

## A Comprehensive Review of rFVIIa Use in a Tertiary Care Pediatric Center

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**Background.** Recombinant activated factor VII (rFVIIa) is a hemostatic agent developed for the treatment of bleeds in patients with hemophilia and inhibitors. Case reports/series document its growing use in patients without hemophilia. Such reports however do not accurately describe the proportion of rFVIIa used for various indications. We sought to document the complete use of rFVIIa at our institution over a 6-year period (2000–2005). **Procedure.** Using a computerized registry documenting all rFVIIa use in our institution a complete list of patients receiving rFVIIa was generated. Clinical data on these patients was obtained through chart review. **Results.** 111 patients received 7,016,400 µg of rFVIIa over the 6 years: 23 patients had congenital bleeding disorders (10 patients with hemophilia and inhibitors; 7 with congenital FVII deficiency; 6 with platelet function

disorders). These 23 patients (21% of all patients receiving rFVIIa) accounted for 79.9% of all rFVIIa used; patients with hemophilia alone accounted for 68.6%. The 88 patients without a congenital bleeding disorder (79% of all patients using rFVIIa) accounted for 20.1% of rFVIIa used. However their annual use of rFVIIa increased 10-fold during the 6 years. **Conclusions.** Patients with hemophilia use massive amounts of rFVIIa repeatedly while patients without hemophilia use rFVIIa infrequently and at smaller doses. The use of rFVIIa in patients without congenital bleeding disorders (all “off-label” use) is rapidly growing in both number of patients and in total use and has likely significant clinical and economic ramifications. *Pediatr Blood Cancer* 2008;50:1013–1017.

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### INTRODUCTION

Recombinant activated factor VII (rFVIIa; NiaStase<sup>®</sup>, Novo-Seven<sup>®</sup> Novo Nordisk A/S., Bagsvaerd, Denmark) is a hemostatic agent initially developed and licensed for the treatment of bleeds in patients with hemophilia and inhibitors. In such patients rFVIIa has generally been found to be safe and effective [1].

In Canada, rFVIIa is as yet only licensed for use in patients with hemophilia and inhibitors (to treat bleeds or to prevent bleeding in patients undergoing surgery) while in the USA it is also licensed for use in patients with congenital factor (F)VII deficiency. In many European countries it is also licensed for use in patients with Glanzmann's thrombasthenia. All 3 of these congenital bleeding disorders account for very small patient populations. In Canada, for example, there are approximately 81 patients with hemophilia and inhibitors, 34 patients with Glanzmann's thrombasthenia and 153 with congenital FVII deficiency (41 of whom have severe/moderate deficiency (<5% FVII)) [2].

Due to its perception as a “universal hemostatic agent” rFVIIa is increasingly being used, with as yet scant data demonstrating effectiveness, for “off-label/unlicensed” indications [3–6]. Reports (mainly case reports, case series and a few recent randomized studies) document its use in treating bleeds in patients with other congenital bleeding disorders [7–9] and in individuals (primarily adults) without congenital bleeding disorders in the context of trauma [10,11], intracranial hemorrhage (ICH) [12,13], surgery [14], liver failure [5], thrombocytopenia [15] and acquired abnormal coagulation profiles [16,17]. Neither case reports, case series, registries [18,19] or randomized clinical trials provide an accurate unbiased representation as to what proportion of rFVIIa is being used for various licensed/“on-label” and un-licensed/“off-label” indications.

rFVIIa, like other recombinant coagulation factors, is very expensive. The cost of rFVIIa is estimated at approximately \$1.00 US/µg [5]. Contributing to its cost is the fact that due to its rapid clearance it generally has to be given every 2–4 hr to be effective in patients with hemophilia and inhibitors; for patients without hemophilia the half-life of rFVIIa is not well known. Consequently patients, even children, depending on their size, using a commonly

prescribed dose of 90 µg/kg every 2 hr (for 2 or 3 doses) can easily use \$5,000.00 to \$10,000.00 US in just 1 day.

It is suspected, although not proven, that the use of rFVIIa is increasing as a result of increasing off label use. This is of concern to organizations that fund the cost of rFVIIa since the potential number of patients who might receive rFVIIa for “off-label” indications is considerably larger than the number of patients with congenital bleeding disorders. We sought to document the complete use of rFVIIa at the Hospital for Sick Children, a major Canadian pediatric tertiary care facility, over a 6-year period (2000–2005) to better understand the current pattern of rFVIIa use and of the changes in its use over time.

### METHODS

rFVIIa usage in our institution has not been regulated by any type of gate keeper mechanism. Any physician in the hospital can order rFVIIa although traditionally until the last 3–4 years it was almost always ordered after consultation with a hematologist. A computerized registry of all rFVIIa issued by the hospital's Transfusion Services has been maintained since January 1, 2000. From this a complete list of patients receiving rFVIIa was generated. Patients were assigned an indication for receiving rFVIIa according to chart documentation. When a reason for receiving rFVIIa was not documented an indication was assigned after detailed chart review. The study was approved by the hospital's Research Ethics Board. Individual patient consent was not needed as all data were anonymized.

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## RESULTS

During the 6 years, 7,016,400 µg of rFVIIa were used in our institution by 111 patients (23 with congenital bleeding disorders and 88 without) to treat bleeds or prevent peri-operative bleeding; no patient received rFVIIa on a regular prophylactic basis (Table I). Patients with hemophilia and inhibitors (n = 10) accounted for 4,814,400 µg (68.6%) of the total rFVIIa used. Patients with congenital FVII deficiency, Glanzmann thrombasthenia and Bernard Soulier Syndrome (13 patients in total) accounted for 11.3% of the total rFVIIa used. The other 88 patients (all without a congenital bleeding disorder) who received rFVIIa (all "off-label") accounted for only 20.1% of the total rFVIIa used.

The age distribution of the 111 patients at the time of receiving their first dose of rFVIIa is shown in Table II. The mean age of first exposure to rFVIIa was slightly higher in patients with hemophilia and inhibitors than in patients without hemophilia. All patients with hemophilia were male; patients without hemophilia consisted of 44 females and 57 males. Due to successful inhibitor eradication and/or patients turning 18 years old (at which point they were transferred to an adult hospital for ongoing care) no patient with hemophilia and inhibitors was inhibitor positive for the entire 6-year period. The median time for which these patients were inhibitor positive was 1.6 years (range: 1 month to 5 years).

## Patterns of Use of rFVIIa

**In patients with congenital bleeding disorders (essentially on-label use).** Patients with hemophilia and inhibitors used the most rFVIIa on a daily basis (24,945 µg/patient/day), accounted for the largest number of exposure days (ED)/patient (mean: 19.3 ED/patient over the 6 years; median: 11 ED; range 1–107 ED), and had the highest per capita use of rFVIIa at 481,440 µg/patient. An ED was defined as a day in which a patient is exposed to rFVIIa regardless of the dose of rFVIIa received. Use of rFVIIa among

patients with inhibitors varied tremendously; the least rFVIIa (2,400 µg) was received by one boy (on a single day) while the most (2,096,400 µg; represents 30% of the total use of rFVIIa by all patients during the 6 years) was received by 1 boy over 107 days spread out between the ages of 2.7 and 8 years. Patients with hemophilia and inhibitors received rFVIIa primarily to treat musculoskeletal bleeds, intracranial bleeds or to prevent peri-operative bleeding.

Patients with congenital FVII deficiency (2 patients with FVII level < 1%, 1 with FVII level of 3% and 4 with mild FVII deficiency (FVII > 5%)), Glanzmann thrombasthenia or Bernard Soulier syndrome received fewer EDs to rFVIIa and smaller daily amounts (in comparison to hemophilia patients). In these patients rFVIIa was usually given in the context of mucocutaneous bleeding or to prevent peri-operative bleeding.

**Patients without congenital bleeding disorders (off-label use).** Patients without congenital bleeding disorders generally received rFVIIa infrequently and in small amounts. Specifics of use according to indication are detailed below:

**Bone marrow transplantation (BMT).** These patients tended to receive relatively large doses of rFVIIa on consecutive days to manage gastrointestinal or surgical bleeding not responding to conventional treatment (platelets, fresh frozen plasma (FFP), cryoprecipitate). In seven of these this was primarily in the context of unresponsive thrombocytopenia while in three it was primarily because of liver dysfunction and resulting prolonged INRs.

**Thrombocytopenia.** These consisted of five patients with decreased platelet production (one with leukemia, two with chemotherapy induced thrombocytopenia, one with Nieman-Pick disease and one with Wiskot–Aldrich syndrome) and eight with increased platelet destruction (seven with unresponsive immune thrombocytopenia purpura (ITP) and one with hypersplenism). All patients receiving rFVIIa for thrombocytopenias had severe thrombocytopenia (platelet counts of <20 × 10<sup>9</sup>/L). In 10 this was

TABLE I. Pattern of rFVIIa Usage in Patients According to Indications for use (Ranked According to Total Use)

Indication for rFVIIa use	Patients using rFVIIa	rFVIIa used in µg	% of total use of rFVIIa	Mean rFVIIa used µg/pt	#ED	Mean ED/pt (range)	Mean rFVIIa used µg/pt/day
Patients with congenital bleeding disorders ("on-label" indications)							
Hemophilia with inhibitors	10	4,814,400	68.6	481,440	193	19.3 (1–107)	24,945
Glanzmann's Thrombasthenia	5	501,600	7.2	100,320	76	15.2 (1–46)	6,600
Bernard Soulier Syndrome	1	4,800	0.06	4,800	1	1	4,800
Congenital FVII deficiency	7	280,800	4	40,114	49	7 (1–21)	5,731
Subtotal	23	5,601,600	79.9	243,547	319	13.9	17,560
Patients without congenital bleeding disorders ("off-label" indications)							
Patients undergoing BMT	10 <sup>a</sup>	829,200	11.8	82,920	76	7.6 (1–15)	10,911
Thrombocytopenia	13	273,600	3.9	21,046	37	2.8 (1–19)	7,394
Liver failure	15 <sup>a</sup>	134,400	1.9	8,960	41	2.7 (1–10)	3,278
CPB/ECMO	37	103,200	1.5	2,789	41	1.1 (1–3)	2,517
Prolonged INR	11	62,400	0.9	5,673	14	1.3 (1–2)	4,457
CNS bleed without coagulopathy	1	9,600	0.1	9,600	2	2	4,800
Prolonged PTT	2	2,400	0.03	1,200	2	1	1,200
Subtotal	89 <sup>b</sup>	1,414,800	20.1	16,077	214	2.4	6,611
Grand total	112 <sup>b</sup>	7,016,400	100	63,211	532	4.8	13,189

ED, exposure day; BMT, bone marrow transplantation; CPB/ECMO, cardiopulmonary bypass/extracorporeal membrane oxygenation; <sup>a</sup>One patient initially received rFVIIa for liver failure and 1.5 years later received it in context of BMT; <sup>b</sup>Hence the total of 88 rather than the true number of 87 patients and the grand total listed as 112 rather than 111 patients.

TABLE II. Age Ranges of Patients Treated With rFVIIa

Age at first exposure to rFVIIa	# of patients with hemophilia	# of patients without hemophilia
<1 month	0	10
1 month to <1 year	1	19
1 to <5 years	4	25
5 to <12 years	3	20
12 to 18 years	2	27
Mean age	7.7 years	6.7 years

unresponsive to other treatment modalities (platelet transfusions or immunosuppressive therapy) while in 3 patients rFVIIa was given in lieu of platelet transfusions to manage epistaxis as the patients' families refused blood products on religious grounds (Jehovah's Witnesses). Most patients received rFVIIa for 1–4 days with the exception of one patient with chronic unresponsive ITP and an ICH who received rFVIIa on 19 separate days. The experience in this patient was previously documented [12].

**Liver failure.** These primarily consisted of patients undergoing liver transplantation for fulminant liver failure. In nine patients rFVIIa was administered only on the day of surgery. The other six patients received rFVIIa on multiple days (max: 10 ED).

**Cardiopulmonary bypass surgery/extracorporeal membrane oxygenation (ECMO).** Most patients receiving rFVIIa for this indication received relatively small amounts of rFVIIa generally on the day of surgery. In most cases rFVIIa was given for peri-operative bleeding. Four of these 37 patients received rFVIIa while on ECMO.

**Acquired prolonged INR.** These consisted of two patients with warfarin overdose, four patients with leukemia undergoing lumbar punctures (LP) or central venous line insertions, one patient with an ICH, two patients undergoing neurosurgery, one newborn with vitamin K deficiency and one patient with post-operative bleeding. In these patients the lowest "prolonged" INR was 1.2 and the most prolonged was 3. Generally these were patients in whom FFP and/or Vitamin K had failed to sufficiently correct the INR.

**CNS bleed not associated with coagulopathy.** One patient (3-year-old) received rFVIIa for an unexplained subdural bleed. The patient had a normal INR, PTT and platelet count.

**Acquired prolonged PTT.** A 5-year-old child with leukemia and a prolonged PTT (53 sec) caused by an antiphospholipid antibody received rFVIIa prior to a LP. A second patient with a prolonged PTT (67 sec) in the setting of acquired von Willebrand's disease (secondary to a Wilms' tumor) received rFVIIa to manage bleeding following a kidney biopsy.

There were four patients for which being Jehovah's Witnesses contributed to them receiving rFVIIa; three with thrombocytopenia and one patient undergoing cardiopulmonary bypass surgery.

One of the most common scenarios for patients to receive rFVIIa "off-label" was in the setting of actual intracranial bleeding ( $n = 7$ ) or to prevent peri-operative intracranial/intraspinal bleeding from lumbar punctures ( $n = 8$ ) in conjunction with one of the following: thrombocytopenia, abnormal INR/PTT. Another common "off-label" setting to see rFVIIa being used was in patients with leukemia. These patients, all of whom are treated by hematologists/oncologists, received rFVIIa in the context of thrombocytopenia ( $n = 3$ ), acquired prolonged INR ( $n = 3$ ), BMT setting ( $n = 3$ ), congenital FVII deficiency ( $n = 1$ ), and acquired prolonged PTT ( $n = 1$ ).

## Trends in rFVIIa Use

The total use of rFVIIa in patients with hemophilia and inhibitors varied immensely from year to year (Table III and Fig. 1). Part of this variation was caused by an abnormally high number of patients with inhibitors in the year 2000; this included two 17-year-old males each weighing in excess of 80 kg and a 3-year-old boy who suffered 2 ICHs in that year. These three males used 2,751,600  $\mu\text{g}$  of rFVIIa in that year alone. In subsequent years the number of patients with inhibitors in our institution fell substantially due to successful immune tolerance of most patients with inhibitors, a low incidence of new inhibitor development and transferring the 17-year-old males to the adult hemophilia clinic in our city in the year 2000 (one of them was successfully immune tolerized while still being our patient).

Other than in 2002 there was a steady rise in the use of rFVIIa in patients without hemophilia (use in 2005 was fivefold greater than in 2000). This rise was particularly the case in patients using rFVIIa off-label. In such patients there was a 10-fold rise in the use of rFVIIa over the 6 years.

rFVIIa use increased most consistently in the context of cardiopulmonary bypass surgery/ECMO. The first use of rFVIIa for this indication at our hospital was in 2002. In that year 8,400  $\mu\text{g}$  were administered to three patients for this indication. Over the next 3 years the number of patients using rFVIIa for this indication and their total cumulative use of rFVIIa grew significantly.

## DISCUSSION

Our study provides a complete and accurate representation as to how rFVIIa is being used in a large pediatric tertiary care setting. Our study was not intended to justify the use or potential misuse (e.g., correcting the PTT in patients with anti-phospholipid antibodies) of rFVIIa. We found a large increase in the number of patients without hemophilia using rFVIIa to the point where currently the majority (91%) of patients using rFVIIa are patients without hemophilia. Despite this, most rFVIIa (68.6%) is still being used by patients with hemophilia and inhibitors. Nevertheless the use of rFVIIa for off-label indications is growing significantly in both number of patients and in their total use of rFVIIa.

There are many clinical and economic ramifications to our findings. The increasing use of rFVIIa for off-label indications may result in an increasing risk of thrombotic complications (myocardial infarction, stroke, pulmonary embolism, and deep venous thrombosis) as studies have shown an increased risk of such when rFVIIa is used in patients without congenital bleeding disorders [20–22]. This is particularly a concern in patients receiving rFVIIa in the context of cardiopulmonary bypass surgery/ECMO where the potential benefit of using rFVIIa to stop bleeding needs to be balanced with potential risks of circuit thrombosis.

Until 3–4 years ago, rFVIIa was generally only being prescribed by hematologists specialized in treating patients with hemophilia whereas now it is being prescribed by an increasing assortment of physicians (other hematologists, anesthesiologists, surgeons, hepatologists, etc). This trend is likely to translate into a greater variety of physicians becoming comfortable with using rFVIIa thus leading to an increased likelihood of these physicians prescribing rFVIIa in the future.

Being a retrospective review, our study was limited by what physicians chose to record in patient charts (at times sparse) and was

TABLE III. Trends in Use of rFVIIa (2000–2005)

	rFVIIa use in µg (% of total use for year; number of patients using it)					
	2000	2001	2002	2003	2004	2005
Patients with congenital bleeding disorders (“on-label” indications)						
Hemophilia with inhibitors	3,481,200 (97; n = 5)	424,800 (55.4; n = 2)	573,600 (74.8; n = 4)	144,000 (23.2; n = 2)	33,600 (6.4; n = 2)	157,200 (21; n = 2)
Glanzmann’s Thrombasthenia	0	27,600 (3.6; n = 2)	81,600 (10.6; n = 3)	141,600 (22.8; n = 3)	112,800 (21.6; n = 4)	138,000 (18.4; n = 2)
Bernard Soulier Syndrome	0	0	0	0	0	4,800 (0.6; n = 1)
Congenital FVII deficiency	67,200 (1.9; n = 2)	147,600 (19.3; n = 3)	36,000 (4.7; n = 1)	13,200 (2.2; n = 2)	0	16,800 (2.2; n = 2)
Subtotal	3,548,400 (98.9; n = 7)	600,000 (78.3; n = 7)	691,200 (90.1; n = 8)	298,800 (48; n = 7)	146,400 (28; n = 6)	316,800 (42.2; n = 7)
Patients without congenital bleeding disorders (“off-label” indications)						
Patients undergoing BMT	0	162,000 (21.1; n = 2)	24,000 (3.1; n = 1)	43,200 (7.0; n = 1)	242,400 (46.3; n = 3)	357,600 (47.8; n = 3)
Thrombocytopenia	40,800 (1.1; n = 1)	0	12,000 (1.6; n = 2)	166,200 (27.6; n = 5)	27,600 (5.3; n = 3)	21,600 (2.9; n = 3)
Liver failure	0	0	1,200 (0.2; n = 1)	92,400 (14.9; n = 5)	37,200 (7.1; n = 6)	3,600 (0.5; n = 3)
CPB/ECMO	0	0	8,400 (1.1; n = 3)	15,600 (2.5; n = 7)	34,800 (6.7; n = 13)	44,400 (5.9; n = 14)
Prolonged INR	0	4,800 (0.6; n = 1)	30,000 (3.9; n = 2)	0	24,000 (4.6; n = 7)	3,600 (0.5; n = 2)
CNS bleed without coagulopathy	0	0	0	0	9,600 (1.8; n = 1)	0
Prolonged PTT	0	0	0	0	1,200 (0.2; n = 1)	1,200 (0.2; n = 1)
Subtotal	40,800 (1.1; n = 1)	166,800 (21.7; n = 3)	75,600 (9.9; n = 9)	322,800 (52; n = 18)	376,800 (72; n = 34)	432,000 (57.8; n = 26)
Grand total	3,589,200 (n = 8)	766,800 (n = 10)	766,800 (n = 17)	621,600 (n = 25)	523,200 (n = 40)	748,800 (n = 33)

BMT, bone marrow transplantation; CPB/ECMO, cardiopulmonary bypass/extracorporeal membrane oxygenation; Some patients received rFVIIa in multiple years hence the number of patients across the years does not necessarily add up to total for 6 years.

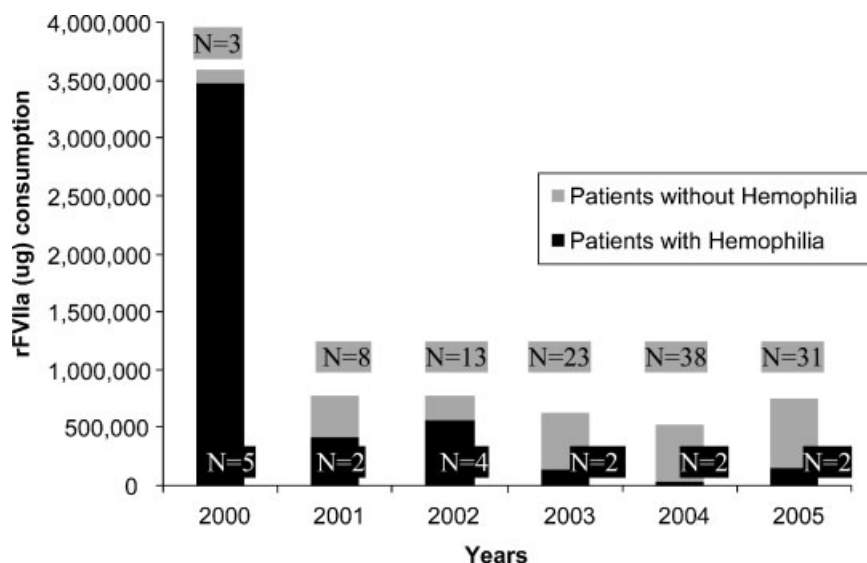


Fig. 1. rFVIIa consumption in patients with and without hemophilia (total amount and number of patients using it is shown).

thus not designed to appropriately document the efficacy and safety of rFVIIa. Similarly, and unfortunately, the manner in which rFVIIa issued to patients was recorded (recorded as amount given per day) did not permit an accurate determination as to how patients were dosed (e.g., one large dose per day or multiple smaller doses).

Our institutional experience with using rFVIIa may not be reflective of what occurs in other institutions as our institution (unlike many others) does not have a gate keeping mechanism in place for using rFVIIa (e.g., requiring consultation with a hematologist or transfusion medicine specialist for use in off-label indications). As well our institution performs a disproportionate number of liver transplants, BMTs and pediatric cardiac surgery in Canada.

Our experience shows that the use of rFVIIa for off-label indications is growing rapidly in an environment such as ours where there is no gate keeping mechanism. If the increasing use of rFVIIa for off-label indications in children is being mirrored in other pediatric institutions and in adult centers then there will likely be a significant increase in the total use of rFVIIa in the future. These potential trends may result in a significant economic impact on organizations that pay for rFVIIa (governments and insurance companies) and as such need to be followed carefully.

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