Control of Bleeding Caused by Thrombocytopenia Associated With Hematologic Malignancy: An Audit of the Clinical Use of Recombinant Activated Factor VII

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Summary: This paper presents an analysis of 24 cases in which recombinant factor VIIa (rFVIIa) was used in the management of hemorrhage in patients with thrombocytopenia associated with hematologic malignancies. This is the largest case aggregation to date and focuses on preliminary experience in the off-label use of this hemostatic agent. Data were extracted from the international, Internet-based registry, www.haemostasis.com, accessed in September 2003. The search results were manually cross-checked against monthly summary reports. The physicians providing the cases were contacted individually to approve the use of their cases, supply any information missing from the database, and validate the data already held. Patients with acute myeloid leukemia, acute lymphoblastic leukemia, Hodgkin’s disease, non-Hodgkin’s lymphoma, Burkitt’s lymphoma, B-cell or T-cell lymphoma, or aplastic anemia received rFVIIa at total doses of between 18 and 1040 μg/kg body weight. Bleeding stopped in 11 of 24 (46%) patients, markedly decreased in 8 of 24 (33%) patients, and decreased in 4 of 24 (17%) patients. In most patients, the response was achieved within 2.5 hours of administration of rFVIIa. The use of rFVIIa was generally well tolerated—1 case of ischemic stroke was considered to be possibly related to rFVIIa administration, but this has yet to be confirmed. A review of these 24 cases submitted to the www.haemostasis.com database suggests that rFVIIa is beneficial in the management of hemorrhage in patients with thrombocytopenia and hematologic malignancies. This warrants further investigation in rigorously controlled clinical trials.

Key Words: Recombinant activated factor VII (rFVIIa)—Thrombocytopenia—Hemorrhage—Malignancy.
Recombinant factor VIIa is believed to exert its effects via a local procoagulant mechanism involving binding to tissue factor and increased thrombin generation at sites of vascular damage (35,36). In pharmacologic doses, rFVIIa binds to the surfaces of activated platelets and initiates a thrombin burst, independent of tissue factor, factor VIII, or factor IX, which leads to the formation of a stable clot. Furthermore, in the presence of normal and reduced platelet counts, rFVIIa-generated thrombin increases platelet deposition to collagen and fibrinogen under flow conditions in vitro (37). Due to this localized mode of action, its usefulness in patients with low platelet counts has been suggested. Indeed, a phase I/II study investigating the use of rFVIIa to control bleeding in 74 patients with thrombocytopenia of various causes, including 8 patients with overt bleeding, was described by Kristensen and colleagues in 1996 (38). In the majority of patients, bleeding time decreased (measured using the Simplate I® device [General Diagnostics, Morris Plains, NJ, USA] or the Surgicutt® device [International Technidyne, Edison, NJ, USA]). All 8 patients with overt bleeding demonstrated a beneficial response to treatment and, in 6 of these cases, bleeding stopped completely.

Preclinical evaluation in a rabbit model of thrombocytopenia showed significant improvements in bleeding time, reductions in blood loss, and reductions in prothrombin time (PT) and partial thromboplastin time (PPT) after administration of rFVIIa (39). Furthermore, case reports suggest efficacy in humans. The successful use of rFVIIa to control life-threatening hemorrhage in a patient with pre-B lymphoblastic leukemia, secondary to chemotherapy, has been reported (40). In 1 patient with acute myeloid leukemia who had diffuse alveolar haemorrhage (DAH) after bone-marrow transplantation, treatment with rFVIIa resulted in the cessation of hemorrhage (41). Pastores and colleagues (42) also reported successfully treating refractory DAH with rFVIIa in a patient who had undergone hematopoietic stem-cell transplantation. In another case, the use of rFVIIa was successful in reducing severe upper gastrointestinal (GI) hemorrhage in a patient with relapsed, refractory acute myeloid leukemia and severe thrombocytopenia induced by treatment with gemtuzumab ozogamicin following autologous peripheral blood stem-cell transplantation (43). A separate case of severe GI hemorrhage, thought to be due to thrombocytopenia during chemotherapy for acute biphenotypic leukemia (although PT and PTT were within normal limits), showed that administration of a single dose of rFVIIa immediately stopped bleeding after the patient had failed to respond to conventional therapy for 5 days (44). There have also been case reports of the use of rFVIIa in pediatric and adult autoimmune idiopathic thrombocytopenic purpura (45,46). A further report showed that rFVIIa was beneficial in controlling life-threatening bleeding following autologous stem-cell transplantation that has been complicated by platelet refractoriness (47). rFVIIa, combined with platelet transfusions, also helped to bring severe intracranial hemorrhage under control in a pediatric patient with severe refractory thrombocytopenia (48).

Although the limitations of anecdotal case data are recognized, in the absence of efficacy and safety data from randomized trials, voluntary registry submissions are being used to provide a preliminary insight into the investigational use of rFVIIa. The site www.haemostasis.com is an international, Internet-based registry that records such cases. The registry, which is currently closed to facilitate the review and analysis of the data it holds, has accumulated more than 1100 patient admissions since it went online in June 2001. The cases describe the use of rFVIIa as a prophylactic or rescue therapy to treat severe bleeding episodes, and fall within a diverse range of therapy areas, including intracranial hemorrhage, surgery/trauma, sepsis, obstetrics/gynecology, coagulopathies, and thrombocytopenia (with or without malignancies). The registry is independently managed and is overseen by a committee of medical experts (49).

This article presents a review of the use of rFVIIa to control hemorrhage in 24 patients with...
thrombocytopenia associated with malignancies, whose cases were entered onto the www.haemostasis.com database; this represents the largest aggregation of such cases to date.

MATERIALS AND METHODS

All cases of thrombocytopenia associated with malignancy were identified from automated searches of the www.haemostasis.com website, using the search terms ‘thrombocytopenia related to haematological malignancy,’ ‘chemotherapy-related thrombocytopenia in haematological malignancy,’ ‘chemotherapy-related thrombocytopenia in solid tumours,’ ‘thrombocytopenia and primary bone marrow disease,’ ‘thrombocytopenia related to other drugs,’ ‘thrombocytopenia related to disseminated intravascular coagulation (DIC),’ ‘thrombocytopenia with coagulopathy,’ ‘thrombocytopenia (other),’ ‘malignancy (solid tumour),’ ‘malignancy (haematological disease),’ and ‘malignancy (other).’ These records were manually cross-checked against monthly summary reports of new entries, which were produced by the registry administrator; all cases that contained sufficient case data and that met the required inclusion criteria were included.

Cases were included if case providers gave consent for their data to be analysed and provided at least a minimum quantity of information. Case providers were requested to complete a registry template on the www.haemostasis.com website and provide the following information: patient age, gender, weight and underlying condition; bleeding severity; all medications administered, including platelet transfusions before and after rFVIIa administration; dosage of rFVIIa, number of doses and interval between doses; bleeding response to rFVIIa (stopped, markedly decreased, decreased, no change, increased) and time to response; adverse events and whether these were related to rFVIIa; results of laboratory tests; patient outcome; and a brief case description. Case providers were later contacted individually to supply any data that were missing from the registry template and to validate the data that were already held. The records were then reviewed by the authors to select all those cases in which thrombocytopenia was related to haematological malignancy; case information was tabulated and analysed by the authors.

RESULTS

Initial searches of the www.haemostasis.com website identified 32 records from thrombocytopenic patients with malignancies. Five patients were excluded because they had diverse solid tissue tumours, 2 more were excluded because the case providers could not be identified or contacted, and 1 was excluded because it was a test case. The remaining 24 case records were all included in the detailed analysis. They had been submitted from Russia (n = 8), the UK (n = 7), the Czech Republic (n = 4), Croatia (n = 2), Australia (n = 1), The Netherlands (n = 1), and Serbia (n = 1).

The mean age of the patients was 25.8 years (range, 2 to 58 years) (Table 1). Patients presented with acute myeloid leukemia (AML; n = 4), acute lymphoblastic leukemia (ALL; n = 4), ALL secondary to AML (n = 1), Hodgkin’s disease (n = 1), non-Hodgkin’s lymphoma (NHL; n = 4), Burkitt’s lymphoma (BL; n = 2), B-cell lymphoma (n = 1), T-cell lymphoma (n = 1), aplastic anaemia (AA; n = 1), and other unspecified leukaemia (n = 2). Bleeding was qualitatively classified by the case providers as mild (n = 1), moderate (n = 4), or severe (n = 17), and was unspecified in 2 cases. A total of 14 patients had coagulopathies that were defined as clinically relevant abnormalities in 1 or more coagulation function tests. Bone-marrow or stem-cell transplantation had been performed in 6 patients.

The median dose of rFVIIa was 85 µg/kg body weight (total dose range, 18 to 1040 µg/kg) (Table 2). Twelve patients received a single dose of rFVIIa, whereas 8 patients received 2 doses, 3 patients received 3 doses and 1 patient received 8 doses. When multiple doses of rFVIIa were given, the subsequent doses were the same as the first except in 1 patient (case 21), who received 53 µg/kg body weight for the first dose and a lower second dose of 27 µg/kg body weight. The interval between doses was between 1.5 and 5 hours in most patients. However, in 1 patient (case 12), the interval between doses was 13 hours and, in another patient (case 14), there was a 1-day interval between the first and second doses and a 3-day interval between the second and third doses. There was no obvious association between the administered dose of rFVIIa and the severity of bleeding.

Efficacy

The response of the 24 patients to rFVIIa treatment is summarized in Table 2. In most patients...
(23/24; 96%), the use of rFVIIa stopped, markedly decreased or decreased the bleeding. In 13 of the 20 patients with relevant data, the response to rFVIIa was recorded within 2.5 hours of the first dose. In 2 patients (cases 2 and 21), a response was achieved immediately or shortly after a second dose of rFVIIa, whereas 1 patient (case 6) responded immediately after a third dose. In case 17, bleeding decreased after the first dose of rFVIIa, but only stopped 10 hours after the second dose, and in case 15, bleeding markedly decreased only after 7 doses of rFVIIa. Neither the initial severity of the bleed nor the dose of rFVIIa administered was correlated to the treatment response.

**Bleeding in both cases of epistaxis (cases 5 and 21) stopped with relatively low doses of rFVIIa (40 and 80 µg/kg body weight), whereas bleeding stopped in only 1 of 5 patients with hemorrhage at multiple sites (rFVIIa doses of 48, 73, 167, 240, and 1040 µg/kg body weight); however, this collection of cases may not be large enough to draw conclusions regarding the effects of rFVIIa on bleeds at different sites. Similarly, there was no evidence that bone-marrow or stem-cell transplantation altered the response to rFVIIa; of the 6 patients who received a transplant, bleeding stopped in 2, markedly decreased in 2, decreased in 1, and did not change in 1.

Of the cases in which the case provider had stated the outcome, 11 patients died and 7 recovered; 3 of the deaths (cases 4, 11, and 13) seemed to be related to the bleeding episode. In case 4, the patient had hemorrhagic syndrome and sepsis.
due to myelosuppressive syndrome, and suffered multiple bleeds before receiving rFVIIa; the cause of death was given as cardiopulmonary failure associated with sepsis and hemorrhagic syndrome despite a decrease in bleeding following rFVIIa treatment. In case 11, the patient had severe aplasia, thrombocytopenia, pleuropneumonia, endotoxic shock, and pulmonary hemorrhage after intubation; she responded to rFVIIa treatment, but bleeding resumed a few hours later and she died of severe pulmonary hemorrhage and endotoxic shock 12 hours after administration of rFVIIa. In case 13, the patient suffered massive gastrointestinal (GI) bleeding during chemotherapy and, despite decreased bleeding after 2 doses of rFVIIa, he died due to a profuse GI bleed 3 hours after the second dose.

Twelve patients received crystalloids or colloids and 20 received replacement blood products (packed cells, whole blood, fresh-frozen plasma [FFP], cryoprecipitate or platelets) within the 24 hours before rFVIIa administration. The use of both fluid therapy and replacement blood products was reduced within the 24 hours after administration of rFVIIa (Fig. 1), although 12 patients still required crystalloids/colloids, and a further 17 patients required replacement blood products.

Other treatments for postoperative hemorrhage were administered to 11 patients: 3 patients received tranexamic acid (TEA), 6 patients received epsilon aminocaproic acid (EACA), 1 patient received etamsylate, and 1 patient received unspecified antifibrinolytics. The timing

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**TABLE 2.** Summary of Treatments and Responses to rFVIIa in 25 Patients with Thrombocytopenia Associated with Malignancy and Uncontrollable Bleeding

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total Dose of rFVIIa (µg/kg Body Weight)</th>
<th>Number of Doses</th>
<th>Dosing Interval (h)</th>
<th>Effect on Bleeding</th>
<th>Time Assessed (h)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133</td>
<td>2</td>
<td>3</td>
<td>Stopped</td>
<td>0 after first dose</td>
</tr>
<tr>
<td>2</td>
<td>297</td>
<td>3, 5</td>
<td>Markedly decreased</td>
<td>3.5 after second dose</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>1</td>
<td>Markedly decreased</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>1</td>
<td>Decreased</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>1</td>
<td>Stopped</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>289</td>
<td>2</td>
<td>Markedly decreased</td>
<td>0 after third dose</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>1</td>
<td>No change</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>1</td>
<td>Stopped</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>2</td>
<td>Markedly decreased</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>240</td>
<td>2</td>
<td>Markedly decreased</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>1</td>
<td>Stopped</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>140</td>
<td>2</td>
<td>Stopped</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>46</td>
<td>1.5</td>
<td>Decreased</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>288</td>
<td>3</td>
<td>Decreased</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1040</td>
<td>8</td>
<td>Markedly decreased</td>
<td>0 after seventh dose</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>24</td>
<td>1</td>
<td>Decreased</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>184</td>
<td>2</td>
<td>Stopped</td>
<td>10 after second dose</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>1</td>
<td>Stopped</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>1</td>
<td>Markedly decreased</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>52</td>
<td>1</td>
<td>Stopped</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>80</td>
<td>3</td>
<td>Stopped</td>
<td>0 after second dose</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>90</td>
<td>1</td>
<td>Stopped</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>30</td>
<td>1</td>
<td>Stopped</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>167</td>
<td>2</td>
<td>Markedly decreased</td>
<td>0 after first dose</td>
<td></td>
</tr>
</tbody>
</table>

*Time between administration of rFVIIa and the assessment of the effect on bleeding.

n/a, not applicable or data not available.
of these treatments was not specified in the case-report forms; therefore, their impact on bleeding episodes is not clear.

Clotting variables such as PT and PTT were slightly lower after the administration of rFVIIa than they were before its use (Fig. 2). Although the mean and median PT and PTT values were reduced by only a small amount, 13 of the 15 patients for whom data are available showed reduced PT values after rFVIIa administration.

Safety
As listed previously, 11 of the patients died; however, no deaths were considered to be related to rFVIIa administration and it was generally well tolerated. Adverse events are listed in Table 3. The recurrence of hemorrhage in 3 patients and 1 case of ischemic stroke were classified as ‘possibly related’ to rFVIIa therapy. The patient who had the ischemic stroke (case 14) had received 3 doses of rFVIIa of 96 µg/kg body weight.

Laboratory measures, including hemoglobin levels, fibrinogen levels, platelet counts, and hematocrit, were recorded for most cases. Hemoglobin levels were below the normal range (males, 13 to 18 g/dL; females, 11.5 to 15.5 g/dL) both before (median 8.2 g/dL; range 1.2 to 12 g/dL) and after (median 8.9 g/dL; range 1.3 to 14.4 g/dL) rFVIIa administration in the 19 patients for whom data are available. Hemoglobin levels reached normal levels in 2 patients (cases 6 and 12) after rFVIIa administration. In the 14 patients with available data, fibrinogen levels remained largely within the normal range (2 to 4 g/L) and were similar before and after rFVIIa administration (median levels, 3.75 g/L before and 3.25 g/L after rFVIIa). Median platelet counts in the 18 cases with available data were well below the normal range (150 to 400 × 10^9/L) before (median, 20 × 10^9/L; range, 3 to 116 × 10^9/L) and after (median, 25.5 × 10^9/L; range, 3 to 133 × 10^9/L) rFVIIa administration, although platelet counts increased in 12 of the 18 patients after rFVIIa administration. The median hematocrit value (normal range: males, 42% to 53%; females, 36% to 45%) was 24% (range, 10% to 36%) before rFVIIa administration and 27% (range, 16% to 41%) after rFVIIa administration.

**FIG. 1.** Median quantities of blood products (packed cells, whole blood, fresh-frozen plasma, cryoprecipitate, or platelets) and crystalloids/colloids given to hemorraging patients with thrombocytopenia associated with malignancies in the 24 hours before and the 24 hours after receiving recombinant factor VIIa (rFVIIa).
A positive response to rFVIIa was observed in a number of patients with a diverse range of underlying conditions, bleeds from a variety of sites, and in those who had received bone-marrow or stem-cell transplants. Although the amalgamation of these cases has limitations—the information gained from www.hemostasis.com is not detailed enough for individual case reports—these results do provide a compelling insight into this potential new treatment for hemorrhage in patients with thrombocytopenia associated with hematologic malignancy.

### TABLE 3

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Adverse Event</th>
<th>Severity</th>
<th>Time after rFVIIa Administration (d)</th>
<th>Related to rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Recurrence of bleed</td>
<td>Not serious</td>
<td>1–2</td>
<td>Possibly</td>
</tr>
<tr>
<td>14</td>
<td>Ischaemic stroke</td>
<td>Serious</td>
<td>1–2</td>
<td>Possibly</td>
</tr>
<tr>
<td>19</td>
<td>Recurrence of bleed</td>
<td>Not serious</td>
<td>8–30</td>
<td>Possibly</td>
</tr>
<tr>
<td>20</td>
<td>Fever</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>21</td>
<td>Recurrence of bleed</td>
<td>Not serious</td>
<td>6 hours</td>
<td>Possibly</td>
</tr>
<tr>
<td>24</td>
<td>Recurrence of bleed</td>
<td>Not serious</td>
<td>5</td>
<td>Not likely</td>
</tr>
</tbody>
</table>

NR, not recorded.

**DISCUSSION**

FIG. 2. Mean clotting variable values for prothrombin time (PT) and partial thromboplastin time (PTT) before and after administration of recombinant factor VIIa (rFVIIa) to hemorrhaging patients with thrombocytopenia associated with malignancies.

TABLE 3. Adverse Events in 25 Patients with Thrombocytopenia Associated with Malignancy and Uncontrollable Bleeding Treated with rFVIIa
In the previously described clinical trial of rFVIIa in patients with thrombocytopenia, rFVIIa administration resulted in the cessation of hemorrhage in 6 of 8 patients with overt bleeding (38). In the case series reported here, rFVIIa was successful in stopping hemorrhage in 11 of 24 patients (46%) with, in most cases, moderate-to-severe bleeding. Although this response is lower than that found by Kristensen and colleagues (38), the patients described in this case series generally had more severe internal bleeds. In light of the severity of bleeding experienced by these patients—significant use of blood products had failed to decrease or stop the bleeding—this response rate is impressive. Furthermore, 11 of the 24 patients described here were administered other treatments (TEA, EACA, etamsylate) to control hemorrhages and rFVIIa was administered only on failure of these agents, thus highlighting the severity of the episodes. In cases in which bleeding was controlled, it is possible that these additional hemostatic agents contributed to successful outcomes; however, because rFVIIa was administered in most cases as a rescue therapy when all else had failed, it seems unlikely that these additional treatments would have influenced patient responses.

In light of the life-threatening nature of the bleeding episodes described here, it seems possible that some of these patients may have had unrecognized concomitant conditions that predisposed them to hemorrhage, such as acquired or inherited von Willebrand’s disease or other platelet or coagulation-factor disorders. In isolation, such mild coagulopathies would be insufficient to cause major bleeding diatheses; however, in combination with severe chemotherapy-related thrombocytopenia, they could result in the failure of the hemostatic system and the onset of excessive bleeding.

It is difficult to draw any conclusions from this case series concerning the optimum dosage of rFVIIa for the management of bleeds in patients with thrombocytopenia related to hematologic malignancies or, indeed, which factors may influence the choice of dosage. A wider range of doses was used in these cases than in the 50 to 150 µg/kg body weight range that was used in the patients with overt bleeding in the previous phase I/II trial (38). In addition, the literature shows variations in the number of doses required for a given type of bleed. For example, Pastores and colleagues (42) found that 2 doses of rFVIIa (90 µg/kg body weight) were sufficient to control DAH after allogeneic bone-marrow transplantation, but Hicks and colleagues (41) concluded that a course of more than 2 such doses of rFVIIa was required to control DAH in a similar setting. An individualized approach to dosing may, therefore, be the most useful.

Although the mechanism of action of high-dose rFVIIa has not been fully elucidated (50,51), the use of rFVIIa is associated with a theoretical risk of thromboembolic events due to its effects on thrombin generation. However, the licensed use of more than 700,000 standard doses of rFVIIa between 1996 and April 2003 and the spontaneous reporting of only 16 thrombotic events and 2 cases of disseminated intravascular coagulation during that time, indicate that this risk is low (52). Furthermore, the thrombotic events that occurred in patients receiving this agent may be attributed to improvements in the clotting mechanism in individuals with underlying conditions that predispose them to thrombosis. Ischemic stroke was experienced by 1 patient in this case series (case 14) and was considered to be possibly related to the use of rFVIIa. More details of this patient’s history are required to determine the likelihood of this event being related to rFVIIa administration. Cases were entered onto the registry at the discretion of the treating physicians, and it cannot be ruled out that they may have selected cases with favorable outcomes. The inclusion of cases with adverse events including 1 serious event (case 14), however, may dispel this suggestion. The rate of thromboembolic events occurring in patients undergoing stem-cell transplantation for hematologic malignancies is currently being evaluated in a prospective randomized controlled trial (53).

These 24 cases highlight the potential benefits of rFVIIa in controlling bleeding caused by thrombocytopenia associated with hematologic malignancy, and comprise the largest single collection of such cases reported so far. Most patients received rFVIIa after significant blood loss, the administration of large quantities of blood products, and the failure of standard therapies to achieve hemostasis. Earlier use of this hemostatic agent may lead to better outcomes and may reduce the need for large volumes of replacement therapies. Controlled clinical trials are needed to fully evaluate the potential benefits of rFVIIa in this indication.

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USE OF rFVIIa IN THROMBOCYTOPENIC BLEEDS

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REFERENCES


