

Prophylactic treatment of haemophilia patients with inhibitors: clinical experience with recombinant factor VIIa in European Haemophilia Centres

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Summary. Many patients with haemophilia develop inhibitors to factor VIII and require bypassing agents to provide haemostatic cover for limb- or life-threatening bleeding episodes. Due to the reduced risk of blood-borne pathogen transmission with recombinant products, on-demand recombinant factor VIIa (rFVIIa; NovoSeven®) is the treatment of choice for children with inhibitors. In haemophiliac patients without inhibitors, primary prophylaxis has been clinical practice for several years. This paper summarises 13 case histories of rFVIIa secondary prophylaxis for haemophilia patients with inhibitors. This was a retrospective survey of adult and paediatric severe haemophilia patients with inhibitors treated with rFVIIa from ten European Haemophilia Centres. There was a wide variation in administered rFVIIa dose, from 200–250 $\mu\text{g kg}^{-1}$ per week to 220 $\mu\text{g kg}^{-1}$ daily. In many cases, this was lower than the recommended

on-demand dose of rFVIIa. In 12/13 cases, prophylaxis with rFVIIa considerably reduced the number of bleeding episodes compared with previous treatment. Eight/nine patients were satisfied or very satisfied with rFVIIa treatment, and in cases reporting subjective quality of life (QoL), all were improved, much improved, or significantly improved. In haemophilia patients with inhibitors, prophylaxis with rFVIIa is highly effective in reducing the number of bleeding episodes and results in good patient compliance and improved QoL. Randomised controlled trials are needed to confirm these findings. Results of a recently completed clinical trial on secondary prophylaxis with rFVIIa in frequently bleeding haemophilia patients with inhibitors are expected in late 2006.

Keywords: haemophilia, inhibitors, prophylaxis, recombinant, rFVIIa

Introduction

Neutralising antibodies (inhibitors) are a severe complication of factor VIII usage. The incidence of inhibitors varies widely according to the different types and severities of haemophilia, occurring in up

to 36% of patients with severe haemophilia A [1]. Children with severe haemophilia A are also at high risk of inhibitor development, and in this population, the incidence of inhibitor development may be more than 50% [2]. Although all haemophilia patients with inhibitors have some degree of bleeding, a small subset develop more severe bleeding complications such as life- or limb-threatening bleeds or bleeding into the cranium or peritoneal space. These patients also often develop target joints and arthropathy leading to permanent disability [3].

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Patients with low-titre inhibitors (low-responders), can often be treated with higher or more frequent doses of clotting factor. However, the majority of haemophilia patients with inhibitors develop high-titre inhibitors [>5 Bethesda Units (BU)] and are usually treated with immune tolerance therapy (ITT) [4]. Several studies have shown that ITT can effectively remove inhibitors [5,6]. However, ITT fails in up to 30% of patients, and about 10% of patients are not eligible for ITT [6].

For pre-ITT patients as well as those who fail ITT or are currently receiving ITT but are affected by breakthrough bleedings, bypassing agents are often used to provide adequate haemostatic cover. For patients with inhibitors, recombinant factor VIIa (rFVIIa; NovoSeven[®], Novo Nordisk, Bagsvaerd, Denmark) has become the treatment of choice for acute life-threatening bleeding episodes because, unlike plasma-derived products, there is no risk of blood-borne pathogen transmission [7–9]. rFVIIa is the safest option for the treatment of patients who have not been infected by viruses and, due to the risk of future exposure to emerging or unknown viruses, also for patients who have already been exposed to viruses through the use of plasma products. Evidence in several hundreds of haemophilia patients has demonstrated that rFVIIa is a potent prohaemostatic agent that may also have fewer side-effects than alternative treatment strategies [8]. In haemophilia patients with inhibitors, rFVIIa can induce effective haemostasis during joint, muscle and soft tissue bleeds as well as during minor and major surgery [10]. Unlike other bypassing agents, rFVIIa does not contain any FVIII antigen and does not produce an anamnestic response [7,8]. The use of rFVIIa as a bypassing agent therefore allows inhibitor titres to reduce to levels acceptable for initiation of ITT (usually less than <5 BU) [11], making it an ideal pre-ITT therapy.

For patients with severe haemophilia, there is a trend away from on-demand treatment towards prophylactic regimens to prevent bleeding and subsequent joint damage. Studies comparing prophylaxis and on-demand treatment in non-inhibitor patients with severe haemophilia have shown that prophylaxis reduces the risk of bleeding, reduces the risk of arthropathies and reduces the number of hospital visits and orthopaedic surgeries [12–15]. The fixed time of prophylaxis is also more convenient for patients who have school or work commitments. Both national and international authorities now recommend prophylaxis for non-inhibitor patients with severe haemophilia [16].

To date, for severe haemophilia patients with inhibitors, prophylaxis with rFVIIa has been repor-

ted in only three case reports involving four patients [17–19]. In this article, we summarise data from 13 historic case histories collected from Haemophilia Centres in six European countries.

Methodology

A retrospective survey was conducted in 2005 from ten European Haemophilia centres (four in Italy, one in Germany, one in France, two in Spain, one in Switzerland, one in Czech Republic) where rFVIIa was used to prevent bleeding episodes in haemophilic patients with inhibitors. Haemophilia centres that were known by the first author and/or Novo Nordisk to have tried rFVIIa prophylaxis for the treatment of haemophilia patients with inhibitors were sent *ad-hoc* questionnaires to collect the principal characteristics of patients and prophylactic regimens from paediatric and adult patients. Here, we summarise data from Haemophilia centres who provided case studies that were considered by the first author to provide sufficient follow-up data for inclusion in this report. The main entry criteria was the availability of a detailed record of bleeding incidence.

Patients in these case studies were treated with prophylactic rFVIIa for one of the following reasons: as preparation for or during ITT, as preparation for surgery, or to control frequent bleeding episodes, particularly during physiotherapy for target joints. Frequent bleeding was classified as one bleed/month.

In January 2006, an investigators' meeting of clinical experts from the participating European Haemophilia Centres took place in Rome for a preliminary presentation of the case study results. Full results from 13 case studies are reported here.

Results

Patient demographics

Patient demographics for the 13 case studies are presented in Table 1. Twelve cases involved patients with haemophilia A and one case involved a patient with haemophilia B. Cases involved eight paediatric patients (≤ 18 years of age) and five adult patients. All patients were high responders, with historical peak titre >5 BU mL⁻¹; two patients (cases 4 and 8) had a low titre inhibitor, 5 and 8 BU mL⁻¹, respectively, when enrolled on prophylaxis (Table 1). All patients had previously been treated with FVIII or FIX and had subsequently developed inhibitors. The case studies presented in this report involve patients with severe haemophilia and inhibitors and the majority had failed a number of previous treatments. The haemo-

Table 1. Case study demographics.

Case no.	Patient's age (years)	Haemophilia type	BU mL ⁻¹	Mean bleeds per month before prophylaxis	Follow up before prophylaxis (months)	Target joint
1	5	A	500	2.14	48	Knee
2	4	A	7500	1.83	24	None
3	30	A	26	1.77	48	None
4	22	A	5	2.13	60	Knee
5	5	A	35	0.75	16	Knee
6	2	A	13	1.50	3	None
7	14	A	37	0.37	48	None
8	7	B	8	1.38	42	None
9	3	A	50	0.25	16	Knee
10	30	A	143	4.33	48	Shoulder, elbow, knee
11	18	A	256	8.33	12	Elbow, ankle
12	9	A	126	5.66	12	Knee
13	16	A	346	2.20	72	Knee

philia B patient (case 8) had experienced repeated anaphylactic reactions when exposed to FIX.

There was a wide variation in the mean number of bleeds per month before rFVIIa prophylaxis, ranging from 0.25 (Case 9) to 8.33 (Case 11) bleeds per month. The majority of cases (10/13) involved patients with a mean of ≤ 2.2 bleeds per month, of whom only three had < 1.0 bleed per month. These patients were children (2) and an adolescent (1) and their treaters decided to start prophylaxis after the first few haemarthroses. Three cases (cases 10, 11, and 12) involved patients with a mean of > 4 bleeds per month (Table 1).

Dosing

The duration of rFVIIa prophylaxis ranged from 4 months (Case 13) to 4 years (Case 7). Many

patients (8/13 cases) are continuing to receive treatment with rFVIIa.

Prophylactic rFVIIa dosing frequency varied between cases, from twice-daily to once-weekly administration. There was a wide variation in the administered dose, ranging from 200–250 to 1540 $\mu\text{g kg}^{-1}$ per week (Cases 8 and 11 respectively) (Table 2).

Efficacy

The mean number of bleeds per month before and during rFVIIa prophylaxis for each case is shown in Tables 1 and 2 respectively. In 12/13 cases, the number of bleeds was lower during rFVIIa prophylaxis compared with previous treatment (Fig. 1).

Table 2. Recombinant factor VIIa dosing and prophylaxis results (listed from higher to lower weekly dose).

Case no.	rFVIIa dose ($\mu\text{g kg}^{-1}$)	Approximately weekly dose ($\mu\text{g kg}^{-1} \text{ week}^{-1}$)	Mean bleeds per month during prophylaxis	Follow-up during prophylaxis (months)
1	200, six days week ⁻¹ *	1200	0.91	12
2	160–170 daily**	1120–1190	0.08	12
3	130–200 eod	455–700	0.21	32
4	95 eod	315	0.25	24
5	80 daily five days week ⁻¹	400	0.25	20
6	100 three times week ⁻¹	300	0	5
7	90 bid	1260	0.14	50
8	200–250 week ⁻¹	200–250	1.0	6
9	330, once or twice week ⁻¹	330–660	0.28	7
10	60 daily	420	1.0	6
11	220 daily	1540	2.25	28
12	210 daily	1470	1.37	40
13	195 eod	585	0.50	4

eod, every other day; bid, twice daily.

*Patient subsequently switched to 120 $\mu\text{g kg}^{-1}$ every other day.

**Patient subsequently switched to 70 $\mu\text{g kg}^{-1}$ daily.

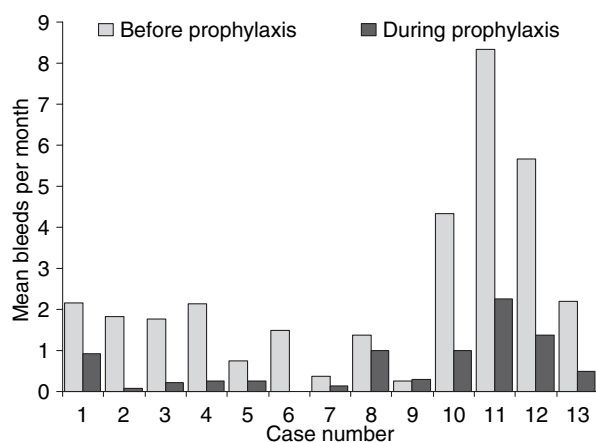


Fig. 1. Mean number of bleeds per month before and during recombinant factor VIIa prophylaxis.

Patient compliance

Patient compliance was good, very good, or excellent in all cases. Of the nine cases that recorded patient satisfaction with treatment, eight patients reported that they were satisfied with their treatment. Of those cases that recorded subjective quality of life (QoL) assessments, all were reported as improved, much improved, or significantly improved.

Discussion

The management of high-titred inhibitor patients to prevent bleeding, progression to arthropathy and morbidity remains an important clinical challenge. Whether or not prophylaxis with bypassing agents can achieve this has yet to be answered in long-term, prospective, comparative studies. One of the reasons for this is that such studies meet with both organisational and cost issues due to the relatively small numbers of haemophilia patients with inhibitors.

Outside of the surgical setting, prophylactic use of rFVIIa has been reported in only three case study publications involving a total of four paediatric haemophilia patients with inhibitors [17–19]. In all of these patients, prophylactic use of rFVIIa successfully reduced the number of bleeds. This paper reports the successful use of rFVIIa as prophylaxis in 13 case histories of adult and paediatric severe haemophilia patients with inhibitors. Frequent bleeding was classified as one bleed per month. In cases 5, 7 and 9 prophylaxis was started albeit less than one bleed per month with the rationale that, prophylaxis for paediatric patients without inhibitors, there is a general consensus among physicians that treatment should be started before or after the first joint bleed.

Due to its short half-life (approximately 2.9 h in adults) and recommended dose frequency (every 2–4 h), rFVIIa may be viewed as an unlikely choice for haemophilia prophylactic therapy [20]. However, despite the theoretical drawbacks, our results demonstrated that rFVIIa prophylaxis (from 3 months to 4 years' treatment duration) was highly effective in reducing the number of bleeding episodes in haemophilia patients with inhibitors. Our results are in line with the clinical observations of other groups, which have reported successful use of rFVIIa prophylaxis for up to 21 weeks in haemophilia patients with inhibitors [17–19]. In a recent study evaluating the efficacy of anti-inhibitor coagulant complex in patients treated prophylactically for between 4 and 6 years, all of the joints had progressed and developed synovitis [21].

It has been suggested that the biological effect of rFVIIa is actually much longer than indicated by its half-life [17,18]. There are a number of possible explanations for this. First, rFVIIa prolongs the haemostatic effect by improving the stability of the clot structure. It has been reported that rFVIIa enhances platelet activation and thrombin generation on the thrombin-activated platelet surface, contributing to the formation of tighter, more stable fibrin haemostatic plugs that are resistant to premature lysis [9,22]. Indeed, rFVIIa has been successfully used in a number of patients experiencing massive bleeding from various etiologies [9]. It has been hypothesised that, following regular daily dosing of rFVIIa, the extravascular diffusion of rFVIIa at the site of injury may increase its local concentration and contribute haemostasis of the plug [23]. Second, we suggest that regular treatment with rFVIIa may prevent small bleeds (such as microhaemarthroses), which often develop over a period of hours or days, from developing into more severe bleeding episodes. It is possible that further benefits can be obtained from administration of rFVIIa at bedtime, which may prevent small bleeds that began during the day from becoming more severe during the night (P. Petrini, personal communication). As demonstrated *in vitro* in an umbilical vein model, long-term rFVIIa administration may also result in the uptake of tissue factor-FVIIa complex by extracellular matrix [24]. Finally, it has been reported that rFVIIa has several tissue-factor-mediated non-haemostatic properties, including the induction of intracellular signalling and inhibition of apoptosis, as well as angiogenesis and chronic inflammation, all of which are mechanisms involved in the progressive joint damage characteristic of arthropathy [25–31]. Increased tissue-factor and reduced tissue-factor pathway

inhibitor concentration has been reported in rheumatoid arthritis and experimental murine antigen-induced arthritis [29]. In this animal model, systemic administration of active site-blocked recombinant activated factor VII (rFVIIa) led to decreased synovial thickness and decreased joint cartilage damage [29]. Long-term administration of rFVIIa, above that which reduces fibrin deposition, may saturate the over-expressed and de-encrypted tissue-factor at the level of the hypertrophic synovial tissues characteristic of haemophilic arthropathy. In addition, the minimal dosage of rFVIIa used during the prophylaxis regimen ($60 \mu\text{g kg}^{-1}$) may achieve a plasma concentration that is 150–300 times greater than the endogenous FVII concentration in haemophilic plasma ($5\text{--}10 \text{ ng mL}^{-1}$).

The standard recommended dose of rFVIIa is $90\text{--}120 \mu\text{g kg}^{-1}$ every 2–4 h. In the cases presented here, there was a wide variation both in dose concentration and frequency of rFVIIa dose. However, excellent efficacy was observed in patients receiving rFVIIa daily and in those receiving the drug only once or twice per week, suggesting that the optimal dose of rFVIIa is likely to be patient- and bleeding-dependent. In some cases, physicians used doses that were lower than the recommended dose, mainly due to concerns over the cost of treatment. Although this variation in dose may be perceived as a study limitation, it led to the discovery that low doses of rFVIIa can achieve very good success rates. This unexpected finding may offer some hope for physicians that may struggle with the annual cost of prophylactic therapy as it approaches approximately Euro 0.8 per μg . There are several factors that should be considered when evaluating the cost-benefit of such as treatment. First, the amount of drug used for rFVIIa prophylaxis does not differ significantly from that used during on-demand treatment. In addition, rFVIIa does not produce an anamnestic response. Therefore, the success rate of ITT and the overall cost of treatment is likely to be lower compared with the use of drugs that may produce anamnestic responses, such as anti-inhibitor coagulant complex, in which anamnestic responses have occurred in 31.5% of treated patients [32]. It is also noteworthy that prophylactic treatment with rFVIIa achieved a high level of patient compliance and satisfaction, and many patients reported improvements in their QoL, a measure that is very difficult to evaluate in monetary terms.

There are two limitations to this report that should be mentioned. First, it is well known that patients with inhibitors may have dramatic shifts in their

bleeding patterns. In this respect, the lack of control in these cases prevents any detailed evaluation of efficacy. Second, as mentioned earlier, there was a wide variation in dose between these cases. Future studies will be required to define the minimally effective dose to achieve the best clinical outcome at the lowest possible cost.

Due to the number of cases we have presented, it is impossible to present detailed information of each case. Rather, we have attempted to provide an overview summarising the experience of the participating European Haemophilia Centres to demonstrate the potential efficacy of rFVIIa as prophylactic treatment of haemophilia patients with inhibitors. The recently completed clinical trial on secondary prophylaxis with rFVIIa in frequently bleeding haemophilia patients with inhibitors has addressed these same questions. Results of this trial are expected at the end of 2006.

Conclusions

Our experience adds to that reported from other groups and, in these cases, rFVIIa prophylaxis dramatically reduced the number of bleeding episodes with good patient compliance and improved QoL. This efficacy was demonstrated even at low doses, making rFVIIa a potentially cost-effective approach for haemostatic control in selected haemophilia patients with inhibitors.

Addendum

Morfini Massimo set up the questionnaires, coordinated the Study Group and wrote the paper. Günter Auerswald, Rainer A Kobelt, Gianna Franca Rivolta, Javier Rodriguez-Martorell, Antonio Scaraggi, Carmen Altisent, Jan Blatny, Annie Borel-Derlon, and Enza Rossi provided their own patient information and participated in the discussion and to the review of the paper.

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Disclosures

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