Ten-year experience of recombinant activated factor VII use in surgical patients with congenital haemophilia with inhibitors or acquired haemophilia in Japan

H. TAKEDANI,* M. SHIMA,† Y. HORIKOSHI,‡ T. KOYAMA,§ K. FUKUTAKE,¶ M. KUWAHARA|| and N. ISHIGURO**

*Hospital of the Institute of Medical Science of the University of Tokyo (IMSUT), Tokyo; †Nara Medical University, Kashihara; ‡Shizuoka Children’s Hospital, Shizuoka; §Tokyo Medical and Dental University, Tokyo; ¶Tokyo Medical University, Tokyo; ||Novo Nordisk Pharma Ltd., Tokyo; and **Nagoya University School of Medicine, Nagoya, Japan

Summary. Patients with congenital haemophilia with inhibitors or acquired haemophilia are at risk of bleeding complications during surgery. In these patients, replacement therapy for the missing coagulation factor is ineffective, and a bypassing agent such as recombinant activated factor VII (rFVIIa) is required to manage bleeding. To evaluate the safety and haemostatic efficacy of rFVIIa treatment in Japanese patients with congenital haemophilia with inhibitors to FVIII/FIX or acquired haemophilia undergoing surgery. Postmarketing surveillance data from May 2000 to March 2010 were analysed to assess the haemostatic efficacy of 38 procedures in 22 patients with congenital haemophilia A, 13 procedures in seven patients with congenital haemophilia B, and five procedures in five patients with acquired haemophilia. Postoperative bleeding control was judged to be effective (bleeding was stopped completely or reduced considerably) for 34/38 procedures (89%) in patients with congenital haemophilia A, 10/13 procedures (77%) in patients with congenital haemophilia B, and 4/5 procedures (80%) in patients with acquired haemophilia. Tranexamic acid was used concomitantly for 36/56 procedures (64%). Safety was analysed for 66 procedures in 37 patients. Adverse effects potentially related to rFVIIa treatment included mild superficial thrombophlebitis, mild decrease in platelet count, and mild elevation of the serum alanine transaminase level in one patient each. All adverse effects resolved without treatment. Administration of rFVIIa provided adequate haemostasis without serious adverse effects in the majority of cases. The efficacy and safety data in Japanese patients were similar to previously published data from other countries.

Keywords: continuous infusion, haemophilia with inhibitors, Japan, postmarketing surveillance, recombinant factor VIIa, surgery

Introduction

In congenital haemophilia, the intrinsic coagulation mechanism is deficient because of a lack or abnormality of factor VIII (FVIII, haemophilia A) or FIX (haemophilia B). Bleeding is managed by FVIII or FIX replacement therapy, which can result in the production of alloantibodies (inhibitors) to the relevant coagulation factor [1]. Replacement therapy then becomes ineffective, and alternative methods of managing bleeding are required. Administration of 90 µg kg⁻¹ of recombinant FVIIa (rFVIIa) produces a plasma rFVIIa level of approximately 25 nm [2] and initiates the coagulation reaction via direct activation of FX on the activated platelet membrane at the site of vascular injury, resulting in bypassing of FVIII or FIX [3]. rFVIIa (NovoSeven®; Novo Nordisk, Tokyo, Japan) has been commercially available since 1996 for the treatment of bleeding in patients with haemophilia A or B with inhibitors to FVIII or FIX.

As the joints of haemophilia patients with inhibitors are generally in a poorer condition than those of haemophilia patients without inhibitors [4], patients with inhibitors may have a particularly high
requirement for surgery. However, surgery is challenging in patients with haemophilia with inhibitors because of the increased risk of bleeding complications. It is therefore important to determine the optimal methods of bleeding control during surgical procedures in these patients. The first surgical procedure performed with rFVIIa treatment was reported in 1988, in a patient with haemophilia with an inhibitor who underwent synovectomy of the knee [5]. A randomized trial was subsequently conducted to investigate the clinical safety and efficacy of rFVIIa treatment in haemophilia patients with inhibitors undergoing surgical procedures [6]. rFVIIa was approved for use in Japan in 2000, but there was limited information available regarding its safety and efficacy at that time. Ten years of postmarketing surveillance was therefore performed to accumulate data regarding the outcomes of rFVIIa treatment in Japanese patients with haemophilia with inhibitors. This report describes the use, haemostatic efficacy and safety of rFVIIa treatment in patients who underwent surgery, based on the data collected by case report forms during the surveillance period.

Methods

Subjects and data collection

All patients with congenital haemophilia with inhibitors to FVIII or FIX or acquired haemophilia who received rFVIIa for the management of bleeding during surgical procedures at the 18 sites participating in the postmarketing surveillance conducted by Novo Nordisk Pharma Ltd. from May 2000 to March 2010 were included in this study.

During the surveillance period, the following data were collected for patients who received rFVIIa treatment: haemophilia type, age, sex, body weight, medical history and complications, date and type of surgery, transfusions, use of rFVIIa, haemostatic efficacy of rFVIIa treatment, laboratory test results before and after surgery, adverse events and concomitant administration of other drugs. Observations were continued for 6 months after surgery. Adverse events were defined as all medically unfavourable events that occurred during or after administration of rFVIIa (adverse drug reactions, abnormal laboratory test results and unexpected symptoms). Events for which a causal relationship with rFVIIa could not be ruled out by the participating investigators were classified as adverse drug reactions.

The study protocol was approved by the institutional review boards of all participating institutions, and was conducted in accordance with the principles of the Good Post-Marketing Study Practice [7].

Haemostatic efficacy of rFVIIa treatment

The haemostatic efficacy of rFVIIa treatment during and after surgery was evaluated by the participating investigators. Intraoperative bleeding was judged subjectively based on the experience of the investigators as less than, the same as, or more than expected for patients with haemophilia undergoing surgery (including those who receive other haemophilia inhibitor products or blood coagulation factor products), regardless of the inhibitor status of individual patients. Postoperative bleeding control (up to 3 days after surgery) was judged as effective (bleeding stopped or considerably reduced), slightly effective (bleeding slightly reduced) or not effective (bleeding not reduced). Maintenance of haemostasis of the surgical wound (until suture removal) was classified as yes or no.

‘Complete haemostasis’ was defined as complete control of bleeding that satisfied all of the following criteria: blood loss judged as less than expected or the same as expected, postoperative bleeding control (up to 3 days after surgery) judged as effective, and maintenance of haemostasis classified as yes. Haemostatic efficacy results are presented in a descriptive manner.

Results

Subjects

Thirty-seven patients received rFVIIa treatment during the study period, including 24 with congenital haemophilia A, seven with congenital haemophilia B and six with acquired haemophilia. All 37 patients (66 procedures) were included in the safety analysis. The 34 patients for whom haemostatic efficacy data were available were included in the efficacy analysis, including 38 procedures in 22 patients with congenital haemophilia A (median age: 18.5 years, age range: 1–65 years), 13 procedures in seven patients with

Table 1. Characteristics of patients in the haemostatic efficacy analysis.

| Procedure Type | Congenital haemophilia A | Congenital haemophilia B | Acquired haemophilia |
|----------------|-------------------------|-------------------------|---------------------|
| Patients (n)   | 22                      | 7                       | 5                   |
| Procedures (n)| 38                      | 13                      | 5                   |
| Age (years, median) (range) | 18.5 (1–65) | 18 (10–37) | 62 (39–79) |
| Surgical procedures, n (%) | Orthopaedic | 16 (42) | 8 (62) |
| | Central venous access device placement | 6 (16) | 2 (15) |
| | Dental/oral | 6 (16) | 1 (8) | 1 (20) |
| | Gastrointestinal | 4 (11) | 1 (8) | 2 (40) |
| | Small incision or suturing | 4 (11) | 1 (8) |
| | Thoracic | 2 (5) | 1 (20) |
| | Obstetric | 2 (5) | 1 (20) |

*Of the 24 cases, 11 underwent arthroscopic synovectomy and 4 underwent joint replacement.
†Of the 8 cases, 6 underwent port placement.
congenital haemophilia B (median age: 18 years, age range: 10–37 years) and five procedures in five patients with acquired haemophilia (median age: 62 years, age range: 39–79 years) (Table 1). Twelve of the patients with congenital haemophilia with inhibitors were also included in previous studies [8–10].

The 38 surgical procedures in patients with congenital haemophilia A included 16 orthopaedic procedures (42%), six central venous catheter or port placement procedures (16%), six dental/oral procedures (16%), four gastrointestinal procedures (11%), four suture/incision procedures (11%) and two thoracic procedures (5%). Continuous rFVIIa infusion was administered after bolus injection for nine procedures (24%). Tranexamic acid was used concomitantly for 24 procedures (63%) (Tables S1 and S2).

The 13 surgical procedures in patients with congenital haemophilia B included eight orthopaedic procedures (62%), two central venous catheter or port placement procedures (15%), 1 dental/oral procedure (8%), one gastrointestinal procedure (8%) and one suture/incision procedure (8%). Continuous rFVIIa infusion was administered following bolus injection for six procedures (46%). Tranexamic acid was used concomitantly for nine procedures (69%) (Tables S3 and S4).

The five surgical procedures in patients with acquired haemophilia were two gastrointestinal procedures (40%), one dental/oral procedure (20%), one obstetric procedure (20%) and one neurosurgical procedure (20%). Tranexamic acid was used concomitantly for three procedures (60%) (Tables S5 and S6).

rFVIIa doses

Table 2 shows the doses of rFVIIa administered for common procedures in patients with congenital haemophilia A or B with inhibitors. Five of the six port placement procedures were performed with bolus injections and one was performed with continuous infusion of rFVIIa. In the patients who received bolus injections, the median dose per injection was 109 µg kg⁻¹ (range: 96–117 µg kg⁻¹) and the median number of injections was 15 (range: 3–64). The initial infusion rate in the patient who received a continuous infusion was 28 µg kg⁻¹ h⁻¹. In these six patients, the median duration of treatment was 4.5 days (range: 3–28 days) and the median total dose was 1765 µg kg⁻¹ (range: 330–7460 µg kg⁻¹).

Five of the 11 arthroscopic synovectomy procedures were performed with bolus injections and six were performed with continuous infusion of rFVIIa. In the patients who received bolus injections, the median dose per injection was 125 µg kg⁻¹ (range: 107–141 µg kg⁻¹) and the median number of injections was 39 (range: 29–55). In the patients who received continuous infusion, the median initial infusion rate was 32 µg kg⁻¹ h⁻¹ (range: 17–60 µg kg⁻¹ h⁻¹). In these 11 patients, the median duration of treatment was 13 days (range: 5–16 days) and the median total dose was 5441 µg kg⁻¹ (range: 1690–7340 µg kg⁻¹).

One of the three joint replacement procedures was performed with bolus injections and two were performed with continuous infusion of rFVIIa. In the patient who received bolus injections, the mean dose per injection was 120 µg kg⁻¹ and 72 injections were administered. The median initial infusion rate in the patients who received continuous infusions was 32.5 µg kg⁻¹ h⁻¹ (range: 29–36 µg kg⁻¹ h⁻¹). In these three patients, the median duration of treatment was 12 days (range: 7–15 days) and the median total dose was 5000 µg kg⁻¹ (range: 3890–8640 µg kg⁻¹). The doses and haemostatic efficacy for all procedures are available in the online data supplements (Tables S1–S6).

Efficacy

Table 3 shows the haemostatic efficacy of rFVIIa treatment. In patients with congenital haemophilia A, the blood loss was judged as less than expected for 20/38 procedures (53%), the same as expected for 15/38 procedures (39%) and more than expected for 3/38 procedures (8%). Postoperative bleeding control was judged as effective for 34/38 procedures (89%), slightly effective for 4/38 procedures (11%) and not effective for 0/38 procedures (0%). Two of the three procedures judged as having more blood loss than expected were also among those judged as having slightly effective postoperative bleeding control. Maintenance of haemostasis was classified as yes for 36/38 procedures (95%) and no for 2/38 procedures (5%). ‘Complete haemostasis’ was achieved for 32/38 procedures (84%).

In patients with congenital haemophilia B, the blood loss was judged as less than expected for 7/13 procedures (54%), the same as expected for 2/13 procedures (15%) and more than expected for 4/13 procedures (31%). Postoperative bleeding control was judged as effective for 10/13 procedures (77%),...
RFVIIA IN SURGICAL PATIENTS WITH HAEMOPHILIA

Table 3. Haemostatic efficacy of RFVIIa treatment.

| Blood loss, n (%) | Congenital haemophilia A n = 38 | Congenital haemophilia B n = 13 | Acquired haemophilia n = 5 |
|-------------------|---------------------------------|---------------------------------|---------------------------|
| Less than expected| 20 (53)                          | 7 (54)                          | 1 (20)                    |
| The same as expected| 15 (39)                        | 2 (15)                          | 2 (40)                    |
| More than expected| 3 (8)                           | 4 (31)                          | 2 (40)                    |
| Maintenance of haemostasis, n (%) | 34 (89)                      | 10 (77)                          | 4 (80)                    |
| Maintenance of haemostasis, n (%) | 4 (11)                        | 3 (23)                          | 0 (0)                     |
| Complete haemostasis*, n (%) | 32 (84)                       | 8 (62)                          | 1 (20)                    |

*Blood loss judged as less than expected or the same as expected, postoperative bleeding control judged as effective, and maintenance of haemostasis classified as yes.

Discussion

RFVIIa doses for minor and major surgery

For the six port placement procedures in the present study, the total number of RFVIIa injections ranged from three to 64, the treatment period ranged from 3 to 28 days, and the total dose ranged from 330 to 7460 µg kg⁻¹ (Table 2). The patient who received the smallest total dose (330 µg kg⁻¹) received supplementary RFVIIa in addition to the main treatment with aPCC (Table S1, surgical procedure 11). In the patient who received the smallest number of injections over the shortest period (three injections over 3 days), use of RFVIIa was stopped when immune tolerance induction with RFVII was started (Table S1, surgical procedure 12). The patient with the longest treatment period (28 days) required longer-term use of RFVIIa because of surgical wound dehiscence (Table S3, surgical procedure 42). For the remaining three port placement procedures, only rFVIII was used, the number of injections ranged from 11 to 64, the treatment period ranged from 3 to 11 days, and the total dose ranged from 1080 to 7460 µg kg⁻¹. For these three procedures, the treatment was similar to the previously reported treatment for eight Broviac catheter or port placement procedures in patients who received 90 µg kg⁻¹ per injection, where the number of injections ranged from 26 to 98 and the treatment period ranged from 3 to 13 days [6].

Concomitant use of aPCC, PCC or rFVIII makes it difficult to assess the efficacy of RFVIIa treatment alone. In the six patients who underwent arthroscopic synovectomy and received only RFVIIa, the treatment period ranged from 7 to 15 days and the total dose ranged from 3090 to 7340 µg kg⁻¹. In the three patients who underwent joint replacement and received only RFVIIa, the treatment period ranged from 7 to 15 days and the total dose ranged from...
medical procedures) in 263 patients with haemophilia with inhibitors, including data from the randomized comparative trial described above, the Hemophilia Research Society/Hemophilia and Thrombosis Research Society database and other studies [6,10,19]. The reported overall efficacy rate was 84% (333/395), but the definitions of efficacy varied among studies.

Safety

In the present study, mild superficial thrombophlebitis was reported in one patient who received a continuous infusion of undiluted rFVIIa. In the previously published review article, serious thrombotic events (not including superficial thrombophlebitis) were reported in 2/263 patients [19]. One of these patients was a 4-year-old who underwent port placement and developed thrombosis of an internal jugular vein [6], and the other patient underwent left knee arthroplasty and developed thrombosis of the popliteal and fibular veins [13].

Conclusion

Japanese data show similar efficacy and safety of rFVIIa treatment in surgical patients compared with previous reports. In addition to previously reported data, our detailed data may help physicians to plan rFVIIa dosing schedules for patients with congenital haemophilia with inhibitors or acquired haemophilia undergoing surgical procedures.

Acknowledgements

The authors thank the physicians at the investigation sites for their assistance in collecting the surveillance data (Table S7).

Author contributions

All authors provided substantial contributions to the acquisition and interpretation of data, and writing and critical revisions of the manuscript. All authors approved the final version of the manuscript.

Disclosures

This study was sponsored by Novo Nordisk Pharma Ltd. Medical writing and editorial support were provided by Dr. Marguerite Elgin and ELMCOM®, and was funded by Novo Nordisk Pharma Ltd. MG is an employee of Novo Nordisk Pharma Ltd., and HT, MS, YH and NI received consulting fees for an expert panel meeting for surgery sponsored by Novo Nordisk Pharma Ltd.

References

1 Berntorp E, Shapiro A, Astermark J et al. Inhibitor treatment in haemophiliias A and B: summary statement for the 2006 international consensus conference. Haemophilia 2006; 12(Suppl. 6): 51–7.
2 Hedner U. Factor VIIa and its potential therapeutic use in bleeding-associated pathologies. Thromb Haemost 2008; 100: 557–62.
3 Hoffman M, Monroe DM 3rd, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. Blood Coagul Fibrinolysis 1998; 9(Suppl. 1): S61–5.
4 Morfini M, Haya S, Tagariello G et al. European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 2007; 13: 606–12.
RFVIIa in Surgical Patients with Haemophilia

5 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.

6 Shapiro AD, Gilchrist GS, Hoots WK, Coo-per HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80: 773–8.

7 Ministry of Health, Labour and Welfare, Japan. Ordinance on Standards for Conducting Post-Marketing Surveillance and Studies on Drugs (Ordinance 171; December 20. Tokyo, Japan: Ministry of Health, Labour and Welfare, 2004.

8 Takedani H, Kawahara H, Kajiwara M. Major orthopaedic surgeries for haemophilia with inhibitors using rFVIIa. *Haemophilia* 2010; 16: 290–5.

9 Takedani H, Mikami S, Kawasaki N et al. Excision of pseudotumour in a patient with haemophilia A and inhibitor managed with recombinant factor VIIa. *Haemophilia* 2004; 10: 179–82.

10 Nakamura M, Terashima K, Takashima Y, Amano K, Horikoshi Y, Mimaya J. Continuous infusion of recombinant activated factor VII during and after elbow arthroplasty in a hemophilia A patient with inhibitors. *Rinsho Ketsueki* 2002; 43: 183–8.

11 Smith MP, Ludlum 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 is associated with an increased incidence of bleeding. *Thromb Haemost* 2001; 86: 949–53.

12 Mauser-Bunschoten EP, Koopman MM, Goede-Bolder AD et al., Recombinant Factor VIIa Data Collection Group. Efficacy of recombinant factor VIIa administered by continuous infusion to haemophilia patients with inhibitors. *Haemophilia* 2002; 8: 649–56.

13 Pruthi RK, Mathew P, Valentino LA, Sum-ner MJ, Seremetis S, Hoots WK, NovoSev-en in Surgery Study Investigators. 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.

14 Ludlum CA, Smith MP, Morfini M, Grin-geri 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.

15 Monroe DM, Mackman N, Hoffman M. Wound healing in hemophilia B mice and low tissue factor factor mice. *Thromb Res* 2010; 125(Suppl. 1): S74–7.

16 Schulman S, d’Oron R, Martinowicz U et al. Experiences with continuous infusion of recombinant activated factor VII. *Blood Coagul Fibrinolysis* 1998; 9(Suppl. 1): 97–101.

17 Lak M, Sharifian RA, Karimi K, Mansouri-torghabeh H. Acquired hemophilia A: clinical features, surgery and treatment of 34 cases, and experience of using recombinant factor VIIa. *Clin Appl Thromb Hemost* 2010; 16: 294–300.

18 Notarnicola A, Pesce V, Scaraggi A, Mac-cagnano G, Vicenti G, Moretti B. Total hip replacement in a patient with acquired haemophilia A: a case report and literature review. *Blood Coagul Fibrinolysis* 2011; 22: 436–9.

19 Valentino LA, Cooper DL, Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. *Haemophilia* 2011; 17: 579–89.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Minor surgical procedures in patients with congenital haemophilia A with inhibitors.

Table S2. Major surgical procedures in patients with congenital haemophilia A with inhibitors.

Table S3. Minor surgical procedures in patients with congenital haemophilia B with inhibitors.

Table S4. Major surgical procedures in patients with congenital haemophilia B with inhibitors.

Table S5. Minor surgical procedures in patients with acquired haemophilia.

Table S6. Major surgical procedures in patients with acquired haemophilia.

Table S7. Participating sites.