Off-Label Use of Recombinant Activated Factor VII (NovoSeven®)

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ABSTRACT

NovoSeven® (Novo Nordisk, Denmark) is a recombinant DNA preparation of activated blood coagulation factor VII (rFVIIa). It is used to manage bleeding in hemophilia patients for whom standard therapy is inadequate because of the presence of inhibitors to either factor VIII (hemophilia A) or factor IX (hemophilia B). It poses no risk for the transmission of human pathogens, and it is infused in relatively low volumes.

As a drug that has been approved by the Food and Drug Administration (FDA), NovoSeven® may be prescribed for off-label purposes, including neonatal coagulopathies; severe hepatic disease; high-risk surgical procedures; traumatic blood loss; bone marrow transplantation; thrombocytopenias and platelet function disorders; urgent reversal of oral anticoagulation; congenital deficiencies of factors V, VII, X, and XI; and von Willebrand disease with inhibitors to von Willebrand factor. Most of these uses are constrained by cost and limited clinical evidence, and additional work is needed to extend the FDA-approved labeling for this product.

INTRODUCTION

Blood coagulation factor VII (FVII) is a vitamin K–dependent glycoprotein with a molecular weight of 50 kilodaltons (kd) that circulates in human plasma at a concentration of about 0.5 mcg/ml.1 Factor VII initiates coagulation through the extrinsic pathway by binding with tissue factor (TF), a cell-bound component of the deep layers of blood vessel walls that is exposed to blood only through injury. This results in the conversion of factor VII to its activated form (FVIIa), which cleaves factor X and factor IX, eventually leading to active production of the procoagulant thrombin and clot formation.

NovoSeven® is a genetically engineered preparation of factor VIIa that is produced in cultured baby hamster kidney (BHK) cells. This agent is nearly identical to plasma-derived factor VIIa in its structure and function.2–4 It received marketing approval in the U.S. in 1999 for the treatment of patients with factor VIII or factor IX deficiencies refractory to traditional replacement therapies resulting from the presence of circulating factor inhibitors.

Several characteristics of NovoSeven® make it an appealing candidate for the treatment of bleeding disorders other than the hemophilias. First, because it is not enzymatically active by itself, the drug does not appear to induce systemic activation of the coagulation system, as may occur with concentrates that contain activated coagulation factors. Second, its activity is not affected by circulating inhibitors such as antithrombin. Third, the in vitro production method eliminates the risk for transfusion-transmissible infection that accompanies plasma-derived coagulation-factor concentrates.

However, rFVIIa contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse immunoglobulin G (IgG) and protein from BHK cells and the culture medium. Because these foreign proteins have the potential to induce harmful antibody responses in some individuals, this product is contraindicated in patients with known hypersensitivity to mouse, bovine, or hamster proteins.5

Given those advantages, physicians have shown great interest in using NovoSeven® for off-label indications in patients predisposed to serious bleeding. Many of these indications, but not all, are not the result of the presence of inhibitors, and thus they might be expected to respond to standard replacement therapies.

Specific off-label settings in which NovoSeven® has been used include coagulopathies in newborns; severe liver disease; high-risk surgeries; blood loss from trauma; bone marrow transplantation; thrombocytopenias and platelet function disorders; critical reversal of oral anticoagulation; congenital deficiencies of factors V, VII, X, and XI; and von Willebrand disease (vWD) with inhibitors to von Willebrand factor. This article presents a qualitative systematic review of the off-label use of NovoSeven®.

CLINICAL EVIDENCE SUMMARY: A LITERATURE SEARCH

Literature obtained through a computerized search of the PubMed online database (www.ncbi.nlm.nih.gov/entrez/query.fcgi) reveals a number of off-label uses of rFVIIa. We used the search terms "Novoseven," "rFVIIa," and "recombinant activated factor VIIa" to obtain references to recent review articles and reports of original clinical research studies of this agent.

We limited the electronic search to English-language documents that were published from 1999 through April 2004 and to materials that reported results in humans. This initial search scheme yielded a total of 184 citations. We used the “related articles” function of Medline to locate additional articles that might have been missed in the first electronic search.

We also examined the bibliographies of relevant publications for this purpose. Papers that covered clinical outcomes or that presented surrogate laboratory data for efficacy following off-label use of NovoSeven® were obtained and evaluated for inclusion in this report. We excluded papers that did not contain this type of information and publications that were not peer-reviewed, such as abstracts and meeting summaries, from the analysis.

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We abstracted 42 papers that met those inclusion criteria; these are summarized next. We have organized them according to the clinical setting in which treatment with NovoSeven® was undertaken.

**OFF-LABEL CLINICAL USES**

**Reversal of Anticoagulant Therapy**

Berntorp and colleagues reported that two infusions of NovoSeven® 80 mcg/kg were safe and effective in halting severe epistaxis in a 63-year-old woman.6 The International Normalized Ratio (INR) improved, returning to normal levels, with no reported adverse drug effects (ADEs).

In another case series, rFVIIa was administered, in a single infusion, at 15 to 90 mcg/kg of body weight to 13 patients with critically increased INRs and bleeding complications resulting from therapy with warfarin sodium (Coumadin®, Bristol-Myers Squibb).7 This caused an immediate reduction of the INR and cessation of clinically apparent bleeding in four cases; five other patients who required surgical procedures experienced no adverse bleeding during or after surgery. In several other patients who had significant comorbid conditions and a high risk of bleeding because of warfarin-induced anticoagulation, hemorrhagic complications were apparently averted by rFVIIa treatment.

Bjisterfeld and colleagues reported the results of a randomized, placebo-controlled trial of rFVIIa to neutralize the anticoagulant effects of fondaparinux (Arixtra®, Organon/Sanofi-Synthelabo).8 Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa. Sixteen healthy male subjects received either a single subcutaneous (SQ) 10-mg dose of fondaparinux and a single intravenous (IV) 90-mcg/kg bolus of rFVIIa (n = 8), fondaparinux and placebo (n = 4), or placebo and rFVIIa (n = 4). The rFVIIa injection, given after fondaparinux, normalized the prolonged activated partial thromboplastin time (aPTT) and the prothrombin time (PT), compared with placebo. Thrombin-generation time and endogenous thrombin potential, which were inhibited by fondaparinux, were normalized up to six hours after the rFVIIa injections.

**Perioperative and Traumatic Blood Loss**

rFVIIa was evaluated as a means of controlling perioperative bleeding in 36 patients with normal coagulation systems who were undergoing retroperitoneal prostatectomy in a double-blind, placebo-controlled, randomized trial.9 Administration of the study drug by IV bolus injection significantly reduced perioperative blood loss and transfusion requirements compared with placebo.

An open-label, single-center study evaluated the effect of rFVIIa administration on blood loss and hemostasis in patients undergoing cardiac valve surgery, with or without other surgical procedures.10 After receiving a maximum of four doses by IV bolus, all patients achieved satisfactory hemostasis after a single dose.

Several other case reports have described the use of rFVIIa administered in bolus IV doses to control perioperative bleeding in patients with normal hemostasis during diverse procedures. These included a woman who underwent resection of a giant, recurrent skull base hemangiopericytoma;11 aortic valve replacement in a man with osteogenesis imperfecta;12 two women who had surgery for endometrial cancer and vaginal sarcoma;13 and a man who underwent surgery to control a duodenal ulcer that was bleeding heavily.14 In all of these cases, satisfactory hemostasis was rapidly achieved after rFVIIa administration, with no associated ADEs.

rFVIIa was reported to be successful in treating a soldier with exsanguinations and traumatic injury complicated by severe coagulopathy.15 The drug has also been effective as an adjunctive therapy in seven massively bleeding, multi-transfused, coagulopathic trauma patients when it was given by IV bolus after failure of conventional hemostatic measures.16

**Platelet-Related Bleeding Disorders**

A phase I/II study was conducted to evaluate the effect of rFVIIa, given as an IV bolus injection, on bleeding time in 74 patients with thrombocytopenia caused by impaired platelet production or immune destruction.17 The bleeding time was reduced in most patients, and the decrease was significantly pronounced in those with platelet counts of at least 20,000/µL.

Two case reports have described successful clinical outcomes following the use of rFVIIa in patients with Glanzmann’s thrombasthenia. In one report, rFVIIa was administered as first-line therapy to three patients with inherited type I Glanzmann’s thrombasthenia and anti–GPIIb-IIIa iso-antibodies and who were scheduled for invasive procedures.18 Excellent clinical results were obtained in two patients; in the third, rFVIIa was effective in preventing bleeding at the surgical site, but nasal bleeding episodes of traumatic origin persisted for 10 days. A severe thromboembolic complication occurred five days after the drug was discontinued.

The second report described good clinical results of rFVIIa treatment in a man with Glanzmann’s thrombasthenia who was scheduled to undergo surgery to treat recurrent, non-ulcer duodenal bleeding that was refractory to conservative medical treatment.19 Surgery was successfully performed with no major blood loss or other complications.

rFVIIa has been used to treat patients with vWD. One woman had a lifelong history of vWD with recurrent gastrointestinal (GI) bleeding from angiodyplasia that did not respond adequately to standard therapy. As a result, she required frequent blood transfusions.20 After rFVIIa was added to her regular replacement therapy, no blood transfusions were necessary.

In another case, rFVIIa was used successfully in an older man with life-threatening hematuria and GI bleeding caused by acquired vWD. Standard therapy had failed to achieve adequate hemostasis.21 A man with Hermansky–Pudlak syndrome underwent a thyroidectomy under cover of rFVIIa.22 During surgery, the surgeon considered hemostasis of the operative field to be normal and no ADEs were observed.

NovoSeven® was used successfully to treat two patients with acquired severe thrombocytopenia and life-threatening hemorrhage.23 In one case, bleeding in a man with Waldenström’s macroglobulinemia had not responded to multiple platelet transfusions. In the other case, a woman with acute pre-B lymphoblastic leukemia developed severe chemotheraphy-induced thrombocytopenia and life-threatening GI bleeding that had not been controlled by multiple platelet, red blood cell (RBC), or plasma transfusions.

continued on page 717
Bone Marrow Transplantation

rFVIIa has been used to support patients undergoing bone marrow transplantation (BMT). In one series, one patient received rFVIIa by IV bolus to treat pulmonary hemorrhage, three were treated for hemorrhagic cystitis, and two were treated for GI bleeding.\textsuperscript{24} The patients had responded incompletely or not at all to various standard therapeutic modalities. Transient clinical responses in gross hematuria were noted in two patients and in one patient with pulmonary hemorrhage, but bleeding in a new site in two patients and renewed bleeding of the initial site in the third patient resulted in discontinuation of the drug.

rFVIIa has been used to treat diffuse alveolar hemorrhage in a BMT patient.\textsuperscript{25} Although the patient rapidly improved with several doses of the study drug, her clinical condition began to deteriorate after it was stopped. After the regimen was re-instituted, the patient improved and rFVIIa therapy was discontinued after 16 additional doses. There was no further evidence of diffuse alveolar hemorrhage, toxicity, or ADEs.

Hepatic Dysfunction

A multicenter, randomized, double-blind study was designed to evaluate the efficacy of different doses of rFVIIa on specific laboratory and clinical hemostatic parameters in 66 patients with liver disease who were undergoing laparoscopic liver biopsies.\textsuperscript{26} The PT was corrected to normal levels (in less than 13.1 seconds) in the majority of patients, with the duration of normalization dependent on the dose. Hemostasis was achieved in 48 of 65 patients (74%) within 10 minutes and was maintained for 18 hours. None of the patients required operative intervention or transfusion of blood or blood products to control bleeding. No ADEs were considered to be related to the study drug.

Shami et al. reported the results of a case series with historical controls that examined the efficacy of rFVIIa in treating the coagulopathy of fulminant hepatic failure prior to liver transplantation.\textsuperscript{27} All patients who received rFVIIa with plasma experienced a temporary (two- to six-hour) correction of coagulopathy. An intracranial pressure (ICP) transducer was able to be placed, before liver transplantation, in all of the rFVIIa patients but in only three of the plasma patients (controls).

A preliminary, single-center, dose-escalation trial evaluated the safety, pharmacokinetics, and efficacy of rFVIIa in non-bleeding volunteer patients with liver cirrhosis.\textsuperscript{28} Ten patients with elevated PTs, despite previous vitamin K treatment, were given three successive doses of rFVIIa during a three-week period. All patients showed transient normalization of the mean PT with a dose-dependent duration.

In a single-center, open-label trial, Ejlersen et al. studied the efficacy of rFVIIa for liver cirrhosis and bleeding esophageal varices.\textsuperscript{29} They were able to achieve immediate bleeding control in all cases after an IV bolus injection of the study drug. PTs were normalized within 30 minutes of infusion and were maintained in a normal range for at least four hours afterward.

Several other reports describe clinical outcomes in patients with cirrhosis-associated coagulopathy who received rFVIIa as hemostatic coverage for diverse invasive procedures, such as ultrasound-directed percutaneous needle aspiration biopsy of the pancreas,\textsuperscript{30} dental extractions,\textsuperscript{31} or transurethral resection.\textsuperscript{32} In another single-center, open-label pilot study, six adults who were undergoing orthotopic liver transplantation (OLT) for Child–Pugh class B or C cirrhosis received rFVIIa and other therapies at the start of the operation.\textsuperscript{33,34} A single dose of the study drug was sufficient to significantly reduce the transfusion requirements of these patients compared with the needs of the matched historical controls, although baseline coagulation parameters were comparable in both groups.

rFVIIa was used to treat two female patients who required OLT as a result of acute liver failure in the course of Wilson’s disease.\textsuperscript{35} The study drug was administered by IV bolus injection at the start of surgery, which then proceeded normally.

Two additional series describe outcomes with rFVIIa therapy in patients with severe hepatic disease and disseminated intravascular coagulation (DIC). Three children with acute bleeding secondary to surgical or diagnostic procedures received bolus doses of rFVIIa in combination with plasma, cryoprecipitate, and platelet transfusions.\textsuperscript{36} Hemostasis was restored, and no ADEs resulted from use of the study drug.

A pregnant woman with liver dysfunction and DIC developed severe post-ceasarean intra-abdominal bleeding that did not respond to plasma, fibrinogen, or platelet transfusions.\textsuperscript{37} Initiation of rFVIIa treatment stabilized her condition hemodynamically, with adequate diuresis. She responded well to transfusions, and no side effects were noted.

Neonatal and Pediatric Coagulopathy

Olomu and colleagues administered rFVIIa in multiple doses to two neonates with severe pulmonary hemorrhage who were not responding to conventional treatment, which included RBC and platelet transfusions.\textsuperscript{38} In both cases, the PTs were reduced in conjunction with cessation of bleeding soon after the study drug was given. Similar results were reported in two preterm neonates with life-threatening hemorrhage from the liver and spleen in one patient and from the lung in the other.\textsuperscript{39}

In a third report, a single-bolus dose of rFVIIa was followed by significant shortening of the PTs in five infants.\textsuperscript{40} In a second group of six cases, the neonates who received rFVIIa treatment demonstrated greater reductions in PT than did four patients who received plasma. The effect of rFVIIa lasted for six hours after administration, and no ADEs were noted.

Chuansumrit et al. reported the successful use of rFVIIa to control life-threatening bleeding resulting from a ruptured umbilical artery in a pre-term infant.\textsuperscript{41} Hemorrhaging ceased after two doses of rFVIIa without the need for additional transfusion therapy and with no ADEs.

A retrospective case series reported the efficacy of rFVIIa in the treatment of coagulation dysfunction in 10 pediatric patients ranging in age from three months to 19 years.\textsuperscript{42} Coagulation function was restored by IV doses of rFVIIa, as reflected by significant decreases in PTs, INRs, and aPTTs.

Coagulation Factor Deficiencies

A primigravida with complaints of vaginal bleeding was found to have a factor VII level of 1%. She received prophylactic rFVIIa before the induction of labor.\textsuperscript{43} She did not show any signs or symptoms of excessive bleeding during labor or after delivery, and no neonatal complications were noted. In a sec-
Off-Label Use of rFVIIa (NovoSeven®)

DISCUSSION

Because NovoSeven® has received marketing approval in the U.S. for the treatment of bleeding in hemophilia patients with inhibitors to factor VIII or factor IX, there are no legal barriers that limit its discretionary off-label use. The main issues that serve, at present, to constrain the widespread use of this drug are its substantial cost and the limited clinical evidence available to support off-label uses.

Even though NovoSeven® is considered to be safe in most clinical situations, with a low risk for associated thrombotic ADEs, the product label warns that patients with DIC, advanced atherosclerotic disease, crush injury, or septicemia may be at an increased risk for the development of thrombotic events resulting from circulating tissue factor or predisposing coagulopathy. Patients who receive this product should be monitored if signs or symptoms of activation of the coagulation system or thrombosis develop; in such cases, treatment should be stopped or the dosage should be reduced.

Several randomized, multicenter clinical trials are under way to determine the efficacy and safety of rFVIIa for investigational uses in non-hemophilic patients (Table 1).49 Well-designed, randomized, controlled trials in selected patient groups are necessary to evaluate the clinical efficacy of rFVIIa in these conditions and others and to determine dose regimens that allow the most efficient use of this expensive product. In particular, studies are needed to correlate normalization of laboratory values and clinical benefits and to establish clinical indications beyond the FDA-licensed label.

Relevant issues for study include:

- confirmation of the clinical efficacy of rFVIIa for several conditions that have been preliminarily investigated.
- the failure rate of rFVIIa.
- determination of additional appropriate indications.
- the potential for ADEs, particularly the risk for thromboembolic complications.
- the agent's cost-effectiveness.

CONCLUSION

Efficacy and safety data have been reported for various off-label uses of rFVIIa, including bleeding associated with thrombocytopenia, platelet dysfunction, traumatic or surgical blood loss, liver disease, oral anticoagulant activity, inherited non-hemophilia coagulation factor deficiencies, neonatal coagulopathies, and BMT. The evidence suggests that NovoSeven® is clinically efficacious in several off-label settings, but it is premature to recommend its routine use for several reasons:

1. Most of the available data about off-label uses come from case reports, case series, or uncontrolled or historically controlled studies that have enrolled small numbers of patients rather than from randomized, controlled trials. Controlled trials are generally recognized as yielding the most reliable data based on the study design.50
2. Interstudy design heterogeneity makes it difficult to evaluate and compare clinical interventional findings, even among patients with the same condition.
3. Finally, it is important to recognize the potential impact of “publication bias” on this type of literature analysis.51
Publication bias refers to a situation in which only those papers reporting positive results would be submitted and accepted for publication, whereas negative findings generally would not be. This phenomenon may skew the body of published evidence, giving a falsely elevated impression of an intervention’s true clinical effectiveness.

Given those caveats, published data from randomized, controlled clinical trials suggest that rFVIIa might have clinical efficacy in the following settings:

- neutralizing the anticoagulant effects of fondaparinux
- controlling perioperative bleeding in patients with normal coagulation systems who are undergoing retropubic prostatectomy
- correcting or normalizing laboratory and clinical hemostatic parameters in patients with liver disease prior to laparoscopic liver biopsy

For the purposes of evidence-based medicine, the data from these randomized trials provide the highest-quality evidence for the safety of rFVIIa in those conditions and suggest that this agent provides some clinical benefit. Compared with most of the published evidence that comprises anecdotal or uncontrolled series, the studies were relatively well designed and executed. However, the small numbers of patients involved limits extrapolation of the results, and the clinical significance of surrogate laboratory evidence proposed to reflect the efficacy of NovoSeven® has not been established.

REFERENCES


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Table I  Summary of Ongoing Randomized Clinical Trials of Recombinant Activated Factor VII (rFVIIa)

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Moderate-to-severe bleeding after allogeneic BMT</td>
<td>100</td>
<td>• Standard therapy + rFVIIa 40, 80, or 160 mcg/kg or placebo</td>
<td>• Change in bleeding score with time</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Severe blunt or penetrating trauma</td>
<td>280</td>
<td>• Standard therapy + three doses of rFVIIa</td>
<td>• RBC transfusion in first 48 hours</td>
</tr>
<tr>
<td>• Intracranial hemorrhage</td>
<td>80</td>
<td>• rFVIIa 10, 20, 40, 80, or 120 mcg/kg or placebo</td>
<td>• Change in volume of intracranial hemorrhage after 24 hours</td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cirrhosis with acute upper GI bleeding and portal hypertension</td>
<td>240</td>
<td>• rFVIIa 100 mcg/kg or placebo</td>
<td>• Composite five-day endpoint: control of GI bleeding, prevention of re-bleeding, mortality</td>
</tr>
<tr>
<td>• Cirrhosis and partial hepatectomy</td>
<td>240</td>
<td>• rFVIIa 50 or 100 mcg/kg or placebo</td>
<td>• Perioperative RBC transfusion</td>
</tr>
<tr>
<td>• Non-cirrhotic patients and partial hepatectomy</td>
<td>180</td>
<td>• Single dose of rFVIIa 20 or 80 mcg/kg or placebo</td>
<td>• Perioperative RBC transfusion</td>
</tr>
<tr>
<td>• Patients undergoing liver transplantation</td>
<td>180</td>
<td>• rFVIIa 60 or 120 mcg/kg or placebo</td>
<td>• Perioperative RBC transfusion</td>
</tr>
<tr>
<td><strong>Reversal of oral anticoagulant therapy</strong></td>
<td>210</td>
<td>• rFVIIa 40 or 80 mcg/kg or placebo</td>
<td>• Bleeding six hours after initiation of treatment</td>
</tr>
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BMT = bone marrow transplantation; GI = gastrointestinal; RBC = red blood cell.
Off-Label Use of rFVIIa (NovoSeven®)

106:2550–2554.


