

REVIEW ARTICLE

Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors

T. ABSHIRE* and G. KENET†

**Aflac Cancer Center and Blood Disorders Service, Emory University, Atlanta, GA, USA; and †Israeli National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel*

Summary. Recombinant factor VIIa (rFVIIa, NovoSeven®) has been licensed for treatment of haemophilia with inhibitors in Europe since 1996 and in North America since 1999. Overall, approximately 1.5 million doses have since been administered. Safety data from licensure to April 2003 revealed 25 thromboembolic (TE) adverse events (AE) from over 700 000 doses given, a remarkably low incidence of TE events. Recent reports have cited a higher prevalence of TE events with rFVIIa use, especially when used off-label. This report reviews the TE and fatal events with use of rFVIIa for congenital and acquired haemophilia A or B from May 2003 to December 2006. Approximately 800 000 standard doses of rFVIIa have been administered during this time frame. All clinical trials, spontaneous and solicited reports, as well as a detailed literature review, were included in the data analysis. There were a total of 30 TE events

and 6 TE-associated fatal events. Spontaneous reports captured 14/71 (20%) TE/AE and 2/34 TE-associated/total fatal events. From solicited reports, 5/40 (12.5%) were associated with a TE and 1/32 TE-associated fatal events. Literature review revealed 11/19 (58%) TE events and 3/6 TE-associated fatal events. Despite the use of high-dose rFVIIa ($270 \mu\text{g kg}^{-1}$) in some clinical trials and registries, rFVIIa appears safe, when used for congenital and acquired haemophilia. The prevalence of TE associated with rFVIIa use is less than 4/100 000 and a TE-associated fatal event is also extremely rare. However, use of rFVIIa for off-label indications should continue to be monitored closely via clinical trials and carefully designed registries.

Keywords: haemophilia, inhibitors, NovoSeven®, rFVIIa, safety, thromboembolism

Introduction

Recombinant factor VIIa (rFVIIa, NovoSeven®) has been available for use since 1996. In total, approximately 1.5 million doses of rFVIIa have been administered since its licensure in 1996. Review of safety data from the licensure of rFVIIa in 1996 to April 2003 has demonstrated the product to be quite safe for its labelled indication [1]. There have been only 25 events reported during this initial review,

with the data being collected from both clinical trials and spontaneous reports. These events were drawn from approximately 700 000 doses, administered at the standard $90 \mu\text{g kg}^{-1}$ dose for a 40-kg individual. Despite the inherent under-reporting of adverse events (AE) associated with a licensed product, this prevalence of thromboembolic events (TE) certainly appears to be much less than 1%.

Several recent reports have raised questions about the safety of rFVIIa [2,3]. These reports were derived from the MedWatch Pharmacovigilance of the US Food and Drug Administration (FDA) as well as the FDA Adverse Event Reporting System (AERS). Both of these reports included clinical trial data for the non-haemophilia population as well as any reports related to off-label indications. In Dr Aledort's paper [2], the thromboembolic rate for rFVIIa is cited as three times

Correspondence: Thomas Abshire, MD, Aflac Cancer Center and Blood Disorders Service, 2015 Uppergate Dr. NE, Room 426 A, Emory University, Atlanta, GA 30322, USA.
Tel.: +1 404 785 0083; fax: +1 404 727 4455;
e-mail: thomas.abshire@emory.edu

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more likely when compared with Factor VIII Inhibitor Bypass Activity (FEIBA), an activated prothrombin complex concentrate (aPCC). However, aPCC are only indicated for use in haemophilia patients with inhibitors, and are contraindicated for administration to patients with prior normal coagulation systems.

This report will update the safety information on rFVIIa which has been accrued with the product in its labelled indication for treatment of congenital and acquired haemophilia with inhibitors from May 2003 to December 2006.

Patients and methods

All AE, serious AE (SAE), fatal AE and TE were recorded for the use of rFVIIa. During the time period from May 2003 to December 2006, there were five clinical trials dealing with patients with haemophilia A or B with inhibitors: F7haem-2068, F7haem-1505, F7haem-1510, F7haem-2011, F7Haem-USA/4/USA and F7haem-1668. Additionally, all spontaneous reports or events in postmarketing surveillance during the same time frame were recorded. Further, the number of AE, SAE and TE in patients with haemophilia A or B receiving rFVIIa during the previously described period were gathered as solicited reports from regulatory authority sources, from other companies, from postmarketing surveillance and investigator-initiated trials as well as from registries. Finally, a thorough literature review was performed to capture additional safety data.

A careful search was performed to collect all the data from publications and databases for rFVIIa for the labelled indications. The MedWatch Registry includes data for on- and off-label indications. The data from MedWatch for on-label use of rFVIIa were reviewed for this report. The four broad reporting categories listed in Table 1 are: clinical trials, spontaneous reports, solicited reports and literature review. Children were defined as <18 years of age. The average age of the adult patient population was 34.5 years (range: 18–62 years). TE were defined broadly as either thrombosis or haemorrhage and are categorized in Table 1 as myocardial infarction (MI), deep venous thrombosis (DVT) including pulmonary embolus, cerebrovascular accident (CVA) including infarction or haemorrhage and disseminated intravascular coagulation (DIC). TE which were directly linked to death are also recorded and listed as a TE-associated fatal event.

Results

A summary of TE and fatal events with the use of rFVIIa in inherited and acquired haemophilia for the defined study period can be found in Table 1. There appeared to be a similar number of arterial and venous TE events reported in all four of these patient categories. During this period, over 800 000 standard doses of rFVIIa have been given (90 µg kg⁻¹ for a 40-kg individual). This standard dose and weight was utilized for similarity with the initial review.

Table 1. Summary of thromboembolic (TE) and TE-associated fatal events with use of recombinant factor VIIa (rFVIIa) in haemophilia (May 2003–December 2006).

	Patients	Adults	Children	Unknown	TE events	TE-associated/total fatal events
Clinical trials (<i>n</i> = 5)	134	93	41	0	1	0
Spontaneous reports	71	45	19	7	Superficial thrombosis 14 (13 patients) MI: 4 DVT: 7 CVA: 1 DIC: 2	2/34 (28 patients) DIC: 2
Solicited reports	40	30	2	8	5 MI: 1 DVT: 2 CVA: 2	1/32 (26 patients) DVT: 1
Literature review	19	14	3	2	11 (10 patients) MI: 1 DVT: 4 CVA: 5 Thrombophlebitis: 1	3/6 CVA: 2 DVT: 1

TE, thromboembolic events (thrombosis and/or haemorrhage); MI, myocardial infarction; DVT, deep venous thrombosis; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation.

There were a total of 134 patients participating in five clinical trials; 41/134 (31%) were children. There were no fatal AE reported for this group and only one adult who developed a popliteal vein thrombosis (superficial thrombosis) after surgery for a left knee replacement, which did not require anticoagulation. Investigators did not judge this as a SAE as therapy was not given and it did not halt continuation in the study.

There were 71 spontaneous reports, with TE events accounting for 14/71 (20%). One adult patient presented with two TE events: a mural thrombus as well as a CVA. Two children were represented among the 14 events. One of these children had a fatal TE (*Staphylococcal* sepsis and DIC) and one adult had fatal DIC. These accounted for 2/34 fatal TE events among 28 patients. A few of these patients had more than one fatal TE event which was recorded as either accounting for or contributing to, the death.

Forty AE were queried from solicited reports and registries, with five of these comprising a TE event. No children in this category were represented as either a TE or a fatal event. Additionally, there were a total of 32 fatal events represented in this population, but only 1/32 as a TE-associated fatal event (a portal vein thrombosis associated with liver cancer).

Finally, a literature review revealed that of the 19 patients with a reported AE from rFVIIa, 11/19 (58%) had a TE event, with two of these representing children. Two of these events occurred in one patient (upper extremity DVT and a pulmonary embolus). There were no children with a fatal AE, but there were three TE-associated fatal events recorded among the adults (two with CVA and one with sepsis and a DVT).

Review of the MedWatch registry revealed no AE for on-label use of rFVIIa. Overall, there were a total of 130 AE, reported from the data sources used in our analysis, with 30 of these events being TE-related events. These TE events occurred from an estimated

 000 standard dose infusions of rFVIIa. Thus, the average risk of a TE event was approximately 3.75 per 100 000 infusions.

Discussion

The safety of rFVIIa has been recently questioned since the original review by Abshire and Kenet [1]. In that report, the incidence of TE events with the use of rFVIIa was extremely low and did not appear to be dose-related. Despite the fact that it is difficult to accurately assess the total doses of the product given, the number of TE events appears to be much less than 1%. In the Aledort paper [2], the MedWatch

FDA data collected over a 3-year timeframe, supplemented by case reports, showed that TE events were rare for both rFVIIa and aPCC, but the prevalence seemed approximately three times greater for rFVIIa compared with aPCC. However, as has been previously noted, all uses of rFVIIa were reported in this manuscript, both on- and off-label, as well as use in non-haemophilia-related clinical trials, but safety reports regarding the utilization of aPCC was only for its labelled indication for treatment of haemophilia with an inhibitor. Additionally, uniform dosing per kilogram was not addressed and concomitant risk factors were not accessed. Finally, details of these TE events were not available owing to the limitations of the MedWatch Registry [4–6]. Similarly, details of the TE events in our review were not available to us in our data analysis. Despite these limitations, however, the MedWatch Registry holds value in the analysis of both on- and off-label AE [7].

The report by O'Connell *et al.* [3] utilized the AERS system to report TE events. These data were collected over approximately 5½ years and collated global reporting of TE events as well as the use of rFVIIa in both on- and off-label indications. Median age of this patient population was 52 years [3]. TE were characterized as: cerebrovascular, pulmonary embolus, MI, clot-device-related, arterial thrombosis or DVT. A TE event was the probable cause of death in 36/50 (72%). As previously stated, the majority of these events occurred with off-label use and concomitant haemostatic agents were utilized in slightly over one-third of the cases (38%). Additionally, a history of an underlying medical condition was present in 15% of these cases.

rFVIIa is usually localized to the site of tissue injury secondary to tissue factor release or via binding to activated platelets [8]. However, increased risk for TE events may occur when excessive tissue factor is expressed, either during the presence of DIC or when coagulation parameters are normalized during the process of restoring haemostasis [4,8].

When considering safety issues regarding the commonly utilized bypassing products of rFVIIa and aPCC, it is important to recognize that these products have a different mechanism of action and that with both products, safety issues are probably under-reported in the context of postmarketing reporting. Additionally, the newness of licensure of rFVIIa compared with that of aPCC, as well as its use in off-label indications, might allow for more reporting of AE of the former product. This is known as the Weber effect [2,5].

Several of the clinical trials reported here utilized high-dose rFVIIa ($270 \mu\text{g kg}^{-1}$). Three of these randomized controlled trials [9–11] have demonstrated that a single $270 \mu\text{g kg}^{-1}$ bolus dose of rFVIIa has an efficacy comparable with that of a standard $3 \times 90 \mu\text{g kg}^{-1}$ dosing regimen when utilized for home treatment of haemarthroses in haemophilia patients with inhibitors. The results of these studies are supported by retrospective data analysis from the Hemophilia and Thrombosis Research Society (HTRS) Registry [12] as well as by a small, open-label, single-centre pilot study [13]. No safety issues emerged in these studies or in another randomized, controlled study evaluating rFVIIa prophylaxis with standard vs. high-dosing regimen [14]. Additionally, the bolus vs. continuous infusion surgical trial (2011) has recently been published and is another example of the use of higher doses of rFVIIa without thrombosis [15]. In fact, no TE complications have been reported to date among any of the haemophilia patients who have received single high-dose rFVIIa therapy. Based on these data, the use of a single $270 \mu\text{g kg}^{-1}$ rFVIIa dose for treatment of bleeding episodes in haemophilia patients with inhibitors has recently been approved by the European Medicines Agency.

Conclusion

Summary, rFVIIa is safe when used in haemophilia A or B patients with inhibitors and acquired haemophilia and the prevalence of serious TE events is much less than 1%. The safety of rFVIIa use in haemophilia is clearly established, due primarily to the data available from prospectively monitored clinical trials. This is further supported by data from solicited reports, registries and other formal means of triggering reporting. However, potential safety concerns should be considered when rFVIIa is used in off-label indications and when activated coagulation is present or when coagulation parameters are normalized during the process of restoring haemostasis. Accordingly, use of rFVIIa in these settings deserves the safety scrutiny which accompanies controlled clinical trials or carefully controlled registries.

Disclosures

Thomas Abshire is on the Physician Advising Board for NovoNordisk and has attended the Baxter Annual Haemophilia update two of the last three years. Gili Kenet has acted as a paid consultant to Novonordisk and has received honorarium for lectures in international conferences as well as for participation in advisory boards.

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