4	Knee, both elbows	12
7 University Hospital Centre-Rebro, Zagreb.	30 years	A	– (Inhibitor not previously detected)	APCC FVIII Cryoprecipitate rFVIIa 3 × 90 µg kg ⁻¹ (single dose)	N/A	None	One in 2 years
8 Institute of Haematology and Blood Transfusion, Prague.	34 years	A	55.0		2–4	Knee	15

APCC, activated prothrombin complex concentrates; FVIII, factor VIII; FIX, factor IX; N/A, not applicable; rFVIIa, recombinant activated factor VII.

3, 4, 5, 6 and 8). Of the three patients treated at hospital, one had a needle phobia (case 1), and two presented with bleeds related to trauma or surgery (cases 2 and 7) (Table 2).

For patients who received home treatment, the single-dose rFVIIa regimen was reported as being particularly useful for improving the speed of administration in this setting.

Outcome of treatment with single-dose rFVIIa

There was consensus among the physicians that the single-dose rFVIIa regimen appears to be as effective as the rFVIIa 3 × 90 µg kg⁻¹ dose schedule. Successful haemostatic outcomes were achieved in all eight patients (Table 2); in five cases (cases 1, 2, 3, 5 and 6) effective bleeding control was obtained after one dose, two patients (case 5 and 7) received additional doses of rFVIIa. Case 5 received rFVIIa 270 µg kg⁻¹/day for 2 days to maintain haemostasis. Case 7 experienced substantial clinical improvements (no

more paraesthesia and less tenderness in the right forearm) with the single-dose infusion and treatment was considered successful. However, because of the severity of the injuries, the patient went on to receive rFVIIa 6 × 90 µg kg⁻¹/day for 10 days prior to further surgical intervention. Case 8 had previously received single dose rFVIIa on multiple occasions and required, on average, one dose to control target-joint bleeding and other bleeds and major bleeding. Case 4 received two 270 µg kg⁻¹ doses (second dose received 6–7 h after initial treatment) to manage a calf muscle bleed. However, it is important to note that this calf muscle haemorrhage was a new type of bleed for this patient and may not have been recognized quickly. Therefore, the bleed may have already been well established by the time treatment was initiated, leading to the requirement for a second dose.

No safety concerns were raised by the use of single-dose rFVIIa, and no thrombotic or other adverse events were observed in any patient.

Table 2. Single-dose rFVIIa $\mu\text{g kg}^{-1}$: summary of experience from eight cases.

Case no.	Reason for using single-dose regimen	rFVIIa dose administered ($\mu\text{g kg}^{-1}$)	Type of bleed	Location of treatment	No. of doses administered	Outcome
1	Needle phobia Poor venous access	270	Elbow joint bleed	Hospital	1	Successful
2	Damaged veins Ease of use	270	Multiple traumatic injuries (muscle haematoma, joint bleed, laceration to head)	Hospital	1	Successful
3	Poor venous access Ease/speed of use	270	Elbow joint bleed	Home	1	Successful
4	To gain quicker response	270	Calf muscle bleed	Home	2*	Successful
5	Ease of use To avoid hospitalization	270	rFVIIa was administered to prevent intracerebral haemorrhage following a traumatic fall of a young child on his face	Home	3 [†]	Successful
6	Ease of use To gain quicker response To reduce pain	270	Acute knee bleed	Home	1	Successful
7	Rescue therapy	270	Large haematoma of forearm with elements of compartment syndrome	Hospital	1 [‡]	Successful
8	Ease/convenience of use	270	Target-joint bleeds or other major bleeding episodes	Home	1–2	Successful

rFVIIa, recombinant activated factor VII.

*A second dose of rFVIIa $270 \mu\text{g kg}^{-1}$ was administered 6–7 h after initial treatment.

[†]Bleeding stopped after initial dose, but two further doses were administered to maintain haemostasis (the patient received one rFVIIa $270 \mu\text{g kg}^{-1}$ dose per day).

[‡]Single-dose treatment was effective at producing substantial clinical improvements (no more paraesthesia and less tenderness in right forearm). However, the patient went on to receive additional rFVIIa treatment ($6 \times 90 \mu\text{g kg}^{-1}/\text{day}$ for 10 days) prior to further surgical intervention.

Patient satisfaction with treatment and impact on quality of life

The majority of reported patients capable of stating a treatment preference (i.e. all patients except the 19-month-old paediatric patient [case 5]) favoured the single-dose rFVIIa regimen to their previous treatment. One patient (case 4) did not rate single-dose rFVIIa as highly as his pre-inhibitor FVIII treatment. At the time of single-dose rFVIIa use, this patient had had inhibitors for less than 1 year and felt his quality of life had been lowered as a result.

On the whole, patient satisfaction with the single-dose rFVIIa regimen was high and improved convenience (including reduced time spent administering treatment) was cited as a major benefit for both adult patients and carers of paediatric patients. This improved convenience was particularly important for case 1, a 40-year-old patient with severe haemophilia A and a high bleeding frequency (approximately 30 bleeds per year). On-demand treatment for this patient's bleeding episodes was provided by APCC until 1996, at which time rFVIIa $3 \times 90 \mu\text{g kg}^{-1}$ became the treatment of choice. However, bleed management remained suboptimal,

as the patient rejected multiple infusions because of needle phobia and very poor venous access. As the patient preferred no treatment at all to multiple injections, he remained untreated for 7 years until 2003, when he received his first single dose of rFVIIa $270 \mu\text{g kg}^{-1}$ for haemarthrosis of the elbow. After this experience, patient compliance improved and he was committed to early treatment with the single-dose rFVIIa regimen. Early treatment with this single-dose schedule not only provided rapid resolution of haemorrhage but also improved the patient's quality of life by reducing both his suffering and the detrimental impact of bleeds on his working life.

Less injection-related pain and faster relief of joint pain (where applicable) were also reported by the majority of patients, along with substantial improvements in quality of life. Quality of life was assessed by patients and clinicians as an improvement in a variety of factors including control of bleeding (seven of eight patients), interruption to work/school and daily activities (six of eight patients), confidence in the efficacy of treatment (two of eight patients), and co-operation with the treating physician (one patient).

Physicians' perceptions of the single-dose rFVIIa regimen

All physicians agreed that the single-dose 270 $\mu\text{g kg}^{-1}$ rFVIIa regimen appears to be effective and safe when used to treat a variety of target-joint and other bleeding episodes, and all preferred the single-dose rFVIIa schedule to the previous treatment. This preference was based on the following factors: recombinant safety (FVIII, APCC and cryoprecipitate are not recombinant products); improved quality of life; greater convenience; improved ease of administration for both patients and physicians/carers; faster resolution of bleeds; safety of the treatment; and potential for minimizing the extent and severity of arthropathy in target joints. It was hypothesized during the meeting that higher doses might produce a more stable clot. Physicians agreed that early treatment of bleeds with the single-dose rFVIIa regimen is of paramount importance in ensuring a successful outcome, particularly for muscle bleeds. Several physicians also suggested that further studies will be necessary to determine whether single-dose rFVIIa treatment works as effectively for muscle bleeds as for target-joint and other haemorrhages. Finally, physicians were satisfied that the single-dose rFVIIa regimen can be used in the home-treatment setting for the management of target-joint bleeds.

Discussion

Retrospective case data collected from eight inhibitor patients suggest that a single-dose rFVIIa 270 $\mu\text{g kg}^{-1}$ regimen appears to be effective and safe when used for the on-demand treatment of mild-to-moderate bleeding episodes. All patients and physicians preferred the single-dose rFVIIa regimen to their previous treatment, primarily as a result of enhanced quality of life, faster bleeding resolution and improved convenience of treatment. More rapid relief of joint pain, less infusion-related pain and reduced interruption to daily activities (including work and school) were also cited as important considerations for both physicians and their patients when selecting single-dose rFVIIa as their treatment of choice. The improved convenience that may be offered by this regimen is particularly important for patients with needle phobia or restricted venous access, as single-dose rFVIIa treatment removes the need for repeat dosing and thus helps to improve compliance among patients who might otherwise fear or resist multiple infusions. However, it must be noted that early initiation of therapy appears to

be vital for ensuring satisfactory resolution of haemorrhage.

Although the clinical experience discussed in this article was gained from 'real-life' use of the single-dose rFVIIa regimen, the collected data support the results of several trials. In the earliest of these studies, Kenet *et al.*, described how 83% of bleeds in three young inhibitor patients were successfully resolved following a single injection of rFVIIa 300 $\mu\text{g kg}^{-1}$ [3]. Positive results were also obtained from a retrospective analysis of data from the Hemophilia & Thrombosis Research Society (HTRS) Registry, which found a bleeding cessation rate of 97% for bolus doses of rFVIIa > 200 $\mu\text{g kg}^{-1}$ (vs. 84% for rFVIIa < 200 $\mu\text{g kg}^{-1}$; $P < 0.001$) [4].

Recent randomized studies demonstrate equivalent haemostatic efficacy between the 270 $\mu\text{g kg}^{-1}$ single-dose rFVIIa regimen and the $3 \times 90 \mu\text{g kg}^{-1}$ dose schedule. In one multicentre, double-blind, crossover trial, haemostatic efficacy rates were similar between the rFVIIa 270 $\mu\text{g kg}^{-1}$ and repeat-dose rFVIIa 90 $\mu\text{g kg}^{-1}$ schedules (90.5% and 87%, respectively), with an 'equal preference' noted for the two regimens [5]. Similarly, in a second multicentre study, a 'successful' treatment outcome (improvement in signs and symptoms associated with bleeding, and an increase in the patient's visual analogue score) occurred in similar numbers of patients receiving rFVIIa $3 \times 90 \mu\text{g kg}^{-1}$ and single-dose rFVIIa 270 $\mu\text{g kg}^{-1}$ (31% and 25% at 9 h; 53% and 50% at 24 h; and 66% and 64% at 48 h) [6]. Finally, in a recent home-treatment study, haemostasis was achieved without the need for additional rescue medication in 91.7% and 90.9%, of patients treated with rFVIIa 270 $\mu\text{g kg}^{-1}$ and $3 \times 90 \mu\text{g kg}^{-1}$, respectively [9]. As with the eight case studies reported in this study, no dose-related increases in thrombotic or other adverse events have been noted in the published literature describing single-dose rFVIIa use in inhibitor patients. In addition, ongoing and future research will further investigate the need for individualized dosing regimens. A prospective observational registry (ONE Registry) on the use of rFVIIa for the on-demand treatment of mild-to-moderate bleeds in inhibitor patients has just been initiated. Data from this registry should further improve the understanding of the clinical efficacy and utility of the single-dose rFVIIa regimen [10].

Conclusion

Clinical experience from eight inhibitor patients treated with single-dose rFVIIa 270 $\mu\text{g kg}^{-1}$ in a 'real-life' setting supports data from pivotal

randomized trials. In addition, single-dose rFVIIa appears to induce effective and safe haemostasis; it may also enhance patients' quality of life, provide greater convenience of treatment, offer a rapid onset of action and fast pain relief, and represent an effective solution for most patients, in particular, patients with restricted venous access or needle phobia.

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Disclosures

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