Haemophilia

Haemophilia (2011), **17**, 579–589 DOI: 10.1111/j.1365-2516.2010.02460.x

REVIEW ARTICLE

Surgical Experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX

L. A. VALENTINO,* D. L. COOPER,† and B. GOLDSTEIN†[1]

**RUSH Hemophilia and Thrombophilia Center, Rush University Medical Center, Chicago, IL, USA; and †Novo Nordisk Inc., Princeton, NJ, USA*

Summary. Patients with congenital haemophilia with inhibitors are at risk of peri-operative bleeding complications, since replacement of the missing coagulation factor is ineffective, presenting a therapeutic challenge in elective or emergency surgery. Therefore, the management of peri-operative bleeding requires the use of bypassing agents, such as recombinant activated FVII (rFVIIa, NovoSeven®). This article presents an updated evaluation of the safety and effectiveness of rFVIIa in the treatment of peri-operative bleeding in this patient population. Surgical and other medical procedures managed with rFVIIa from two randomized clinical trials, the Hemophilia Research Society/Hemophilia and Thrombosis Research Society (HRS/HTRS) registry databases and the medical literature were analysed. There were 395 rFVIIa-treated procedures (261 surgical, 89 dental and 45 other medical procedures) reported for 263 congenital haemophilia patients with inhibitors. In trials, initial rFVIIa dosing was 35–90 mcg kg^{-1} bolus injection or 50 mcg kg^{-1} h^{-1} continuous infusion. Dosing in the registries and literature was more variable. Recombinant FVIIa effectiveness was comparable across data sources, with an overall rate of 84% (333/395). The incidence of thrombotic events was very low (0.4% of patients and 0.025% of procedures). Prior to the US approval of rFVIIa in 1999, surgical procedures in congenital haemophilia patients with inhibitors were often considered too risky. Recombinant FVIIa has consistently demonstrated effectiveness in treatment of bleeding in these patients during such procedures. Thrombotic events were rare. This analysis confirms the value of corroborating clinical trial results with post-marketing surveillance registries to assess small patient populations with clinically challenging management decisions.

Keywords: dental, inhibitors, operative haemostasis, orthopaedic, rFVIIa, surgery

Introduction

Advances in the treatment of haemophilia with recombinant factors has eliminated the danger of infectious diseases such as HIV and hepatitis, previously associated with plasma product factor replacement therapy. The development of neutralising antibodies (inhibitors) directed against factor VIII (FVIII) or IX (FIX) is now the most common complication of replacement therapy in haemophilia patients. Between 10–30% of patients with haemophilia A and 2–5% of patients with haemophilia B develop an inhibitor to FVIII or FIX, complicating the management of bleeding episodes.

Frequent joint haemorrhages in inhibitor patients predispose them to joint disease, which has a negative impact on their everyday quality of life (QoL). A few studies have reported on the health-related QoL issues in inhibitor patients. A prospective, longitudinal, multicentre cost of care study of 52 Italian inhibitor patients found that approximately 50–70% of the patients reported orthopaedic problems such as reduced joint mobility, crepitus on motion, flexion contractures, joint instability and swelling [1]. Approximately 67% of the patients reported 'some/moderate' problems in their physical sphere, specifically for mobility and pain/discomfort, 50% of them had problems in performing usual activities, whereas 33% reported 'some/moderate problems' in self-care and anxiety/depression. Furthermore, the Cost of Care Inhibitors Study (COCIS) also found that scores obtained from questionnaires (EQ-5D

Correspondence: Leonard A. Valentino, MD, Rush Hemophilia & Thrombophilia Center, RUSH University Medical Center, 1653 W Congress Parkway, Chicago, IL 60612-3833.
Tel.: 312 942 8114; fax: 312 942 8975;
e-mail: lvalentino@rush.edu
[1]Current address: Ikaria, Inc., Clinton, NJ, USA

Accepted after revision 18 October 2010

and SF-36) designed to evaluate health-related QoL were significantly correlated with the orthopaedic joint score, even after adjustment for patient age [2]. In a recent observational, European study [3] it was found that in comparison to the non-inhibitor patients, inhibitor patients had greater severity of arthropathy, more frequent hospitalisation due to orthopaedic and musculoskeletal complications and greater difficulties with mobility and daily activities due to pain/discomfort.

The indications for surgery, namely chronic pain and immobility, are the same in both inhibitor and non-inhibitor patients. However, it has been suggested that, due to the higher bleeding risks associated with surgery for inhibitor patients, surgery might be deferred until inhibitor patients who suffer from increasingly severe pain and/or progressive physical incapacity find no other options. [4].

Prior to 1999, therapeutic interventions in inhibitor patients in the United States had included replacement therapy with massive FVIII infusion (useful in patients with low titre low responding inhibitors only) [5], use of activated and non-activated prothrombin complex concentrates and porcine FVIII, plasmapheresis with or without antibody absorption [6,7], and if time and resources have permitted, immune tolerance therapy. All of these interventions have had significant drawbacks, including high cost, transmission of blood-derived infections and thromboembolic complications [7]. These issues take on greater significance for patients with inhibitors during surgery. These patients are at a particularly high risk of intra- and post-operative bleeding complications, since replacement of the missing coagulation protein is ineffective, presenting a therapeutic challenge. Hence, a barrier to considering elective surgical treatment was lack of a therapy that could effectively maintain haemostasis during surgery in inhibitor patients while eliminating or greatly reducing complications.

Approved by the US Food and Drug Administration (FDA) in 1999, treatment with recombinant activated factor VII (rFVIIa, NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) has been proven to stop or prevent bleeding episodes in the majority of haemophilia patients with inhibitors as it bypasses the need for factors VIII and IX. Recombinant FVIIa is registered in most regions of the world (including Europe, North and South America, Japan and Australia) for the treatment of bleeding episodes in patients with haemophilia A and B with inhibitors to factors VIII or IX. The use of rFVIIa before and after surgery was a logical clinical extension of its approved use for the treatment of bleeding episodes in the same patient population. In 2005, the FDA approved the use of rFVIIa for prevention of bleeding in surgical interventions or invasive procedures in haemophilia A or B patients with inhibitors to factor VIII or factor IX based upon two clinical trials, the Hemophilia Research Society (HRS) registry data, and case reports in the literature.

Herein, we present an updated evaluation of the safety and effectiveness of rFVIIa in congenital haemophilia patients with inhibitors undergoing surgery and other medical procedures, including previously unpublished post-marketing surveillance data from the Hemophilia and Thrombosis Research Society (HTRS) registry obtained since the approval of the new indication for surgery. As the population of patients with haemophilia with inhibitors is small, recruitment for clinical trials is difficult and as such trial sample sizes are also small. For this overview, clinical trial data from the two randomized trials are supplemented with the most up to date patient data available in post-marketing surveillance registries (HRS and HTRS) and published literature.

Methods

During the clinical development programme for rFVIIa, two clinical trials (Study 1 and Study 2) were completed evaluating the use of rFVIIa during surgery in patients with haemophilia A or B with inhibitors.

Study 1

Study 1 (as reported by Shapiro *et al.* [8]) was a multicentre, randomized, double-blinded, parallel-group trial to evaluate the safety and efficacy of two doses (35 or 90 mcg kg^{-1}) of rFVIIa in initiating and maintaining haemostasis, in haemophilia A or B patients with inhibitors [8]. Twenty-eight haemophilia patients with inhibitors, hospitalised for pre-planned surgical procedures, were randomized to treatment with rFVIIa at doses of either 35 or 90 mcg kg^{-1} for 5 days. The patients had a historical inhibitor titre of at least 5 Bethesda units (BU) or had an inadequate haemostatic response to 250 U kg^{-1} of FVIII or FIX and required pre-planned surgery (both major and minor). The majority of the major surgeries were orthopaedic (10 orthopaedic and one kidney biopsy). All the 17 minor surgeries were either placement or removal of a subcutaneous venous access device.

Efficacy of rFVIIa treatment was evaluated during the first 5 days, which constituted the primary study period. During this primary study period, doses were administered intravenously in a double-blinded manner starting just before surgery, intra-operatively as required, and then every 2 h for the next 48 h beginning at wound closure. Dosing continued in a blinded manner every 2–6 h for an additional 3 days to maintain haemostasis. If uncontrolled bleeding occurred at any time, an additional dose (blinded allocated dose) was administered. If bleeding persisted at 30 min after this repeated dose, an open-label dose of rFVIIa (up to 180 mcg kg^{-1}), was administered every 2 h until satisfactory haemostasis was achieved. After a

[no notes on this page]

maximum of 5 days of double-blinded treatment, patients received open-label rFVIIa at a dose of 90 mcg kg^{-1} every 2–6 h until the time when patients were discharged from the hospital with adequate haemostasis, switched to alternative therapy (at the discretion of the Investigator) or discontinued rFVIIa therapy due to an adverse event.

Haemostasis was assessed throughout the intra-operative and post-operative periods until day five. Haemostasis was assessed by the surgeon intra-operatively by comparing blood loss for the same procedure performed on a 'typical' non-haemophilia patient. Grading was 'as expected', 'less than expected' and 'more than expected'. Haemostasis was also assessed as 'effective', 'partially effective', or 'ineffective' following closure of the wound at specified time points up to 5 days after wound closure. Adverse event profiles were also assessed.

An intent-to-treat analysis was performed, using the Mantel-Haenszel chi-squared test with the last value carried forward (LVCF) procedure to account for subjects who completed earlier or discontinued the study.

Study 2

Study 2 (as reported by Pruthi *et al.* [9]) was an open-label, randomized, parallel-group, multi-centre trial comparing the safety and efficacy of rFVIIa when administered as a repeated intravenous bolus injection (BI) or via continuous IV infusion (CI) to 23 haemophilia A or B patients with inhibitors during and after surgery [9]. The patients had a historical inhibitor titre of at least 5 BU or had an inadequate haemostatic response to 250 U kg^{-1} of FVIII or FIX and required pre-planned surgery (both major and minor). These patients underwent 33 major (25 orthopaedic, two pseudotumour removal in abdomen/low pelvis, two inguinal hernia repairs, one craniotomy and tumour removal, one tonsillectomy/adenoidectomy, one mitral valve repair and one orchidectomy) and two minor (circumcision, entropion/ectoprion repair) surgeries.

All patients received a pre-operative bolus dose of 90 mcg kg^{-1} rFVIIa followed by either continuous infusion (50 mcg kg^{-1} h^{-1} through day 5, then 25 mcg kg^{-1} h^{-1} from days 6 to 10) or bolus injection (90 mcg kg^{-1} administered every 2 hours during surgery through day 5, then every 4 h from days 6 to 10). If haemostasis was not achieved for either treatment group, up to two additional bolus doses of 90 mcg kg^{-1} rFVIIa could be administered during any 24-h period. Treatments requiring more than two additional doses of rFVIIa were considered ineffective. The control group consisted of 12 haemophilia A or B patients without inhibitors undergoing surgery and treated with FVIII or FIX (based on current standard of care and physician's choice).

The primary efficacy endpoint was the Investigator's assessment of haemostasis as 'effective' or 'ineffective' at the time of discontinuation of therapy or post-operative day 10 (whichever was earlier) and was termed the 'global haemostasis treatment evaluation'. Additional assessment of haemostasis as 'effective' or 'ineffective' made at specific intervals starting from the time of wound closure were also part of the efficacy analyses. Adverse event profiles were also assessed.

Statistical analyses for treatment comparisons were performed for the Intent-to-Treat (ITT) population by using the Fisher's exact test with the LVCF procedure to account for subjects who completed earlier or discontinued the study. A two-sided test with 5% significance level was used.

Hemophilia Research Society and Hemophilia and Thrombosis Research Society Registry

In October 1999, the HRS registry was implemented as a national registry for the collection of data on treatment of patients with coagulation disorders, particularly, congenital haemophilia. Hemophilia Treatment Centers entered de-identified patient data (socio-demographical, disability, acute haemorrhage, surgery, immune tolerance, adverse event and mortality) into this database in an attempt to gain information that would lead to a better understanding of the clinical management, and outcomes of patients with coagulation disorders. The registry was re-launched on January 1, 2004 as the HTRS Registry, with a new Internet platform and revised case report forms. Until August 2008, information for surgeries and other procedures was entered in acute bleeding forms with very little descriptive information required about the procedures. Since the bleeding location field was not applicable for surgeries, it was expected that the location would be entered as 'other' with the procedure name entered as free text. Hence, the procedures have been simply classified here according to the procedure type entered, as 'surgical (non-dental)', 'dental' or 'other medical procedures (e.g. venipuncture, diagnostic procedure and injection)'. These categories were established by the HTRS and represent the CRF choices available; no other definitions were provided to sites. After August 2008, a specific surgical form was created to capture additional information.

In HRS, individual doses had been entered at an identified time and bleeding outcome was assessed by the treating physician at 72 h after treatment. Bleeding outcomes were categorized as 'bleeding stopped', 'bleeding slowed but not stopped', or 'no improvement'. In HTRS, doses were entered as a series of regimens (dose, frequency, number of doses, start date) and bleeding outcome was assessed after each dosing regimen. Bleeding outcomes categories remained as 'bleeding

[no notes on this page]

stopped', 'bleeding slowed but not stopped', or 'no improvement'.

Reports for a total of 23 rFVIIa-treated procedures (11 patients) identified from the HRS registry from 1999 to November 2004 are considered here. These procedures were entered into the database prior to the licensure of rFVIIa use to mitigate bleeding during surgery of congenital haemophilia patients. In addition, a total of 143 procedures (66 patients) including surgery (44 procedures), dental (54 procedures) and other medical procedures (45) from the ongoing HTRS registry (2004–2008) are also considered. Doses administered reflect the pre-, peri- and post-operative care periods and are reported based upon the total dose, number of infusions, number of days of treatment and average infusion dose for the treatment period around each procedure. Efficacy in the HTRS registry database was assessed for each treatment regimen (product, dose, frequency, number of doses) including factor and non-factor products; one or more regimens were reported for each procedure. One dental procedure treated with a single dose of rFVIIa was entered into both the HRS and HTRS registries. This overlapping procedure was excluded from the HRS registry, but included within the HTRS registry data set.

Published literature

A cross-database literature search (BIOSIS, Current Contents, EMBASE, MEDLINE) from 1988 through May 2008 was used to identify publications describing rFVIIa use during surgery for haemophilia A or B patients with inhibitors. The search terms included 'surgery(ies)' and 'h(a)emophilia and inhibitor(s)' with 'recombinant activated factor VII (± human)' 'rFVIIa', 'rhFVIIa', 'FVIIa', and 'NovoSeven'. Only English language literature was considered. Fifty articles were subsequently identified [10–57]. Underlying coagulopathy and/or the results of rFVIIa treatment in congenital haemophilia patients with inhibitors could be ascertained in only 46 of the 50 articles identified. Two of the four manuscripts excluded were larger case reports by Santagostino *et al.* [44] (28 patients, 35 procedures with CI) and Scharrer *et al.* [45] (17 patients, 22 procedures). In addition, in a report by Rodriguez-Merchan *et al.* [42], data from 31 procedures receiving rFVIIa during radiosynoviorthesis were not included as it was not possible to discern the treatment results specifically attributable to rFVIIa. Efficacy and safety assessments provided here are those reported by the authors.

Results

Demographics and overview

A total of 263 patients from the combined data sources were evaluated. Table 1 provides patient demographical characteristics across the five data sources. Most patients described within these publications had little or no demographical information available. Overall, 54% of the patients were <16 years of age. Caucasians comprised 38% of the patients for whom ethnicity was reported.

Table 1. Demographical information across data sources.

	Number of patients, *n* (%)					
	Clinical trial		Registry			
	Study 1	Study 2	HRS*	HTRS†	Literature	Total
Subjects	28	23	11	66	135	263
Age (years)						
0–4	9 (32)	0	5 (46)	33 (50)	55 (41)	102 (39)
5–16	13 (46)	6 (26)	2 (18)	20 (30)	-	41 (16)
17–59	6 (21)	16 (70)	4 (36)	12 (18)	65 (48)	103 (39)
>59	-	1 (4)	0	1 (2)	-	2 (1)
Unknown	-	-	-	-	15 (11)	15 (6)
Gender						
Male	28 (100)	23 (100)	1 (9)	66 (100)	68	186 (71)
Female	0	0	0	0	0	0
Unknown	-	-	10 (91)	-	67	77 (29)
Race						
Caucasian	20 (71)	14 (61)	9 (82)	44 (67)	12	99 (38)
Black	8 (29)	8 (35)	2 (18)	15 (23)	2§	35 (13)
Asian	0	0 (0)	0	7 (11)‡	1	8 (3)
Other	0	1 (4)	0	0	0	1 (0)
Unknown	-	-	-	-	120	120 (46)

*HRS, Hemophilia Research Society.
†HTRS, Hemophilia and Thrombosis Research Society.
‡Includes Asian/Pacific Islander.
§Includes 1 African-Caribbean and 1 African-American.

The 263 congenital haemophilia patients with inhibitors were treated with rFVIIa for 395 surgical procedures (Table 2). Orthopaedic and catheter insertion/removal procedures comprised the larger sub-groups of procedures reported in the clinical trials and published literature, while dental procedures represented the majority of procedures reported in the registries.

Recombinant FVIIa dosing and exposure

Recombinant FVIIa dosing for the double-blinded randomized clinical study reported by Shapiro *et al.* (Study 1) [8], is summarized in Table 3a. For major surgery, the 90 mcg kg^{-1} group required a lower median (range) duration of treatment than the 35 mcg kg^{-1} group (9.5 [8–17] days vs. 15 [2–26] days) and fewer median (range) number of injections (81 [71–128] vs. 135 [11–186]). For minor surgery, the duration of dosing and number of injections was similar for the 90 mcg kg^{-1} and 35 mcg kg^{-1} groups; however, the median (range) total dose administered was greater for the 90 mcg kg^{-1} than the 35 mcg kg^{-1} group (80 [31–706] mg vs. 42 [10–70] mg). This is partially attributed to one outlier in the 90 mcg kg^{-1} group who required 13 days of treatment and a total rFVIIa dose of 706 mg (98 injections) for a Hickmann catheter placement,

[no notes on this page]

Table 2. Summary of procedures and rFVIIa efficacy by data source.

		rFVIIa effectiveness*			
	No. of Procedures *n* (%)	Effective *n* (%)	Partially effective *n* (%)	Ineffective *n* (%)	Not determined *n* (%)
Clinical trials†					
Study 1 (N = 28)	28 (100)	24 (85.7)	2 (7.1)	2 (7.1)	
Surgical procedures					
Orthopaedic‡	10 (35.7)	8 (80.0)	1 (10.0)	1 (10.0)	
Catheter placement/removal	17 (60.7)	15 (88.2)	1 (5.9)	1 (5.9)	
Other§	1 (3.6)	1 (100.0)			
Study 2 (N = 23)	23 (100)	17 (73.9)	N/A	6 (26.1)	
Surgical procedures					
Orthopaedic‡	16 (69.6)	11 (68.8)	N/A	5 (31.3)	
Circumcision	1 (4.3)	1 (100.0)	N/A		
Pseudotumour removal	1 (4.3)			1 (100.0)	
Inguinal hernia repair	2 (8.7)	2 (100.0)	N/A		
Eye surgery	1 (4.3)	1 (100.0)	N/A		
Other§	2 (8.7)	2 (100.0)	N/A		
Registries					
HRS (N = 11)	23 (100)	19 (82.6)	3 (13.0)		1 (0.04)
Surgical procedures					
Orthopaedic‡	5 (21.7)	2 (40.0)	2 (40.0)		1 (20.0)
Catheter placement/removal	3 (13.0)	3 (100.0)			
Circumcision	2 (8.7)	1 (50.0)	1 (50.0)		
Other§	1 (4.3)	1 (100.0)			
Dental procedures	12 (52.2)	12 (100.0)			
HTRS (N = 66)	143 (100)	130 (90.9)	13 (9.1)		
Surgical procedures					
Surgical (non-dental), not specified	44 (30.8)	39 (88.6)	5 (11.4)		
Dental procedures	54 (37.8)	51 (94.4)**	3 (5.6)		
Other medical procedures¶	45 (31.5)	40 (88.9)**	5 (11.1)		
Published literature					
Publications (N = 135)	178 (100)	147 (82.6)	10 (5.6)	14 (7.9)	7 (3.9)
Surgical procedures					
Orthopaedic‡	69 (38.8)	51 (73.9)	6 (8.7)	7 (10.1)	5 (7.2)
Catheter placement/removal	53 (29.8)	50 (94.3)		3 (5.7)	
Circumcision	2 (1.1)	2 (100.0)			
Plastic surgery, grafts, debridement	4 (2.5)	4 (100.0)			
Pseudotumour removal	2 (1.1)	2 (100.0)			
Inguinal hernia repairs	2 (1.1)			2 (100.0)	
Cholecystectomy	4 (2.5)	4 (100.0)			
Fasciotomy	2 (1.1)	1 (50.0)			1 (50.0)
Eye surgery	7 (3.9)	7 (100.0)			
Other§	10 (5.6)	8 (80.0)	1 (8.3)		1 (8.3)
Dental procedures	23 (12.9)	18 (78.3)	3 (13.0)	2 (8.7)	

N = number of patients; *n* = number of procedures.

*Efficacy data was consolidated by converting 3-category rating scales to correspond with the 'Effective', 'Partially Effective' and 'Ineffective' categories (i.e., for registry data, 'Bleeding Stopped' = 'Effective'; 'Bleeding Slowed but Not Stopped' = 'Partially Effective'; and 'No Improvement' = 'Ineffective') and converting 2-category rating scales to correspond with the 'Effective' and 'Ineffective' categories. The 'Partially Effective' category was reported as 'N/A' where not applicable.

†Clinical trials used a Last Value Carried Forward Approach.

‡'Orthopaedic' includes knee arthroplasty, knee synovectomy, total knee replacement, radial head excision, hip replacement, hip arthroplasty, elbow synovectomy, foreign body removal and Achilles lengthening, knee joint manipulations, knee cartilage repair, femur bone graft, knee amputation, knee evacuation, osteotomy, shoulder surgery, radiosynoviorthesis and those not otherwise specified.

§'Other' includes laparoscopic renal biopsy, tonsillectomy, mitral valve repair, craniotomy, gastrectomy, hernioplasty, liver biopsy, neuroplegia and Linton tube insertion, radical prostatectomy, heart transplantation, removal of redivac drains, staples, muscle, appendectomy (2), cholecystectomy by coelioscopy, partial colectomy, haemorrhoidectomy, and a procedure not otherwise specified.

¶'Other medical procedures' include venipuncture, diagnostic procedure and injection.

**There was 1 patient who underwent 1 dental procedure and one other medical procedure after which bleeding stopped but re-bleeding occurred within 48 h.

about 6 times more rFVIIa than that used for other patients in the same group.

Recombinant FVIIa dosing in the open-label clinical trial reported by Pruthi *et al.* (Study 2) [9], is summarized in Table 3b. The mean duration of exposure was approximately twice as long for the 50 mcg kg^{-1} h^{-1} CI treatment group as for the 90 mcg kg^{-1} BI group (18.3 vs. 9.7 days). However, this difference was largely attributable to a single outlier who experienced severe bleeding and received rFVIIa for 116 days.

[no notes on this page]

Table 3a. Recombinant FVIIa* dosing by surgery category and dose group in study 1†.

	Major Surgery		Minor Surgery	
	35 mcg kg^{-1} (n = 5)	90 mcg kg^{-1} (n = 6)	35 mcg kg^{-1} (n = 9)	90 mcg kg^{-1} (n = 8)‡
Days of dosing				
Median (range)	15 (2–26)	9.5 (8–17)	4 (3–6)	6 (3–13)
No. of bolus injections				
Median (range)	135 (11–186)	81 (71–128)	29 (24–44)	39.5 (26–98)
Total dose, mg				
Median (range)	656 (31–839)	569 (107–698)	42 (10–70)	74 (31–706)

*Recombinant FVIIa: Recombinant activated factor VII.
†Shapiro *et al.* [8].
‡There was one outlier who required 13 days of dosing and received a total rFVIIa dose of 706 mg in 98 injections for a Hickmann catheter insertion.

Table 3b. Recombinant FVIIa* dosing by treatment group in study 2§.

	90 mcg kg^{-1} Bolus Injection (n = 11)	50 mcg kg^{-1} h^{-1} Continuous Infusion (n = 12)¶
Days of dosing		
Median (range)	10 (4–15)	10 (2–116)
No. of bolus injections†,‡		
Median (range)	38 (36–40)	1 (0–3)
Total dose†,‡, mg		
Median (range)	272 (130–460)	297 (125–492)
No. of additional bolus injections†		
Median (range)	0 (0–3)	0 (0–4)
Additional bolus dose†		
Median (range)	0 (0–17)	0 (0–25)

*Recombinant FVIIa: Recombinant activated factor VII.
†From the intraoperative period to 72-hours post-operative.
‡Includes the 2 additional, allowable 90 mcg kg^{-1} bolus doses that could be administered during any 24-hr period to achieve haemostasis.
§Pruthi *et al.* [9].
¶There was one outlier underdoing arthroscopic synovectomy who experienced severe bleeding and received rFVIIa for 116 days.

Patients in the HRS registry enrolled from October 1999 to November 2004 were treated with bolus rFVIIa for 20 of the 23 procedures, and with CI for two procedures. Recombinant FVIIa dosing information was not available for one procedure. For the 20 procedures treated by rFVIIa BI, the median (range) bolus dose was 114.0 (58–226) mcg kg^{-1}, with a median (range) of 8.5 (1–78) injections. For all procedures in which the dosing interval was known, rFVIIa doses were administered at median (range) interval of 3 (0–23.5) h. For the two patients treated with CI, the total dose for the treatment period for the first patient was 188 mcg kg^{-1} body weight and for the second, 120 mcg kg^{-1}.

A total of 413 patients in the HTRS registry were entered between January 2004 and November 2008. Of these patients there were 2,041 bolus rFVIIa-treated episodes including 54 dental, 44 surgical and 45 other medical procedures (e.g., venipuncture, diagnostic procedure and injection) reported for 66 patients. For dental procedures, the median (range) total rFVIIa dose for the treatment period was 366 (60–4,795) mcg kg^{-1}, with a median (range) of 3 (1–35) injections over a median (range) of 1 (1–35) day. The median (range) average dose per infusion across the 54 dental procedures was 122 (60–295) mcg kg^{-1}. For orthopaedic and other surgical procedures, the median (range) total rFVIIa dose for the treatment period was 2,408 (55–8,525) mcg kg^{-1}, with a median (range) of 21 (1–64) injections over a median (range) of 6 (1–29) days. The median average dose per infusion across the 44 surgical procedures was 111 (55–193) mcg kg^{-1}. For other medical procedures, the median (range) total rFVIIa dose was 450 (90–8760) mcg kg^{-1} for the treatment period with a median (range) of three (1–79) injections over 1.8 (1–19) days. The median (range) average infused dose across 45 other medical procedures was 102 (71–300) mcg kg^{-1}. Single doses were used for 15 dental, two non-dental surgeries, and seven other medical procedures.

While the predominant treatment for the surgical, dental and other medical procedures in the HTRS registry reported above was rFVIIa, site reports indicate the sporadic use of one or more doses of concomitant haemostatic agents (including antifibrinolytics) either before, during or after rFVIIa treatment. Concomitant haemostatic medications were reported in 20/44 (45%) surgeries (one to four adjuvants per procedure, most common - FVIII in 12/20 procedures), 25/54 (46%) dental procedures (one to three adjuvants per procedure, most common - aminocaproic acid in 21/25 procedures) and 9/44 (20%) other medical procedures (one to two adjuvants per procedure, most common - pd-APCC in 3/9 procedures).

Patients in publications were treated with rFVIIa before, during and/or following surgical procedures and rFVIIa was administered by either BI or CI. Overall, doses for BI ranged from 35–300 mcg kg^{-1} at 1–24 h intervals for 1–25 days; CI doses ranged from 2.5–50 mcg kg^{-1} h^{-1} for 1–34 days.

Effectiveness

Table 2 describes the overall efficacy of rFVIIa for various surgical, dental and other medical procedures by data source. Overall treatment was deemed effective in the majority of procedures by all sources: Study 1

(86%), Study 2 (74%), HRS (83%) and HTRS (91%) registries and published literature (83%).

In the two randomized clinical trials, haemostasis was achieved in 40 of 51 (78%) haemophilia patients with inhibitors who completed the studies. These included 21 of 25 patients (84%) receiving 90 mcg kg^{-1} bolus injections, nine of 14 (64%) receiving 35 mcg kg^{-1} BI and 10 of 12 patients (83%) receiving CI at 50 mcg kg^{-1} h^{-1}.

Analysis of efficacy by dose and type of surgery reported by Shapiro *et al.* (Study 1) [8] suggests that 90 mcg kg^{-1} is more effective, particularly for major surgeries, as indicated by decreased numbers of injections, reduced days of dosing and numbers of treatment failures seen compared to the 35 mcg kg^{-1} dose. In the report by Pruthi *et al.* (Study 2) [9], both BI and CI of rFVIIa were nearly equally effective in achieving and maintaining haemostasis through day 10. Treatment was effective in 73% (8/11) of subjects treated with BI and 75% (9/12) of subjects treated by CI. Efficacy ratings (effective/ineffective) at pre-specified time points following wound closure through day 10 also indicated very high response rates (75–100%). There was one case each of treatment failure for both BI and CI treatment methods.

Within the HRS registry (October 1999 through November 2004) 11 patients with haemophilia with inhibitors were treated with rFVIIa for 23 surgical procedures. Bleeding was reported as 'stopped' after treatment with rFVIIa in 19 of the 23 procedures (83%). Bleeding slowed, but did not stop, for three procedures, and outcome was not reported for one procedure. There was no observable effect of dose on outcomes. For the three procedures in which bleeding slowed but did not stop, one knee surgery was treated with doses ranging from 58 to 130 mcg kg^{-1}, one knee surgery with doses ranging from 115 to 173 mcg kg^{-1}, and 1 circumcision/catheter placement with doses ranging from 151 to 226 mcg kg^{-1}.

Within the registry (January 2004 to November 2008), efficacy was specifically assessed for all rFVIIa-containing regimens. Bleeding was reported as 'stopped' in 94% of dental, 89% of surgical and 89% of other medical procedures. Bleeding was reported to have slowed but not stopped in 6% of dental, 11% of surgical and 11% of other medical procedures. For one procedure, when rFVIIa was administered as first-line of treatment, plasma derived-activated prothrombin complex concentrates (pd-APCC) was also administered to stop bleeding. In the HTRS registry, rFVIIa was administered as second-line rescue therapy in 12 procedures (three surgical, five dental and four other medical procedures). In these instances, the first-line of treatment was either pd-APCC (five procedures) or aminocaproic acid (five procedures) or aminocaproic acid/rFVIII (one procedure) or rFVIII (one procedure).

Data in the HTRS registry (January 2004 to November 2008) also did not demonstrate an apparent effect of dose on effectiveness. Within each procedural category (surgical, dental or other medical procedures), a range of doses and dosing regimens were used. While surgical procedures used the highest median total dose of 2408 mcg kg^{-1}, dental and other medical procedures used a median total dose of 366 mcg kg^{-1} and 450 mcg kg^{-1}. However, with these differences in dosing, the effectiveness of rFVIIa remained within 89–94% for all three categories of procedures.

For the 178 surgical procedures described in the published literature, treatment with rFVIIa was effective in 147 (83%), partially effective in 10 (6%), and ineffective in 14 (8%) procedures. Treatment effect was not reported for seven (4%) procedures. There was no observable effect of dose on effectiveness either. Of the 14 procedures for which treatment was rated as ineffective, eight were treated with bolus doses ranging from 75 to 240 mcg kg^{-1}, five were treated with CI doses ranging from 16.5 to 50 mcg kg^{-1} h^{-1} and one was treated with a bolus dose of 90 mcg kg^{-1} and then CI of 16.5 mcg kg^{-1} h^{-1}.

Safety

Across the five data sources, 263 patients reported 434 adverse events (AEs). For the two clinical trials, any adverse events were reported irrespective of relationship to treatment. Shapiro *et al.* (Study 1) [8] reported that 17 rFVIIa-treated haemophilia patients with inhibitors (seven in 35 mcg kg^{-1} and 10 in 90 mcg kg^{-1} dose groups) experienced 80 AEs. The AEs occurred in 10/11 patients who underwent major surgery and 7/17 patients who underwent minor surgery. Forty-three percent of the AEs experienced in eight patients (four minor surgery patients and four major surgery patients) were assessed by investigators as probably or possibly related to rFVIIa treatment, of which two were serious (right internal jugular thrombosis and hemarthrosis). The thrombotic event occurred in a 4-year old, 2 days after port-a-cath placement. This patient received 35 mcg kg^{-1} rFVIIa for a total daily dose of 6.67 mg and 7.89 mg.

Pruthi *et al.* (Study 2) [9] reported a total of 305 AEs (83 in the 90 mcg kg^{-1} BI group and 222 in the 50 mcg kg^{-1} h^{-1} CI group) for 23 surgical patients who were treated with rFVIIa. It should be noted that one patient in the 50 mcg kg^{-1} h^{-1} CI treatment group experienced 34% (130/305 events) of the total AEs. Only 5% of the AEs (six in the 90 mcg kg^{-1} bolus injection group and nine in the 50 mcg kg^{-1} h^{-1} continuous infusion group) were assessed by investigators as possibly or probably related to rFVIIa treatment. Of these, three were serious adverse events related to bleeding (haemarthrosis, haemorrhage, haematoma).

[no notes on this page]

One non-serious event of thrombophlebitis of moderate severity occurred in a patient treated with 90 mcg kg^{-1} BI. This event was considered possibly related to rFVIIa treatment.

There were no AEs or thrombotic events reported for rFVIIa-treated surgical patients in the HRS and the HTRS Registries. From the published literature evaluated, 16% (21) of surgical patients treated with rFVIIa experienced 56 AEs. Nine events were considered unlikely to be related to rFVIIa treatment but could not be determined for the remaining 12 events. Four (two mild and two severity not reported) events of thrombophlebitis were reported in three patients [28,29,49].

Discussion

To date, the data from clinical trials indicate that rFVIIa is effective and safe for the management of bleeding in haemophilia A or B patients with inhibitors undergoing surgery. Consistently beneficial effects of rFVIIa have been observed for use in surgical situations in haemophilia patients with inhibitors, despite variability in severity and location of bleeding, treatment episodes and regimens and patients. The approval of rFVIIa for use in surgery was based on a total of 145 haemophilia patients with inhibitors who received rFVIIa during and after surgical procedures: 53 patients from two clinical trials (two with acquired inhibitors), 15 patients from the HRS Registry (including two with platelet defects, one with factor V deficiency), and 82 patients from published literature sources. These 145 patients underwent 182 surgical procedures. The analyses presented for approval of the surgery indication demonstrated rFVIIa treatment was effective in 148 (81%) of these procedures.

Subsequent to FDA approval, additional post-marketing surveillance data gathered through the HTRS registry from 2004–2008 for 66 patients report efficacy of 89–94% for 143 dental, surgical and other medical procedures. While some of the procedures might have also involved use of antifibrinolytic agents, this efficacy is specific to the site-reported outcomes with one or more rFVIIa treatment regimens for each procedure. In addition, published literature reports since 2004 include information on 53 patients with reported efficacy in 60 of 71 (85%) procedures.

A principal consideration in the management of surgery for haemophilia patients with inhibitors is the potential for re-bleeding, even in patients where rFVIIa has demonstrated efficacy at times soon after surgery. Such concerns are typical in the haemophilia patient population irrespective of inhibitor status. For these reasons, contingency plans for haemostasis around surgery that avoid re-bleeding are essential and can include initiating haemostatic coverage for physical therapy sessions or closely monitoring and optimising dose timing. While the possibility of thrombotic events does not appear to present an overriding clinical risk (one event in 263 patients [0.4%] treated for 395 procedures [0.25%]), patients treated with any procoagulant therapy should be observed closely for signs and symptoms of disseminated intravascular coagulation and/or other thrombotic events.

A recent consensus guideline has been published specifically highlighting issues around elective orthopaedic procedures in patients with inhibitors [58]. Giangrande *et al.* [58] published guidelines instituted in the UK and Ireland based upon review of literature and experiences of a group of expert physicians. In their review, the authors provide data on 13 procedures in 10 inhibitor patients (9 haemophilia A and one acquired haemophilia) over a 2 year period. The final outcome was rated by the reporting clinicians as 'excellent' or 'extremely satisfactory' in 100% of the cases. The guidelines suggest the use of a higher initial bolus dose of 120–180 mcg kg^{-1}. Takedani *et al.*, [59] also reported 9 'excellent' and 1 'fair' haemostatic evaluation for 10 orthopaedic procedures using a mean dose of 114 mcg kg^{-1}. Both the guidelines and the Takedani *et al.* study differ from the dosing studied in trials and the currently approved rFVIIa labeling which recommends 90 mcg kg^{-1} rFVIIa immediately before surgery and every 2 h during surgery. The post-surgical dosing for minor surgery is 90 mcg kg^{-1} rFVIIa every 2 h for 48 h and then every 2–6 h, until healing has occurred. For major surgery, the post-surgical dosing is 90 mcg kg^{-1} every 2 h for the first 5 days and then every 4 h, until healing has occurred [60].

Both reviews provide expert commentary on a variety of factors including pre-operative planning, surgical technique, institution of physical therapy and management of post-operative bleeding that can impact the effectiveness and safety of orthopaedic and, by inference, other surgical procedures.

Analysis of surgical outcomes by combining multiple types of data is not without limitations. First, patients with inhibitors represent a very small population in which surgical procedures and particularly major interventions, are infrequent. The two clinical studies reported here on the use of rFVIIa in inhibitor patients undergoing pre-planned surgery represent the only clinical studies of their kind in this population [8,9]. This raises the importance of including data from post-marketing registries and the literature. While this strategy allows us to provide a comprehensive overview of the current treatment practices and outcomes, it also increases the heterogeneity of the data being presented and limits the ability to perform formal meta-analysis or combine sources. In addition, standard efficacy outcome scales for the prevention of perioperative bleeding have yet to be developed. Currently, there is little

[no notes on this page]

standardisation of haemostatic efficacy assessments, even in clinical studies of acute bleeding where there is a greater need, resulting in varying efficacy endpoints that permit only qualitative comparisons. Lastly, despite the willingness of treatment centres to submit registry data or publish their results, there is limited data around the specific procedures and patient comorbidities. This likely accounts for the presence of significant outliers within each data set that lack the details required for further analysis or study.

In patients undergoing orthopaedic procedures, which are often major surgical interventions, the proportion of procedures with effective haemostasis was slightly lower across all data sources compared to other procedures. This could be attributed to the complicated and invasive nature of orthopaedic procedures, as well as the desire to promptly ambulate the patient post-operatively through physical therapy sessions. Furthermore, individual details about these surgeries (apart from the clinical trials), the time course and intensity of rehabilitation (all sources) and the temporal relationship of any post-operative bleeding due to physical activity were not captured. Particularly, for the early registry data (HRS), details were entered on 'acute bleeding' report forms since the surgery indication for rFVIIa for prevention of bleeding during and after surgery had not yet been approved. Therefore, there may have been a bias towards reporting on treatment of post-operative bleeding (instead of prevention of bleeding around surgery) or major procedures, and exclusion of patients who received one or more doses for simple procedures like radionuclide synovectomies.

Just over a decade ago, the thought of performing surgery, let alone a complicated elective orthopaedic procedure, on a patient with haemophilia complicated by inhibitors was daunting. With the introduction of rFVIIa, the successful completion of two randomized trials describing the use of rFVIIa to provide haemostatic coverage in the peri-and post-operative periods, and the increasing volume of literature reporting on the completion of joint arthroplasty and subsequent functional outcome, the evidence around use of rFVIIa for major and elective procedures is increasing. While performing surgery on patients with inhibitors will always be different than in those without inhibitors where factor levels can be tracked, haemophilia treatment centres are developing more expertise and comfort and are able to offer appropriate surgical interventions to their patients.

Acknowledgements

The authors thank Stephanie Golding (Novo Nordisk Inc.) for conducting the literature search at the direction of the authors and for obtaining the manuscripts for review. The authors also acknowledge the assistance of Abha Chandra and Brian Geldziler, PhD (both from Novo Nordisk Inc.) for obtaining relevant information from the clinical study reports and HRS/HTRS post-marketing surveillance reports for the authors to analyse, and for medical writing assistance with the manuscript. The authors acknowledge the assistance of Outcome Sciences Inc., that currently manages the HTRS registry and performed the analysis of 2004-2008 data. The clinical studies described were both funded by Novo Nordisk A/S. The HRS/HTRS registry is owned by HTRS and is supported by funding from Novo Nordisk Inc.

Disclosures

LAV is a consultant for Novo Nordisk Inc. DLC is a Novo Nordisk Inc. employee. BG was a Novo Nordisk Inc. employee.

References

1 Gringeri A, Mantovani LG, Scalone L, Mannucci PM. Cost of care and quality of life in hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; **102**: 2358–63.
2 Scalone L, Mantovani LG, Mannucci PM, Gringeri A, COCIS Study Investigators. Quality of life is associated to the orthopaedic status in haemophiliac patients with inhibitors. *Haemophilia* 2006; **12**: 154–62.
3 Morfini M, Haya S, Tagariello G *et al.* European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia* 2007; **13**: 606–12.
4 Jiménez-Yuste V, Rodriguez-Merchan EC, Alvarez MT, Quintana M, Fernandez I, Hernandez-Navarro F. Controversies and challenges in elective orthopedic surgery in patients with hemophilia and inhibitors. *Semin Hematol* 2008; **45**: S64–7.
5 Nilsson IM, Berntorp E, Freiburghaus C. Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost* 1993; **70**: 56–9.
6 Hay CR, Lozier JN, Lee CA *et al.* Porcine factor VIII therapy in patients with congenital hemophilia and inhibitors: efficacy, patient selection, and side effects. *Semin Hematol* 1994; **31**: 20–5.
7 Lusher JM. Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors–benefits and limitations. *Semin Hematol* 1994; **31**: 49–52.
8 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 890. *Thromb Haemost* 1998; **80**: 773–8.
9 Pruthi RK, Mathew P, Valentino LA, Sumner MJ, Seremetis S, Hoots WK. Haemostatic efficacy and safety of bolus and continuous infusion of recombinant factor VIIa are comparable in haemophilia patients with inhibitors undergoing major surgery. Results from an open-label, randomized, multicenter trial. *Thromb Haemost* 2007; **98**: 726–32.
10 Biron-Andreani C, Dupeyron G, Mainemer M, Schved JF. Successful use of recombinant factor VIIa in a haemophiliac with inhibitor undergoing cataract surgery. *Blood Coagul Fibrinolysis* 2001; **12**: 215–6.
11 Carr ME, Loughran TP, Cardea JA, Smith WK, Kuhn JG, Dottore MV. Successful use of recombinant factor VIIa for hemostasis during total knee replacement in a severe hemophiliac with high-titer factor VIII inhibitor. *Int J Hematol* 2002; **75**: 95–9.
12 Chuansumrit A, Sri-Udomporn N, Srimuninnimit V, Juntarukha R. A single high dose of recombinant factor VIIa combining adjuvant therapy for controlling bleeding episodes in haemophiliacs with inhibitors. *Haemophilia* 2001; **7**: 532–4.
13 Divanon F, Hecquard C, Borel-Derlon A. Experience with use of recombinant activated factor VII. *J Clin Pharm Ther* 2002; **27**: 133–8.
14 Faradji A, Bonnomet F, Lecocq J *et al.* Knee joint arthroplasty in a patient with haemophilia A and high inhibitor titre using recombinant factor VIIa (NovoSeven((R))): a new case report and review of the literature. *Haemophilia* 2001; **7**: 321–6.
15 Goddard N. Case studies: orthopaedic surgery in adult patients with haemophilia A with inhibitors. *Haemophilia* 2005; **11**(Suppl 1): 32–7.

16 Gringeri A, Santagostino E, Mannucci PM. Failure of recombinant activated factor VII during surgery in a hemophiliac with high-titer factor VIII antibody. *Haemostasis* 1991; **21**: 1–4.
17 Hedner U, Glazer S, Pingel K *et al*. Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988; **2**: 1193.
18 Ingerslev J, Feldstedt M, Sindet-Pedersen S. Control of haemostasis with recombinant factor VIIa in patient with inhibitor to factor VIII. *Lancet* 1991; **338**: 831–2.
19 Ingerslev J, Holm M, Christiansen K, Knudsen L, Negrier C. Levels of prothrombin activation peptide F1+2 in patients with a bleeding tendency. *Blood Coagul Fibrinolysis* 1998; **9**(Suppl. 1): S129–34.
20 Janic D, Brdar R, Kristic Z *et al*. Successful concurrent triple surgery in an adolescent patient with haemophilia A and inhibitors treated with recombinant factor VIIa. *Haemophilia* 2007; **13**: 214–6.
21 Kanyike FB, Abdul-Salam SA, Prakash B, Sharhan A, Wahib N, Youssef AH. Use of recombinant factor VIIa (NovoSeven) in a haemophilia A patient with inhibitor in Kuwait. *Haemophilia* 1999; **5**: 273–5.
22 Konkle BA, Nelson C, Forsyth A, Hume E. Approaches to successful total knee arthroplasty in haemophilia A patients with inhibitors. *Haemophilia* 2002; **8**: 706–10.
23 Koyama T, Nagao T, Tsunozaki H, Arai M, Miura O. Successful management of massive intraperitoneal bleeding in a hemophilia A patient with inhibitor by surgical debridement of the incomplete hematoma anad administration of recombinant factor VIII and activated factor VII. *Pathophysiol Haemost Thromb* 2006; **35**: 405–7.
24 Laguna P, Klukowska A. Management of oral bleedings with recombinant factor VIIa in children with haemophilia A and inhibitor. *Haemophilia* 2005; **11**: 2–4.
25 Leblebisatan G, Sasmaz I, Antmen B, Kilinc Y, Sizmaz S, Yagmur M. A successful use of recombinant factor VIIa in a patient with inhibitors, for bilateral cataract operation and circumcision. *Haemophilia* 2006; **12**: 187–9.
26 Leebeek FW, Kappers-Klunne MC, Jie KS. Effective and safe use of recombinant factor VIIa (NovoSeven) in elderly mild haemophilia A patients with high-titre antibodies against factor VIII. *Haemophilia* 2004; **10**: 250–3.
27 Lorenzo JI, Montoro JM, Aznar JA. Postoperative use of rFVIIa by continuous infusion in a haemophilic boy. *Haemophilia* 1999; **5**: 135–8.
28 Ludlam CA, Smith MP, Morfini M, Gringeri A, Santagostino E, Savidge GF. A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation. *Br J Haematol* 2003; **120**: 808–13.
29 Mauser-Bunschoten EP, Goede-Bolder A, Wielenga JJ, Levi M, Peerlinck K. Continuous infusion of recombinant factor VIIa in patients with haemophilia and inhibitors. Experience in The Netherlands and Belgium. *Neth J Med* 1998; **53**: 249–55.
30 Mauser-Bunschoten EP, Goede-Bolder AD, Leebeek FW *et al*. Efficacy of recombinant factor VIIa administered by continuous infusion to haemophilia patients with inhibitors. *Haemophilia* 2002; **8**: 649–56.
31 Mehta S, Nelson CL, Konkle BA, Vannozzi B. Total knee arthroplasty using recombinant factor VII in hemophilia-A patients with inhibitors. A report of three cases. *J Bone Joint Surg Am* 2004; **86-A**: 2519–21.
32 Menart C, Cognet V, Petit PY, Massignon D, Negrier C. Management of an anti-factor VIII inhibitor occurring during surgical procedure with continuous infusion of Novoseven. *Blood Coagul Fibrinolysis* 1998; **9**: 289–90.
33 Montoro JB, Altisent C, Pico M, Cabanas MJ, Vila M, Puig LL. Recombinant factor VIIa in continuous infusion during central line insertion in a child with factor VIII high-titre inhibitor. *Haemophilia* 1998; **4**: 762–5.
34 Morimoto Y, Yoshioka A, Shima M, Kirita T. Intraoral Hemostasis using a recombinant activated factor VII preparation in a hemophilia A patient with inhibitor. *J Oral Maxillofac Surg* 2003; **61**: 1095–7.
35 O'Connell N, McMahon C, Smith J, Khair K, Hann IM, Liesner R. Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors. *Br J Haematol* 2002; **116**: 632–5.
36 O'Connell N, Chen J, Byrne M, O'Shea E, Smyth H, Smith OP. Massive pseudotumour resection with recombinant factor VIIa (NovoSeven) cover. *Br J Haematol* 2002; **116**: 645–8.
37 O'Marcaigh AS, Schmalz BJ, Shaughnessy WJ, Gilchrist GS. Successful hemostasis during a major orthopedic operation by using recombinant activated factor VII in a patient with severe hemophilia A and a potent inhibitor. *Mayo Clin Proc* 1994; **69**: 641–4.
38 Pekcelen Y, Yavuz AS, Namli S, Gucukoglu A. Short-course use of recombinant factor VIIa in a haemophilia patient with inhibitor undergoing cataract surgeries. *Blood Coagul Fibrinolysis* 2005; **16**: 445–6.
39 Perez R, Sosa R. Sequential treatment with bolus and continuous infusion of recombinant factor VIIa for hip arthroplasty in a patient with haemophilia A and inhibitor. *Haemophilia* 2002; **8**: 822–5.
40 Quintana-Molina M, Martinez-Bahamonde F, Gonzalez-Garcia E *et al*. Surgery in haemophilic patients with inhibitor: 20 years of experience. *Haemophilia* 2004; **10**(Suppl. 2): 30–40.
41 Rocino A, Carola A, Papa ML *et al*. Major surgery for a gastric cancer in a haemophilic with high inhibitor titre successfully performed by the use of recombinant FVIIa. *Haemophilia* 1999; **5**: 441–4.
42 Rodriguez-Merchan EC, Wiedel JD, Wallny T *et al*. Elective orthopaedic surgery for inhibitor patients. *Haemophilia* 2003; **9**: 625–31.
43 Saba HI, Morelli GA, Azam RR, Klein CJ, Letson GD. Efficacy of NovoSeven(R) during surgery on a haemophiliac with previous history of inhibitors. *Haemophilia* 2003; **9**: 131–6.
44 Santagostino E, Morfini M, Rocino A, Baudo F, Scaraggi FA, Gringeri A. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. *Thromb Haemost* 2001; **86**: 954–8.
45 Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia* 1999; **5**: 253–9.
46 Schmidt ML, Smith HE, Gamerman S, DiMichele D, Glazer S, Scott JP. Prolonged recombinant activated factor VII (rFVIIa) treatment for severe bleeding in a factor-IX-deficient patient with an inhibitor. *Br J Haematol* 1991; **78**: 460–3.
47 Sheth S, DiMichele D, Lee M *et al*. Heart transplant in a factor VIII-deficient patient with a high-titre inhibitor: Perioperative management using high- dose continuous infusion factor VIII and recombinant factor VIIa. *Haemophilia* 2001; **7**: 227–32.
48 Slaoui M, Lambert T, Stieltjes N, Claeyssens S, Borel-Derlon A. Intestinal surgery with activated recombinant factor VII prophylaxis in patients with haemophilia A and high responding inhibitors: a report of five cases. *Blood Coagul Fibrinolysis* 2004; **15**: 687–91.
49 Smith MP, Ludlam CA, Collins PW *et al*. Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU ml^{-1} is associated with an increased incidence of bleeding. *Thromb Haemost* 2001; **86**: 949–53.
50 Smith OP, Hann IM. rVIIa therapy to secure haemostasis during central line insertion in children with high-responding FVIII inhibitors. *Br J Haematol* 1996; **92**: 1002–4.
51 Smith OP. Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high-responding inhibitors. *Pathophysiol Haemost Thromb* 2002; **32**(Suppl. 1): 22–5.
52 Solimeno LP, Perfetto OS, Pasta G, Santagostino E. Total joint replacement in patients with inhibitors. *Haemophilia* 2006; **12**(Suppl. 3): 113–6.
53 Tagariello G, De Biasi E, Gajo GB *et al*. Recombinant FVIIa (NovoSeven) continuous infusion and total hip replacement in patients with haemophilia and high titre of inhibitors to FVIII: experience of two cases. *Haemophilia* 2000; **6**: 581–3.
54 Tagariello G, Bisson R, Radossi P *et al*. Concurrent total hip and knee replacements in a patient with haemophilia with inhibitors using recombinant factor VIIa by continuous infusion. *Haemophilia* 2003; **9**: 738–40.
55 Takedani H, Mikami S, Kawasaki N *et al*. Excision of pseudotumour in a patient with haemophilia A and inhibitor managed with

[no notes on this page]

recombinant factor VIIa. *Haemophilia* 2004; **10**: 179–82.
56 Vermylen J, Peerlinck K. Optimal care of inhibitor patients during surgery 271. *Eur J Haematol Suppl* 1998; **63**: 15–7.
57 Warner MN, Metrakos P, Deschenes M, Barkun J, Tchervenkov J, Rivard GE. Orthotopic liver transplantation in a severe hemophilia A patient with factor VIII inhibitors. *Blood* 2003; **102**: 800a.
58 Giangrande PL, Wilde JT, Madan B *et al.* Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven] in elective orthopaedic surgery in haemophiliac patients with inhibitors. *Haemophilia* 2009; **15**: 501–8.
59 Takedani H, Kawahara H, Kajiwara M. Major orthopaedic surgeries for haemophilia with inhibitors using rFVIIa. *Haemophilia* 2010; **16**: 290–5.
60 NovoSeven Prescribing Information. NovoSeven (R) RT [Package Insert]. Denmark: Bagsvaerd, Novo Nordisk A/S, 2008.

[no notes on this page]