

Clinical Utility of Recombinant FVIIa

Factor VII is one of the coagulation factors in the extrinsic coagulation pathway. Recombinant activated factor VII (rFVIIa) was introduced in 1996 to treat patients with hemophilia A and hemophilia B with inhibitors to factor VIII and factor IX respectively. Its use has expanded, with many off-label applications for the treatment of life threatening hemorrhage in the setting of platelet disorders, trauma and surgical bleeding. Due to the high cost of rFVIIa and the relative lack of definitive clinical trial data, off-label use has generated substantial controversy. Many reports suggest that rFVIIa displays a dramatic ability to revert uncontrolled bleeding. However, the Food and Drug Administration (FDA) has received reports of rare but serious thrombotic adverse events that led the manufacturer to issue an "Important Drug Warning."¹ This issue of *BloodNews* reviews both label and off-label uses of rFVIIa.

Mechanism of action: Following injury to the vessel wall, Tissue Factor is exposed and forms a complex with rFVIIa. This complex activates a small amount of factor X which leads to conversion of prothrombin to thrombin, and activation of platelets. The surface of the activated platelets serves as a template for further factor X activation by rFVIIa, greatly enhanced thrombin generation, and activation of thrombin activated fibrinolysis inhibitor (TAFI). These events occur even in the absence of factors VIII and IX. The action of rFVIIa is restricted to the surface of activated platelets, explaining its selective action at the site of bleeding, and the low frequency of generalized thrombosis.²

Indications: rFVIIa currently is approved by FDA to treat bleeding episodes and prevention of bleeding in surgical interventions in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and congenital FVII deficiency. It is approved in the European Union for acquired hemophilia and Glanzmann's thrombasthenia refractory to platelet transfusion.

Hemophilia with inhibitors: At least one third of patients with severe Hemophilia A and about 3% of patients

with severe hemophilia B develop inhibitors to factors VIII and IX, causing refractoriness to conventional replacement therapy. Large doses of factor replacement may overcome this refractoriness. Other strategies utilized to overcome the inhibitors include the use of prothrombin complex concentrate (PCC), which carries the potential for thrombotic events, disseminated intravascular coagulation (DIC), and transfusion reactions. Recombinant FVIIa has a low risk of transfusion reactions, and of thromboembolic events. A dose of 90 µg/kg every two hours for the first 48 hours and every 2-6 hours thereafter for an additional 3 days is highly effective for the prevention of bleeding in elective surgery. It has also been used for home treatment with greater than 90% success rate in controlling mild to moderate bleeding episodes within 24 hours.³ This was achieved with a mean of 2.2 doses of 90 µg/kg administered at three hour intervals, within 8 hours of the onset of bleeding. A single episode of superficial phlebitis at an injection site was reported among the 877 bleeding episodes studied.³

Off-label applications

Platelet disorders: rFVIIa has been effective in preventing bleeding in planned surgical interventions and in acute bleeding episodes in patients with inherited platelet disorders such as Glanzmann's thrombasthenia and Bernard Soulier syndrome, when conventional treatment with platelets, EACA, and FFP have failed.^{4,6} It has also been effective in treating life-threatening hemorrhage in patients with severe thrombocytopenia. This may be explained by the enhanced generation of thrombin on the surface of the few platelets available at the site of injury.⁷

Intracranial hemorrhage: In a randomized placebo-controlled clinical trial involving 399 patients, rFVIIa in doses of 40, 80, or 160 µg/kg reduced mortality, reduced the size of hematomas and improved neurologic function at 90 days if used within 4 hours of a documented intracerebral hemorrhage. There was an increase in the incidence of thromboembolic events, mainly myocardial or cerebral infarction (2% in the placebo group vs. 7% in the treatment group).⁸

Correction of drug-induced coagulopathy: rFVIIa quickly normalizes the prothrombin time in patients treated with vitamin K antagonists when needed for urgent invasive interventions or when life-threatening bleeding occurs. It also reverses the effect of fondaparinux (Arixtra) with normalization of PT and aPTT after a single dose of 90 µg/kg.⁷

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Liver failure: In a randomized study involving 15 patients with fulminant hepatic failure undergoing liver transplant, rFVIIa 40 µg/kg with fresh frozen plasma (FFP) was more effective than FFP alone to control coagulopathies, and was associated with a slight survival advantage.⁹

Postpartum hemorrhage: rFVIIa, in addition to standard surgical and medical interventions achieved good or

partial response in 11 of 12 women with severe life-threatening post-partum hemorrhage.

Use in traumatic injury: Conventional replacement therapy with FFP, cryoprecipitate and platelets often fails to control the complex coagulopathy resulting from hemodilution, platelet dysfunction, hypothermia and acidosis associated with trauma. In two parallel randomized, placebo-controlled, double-blind clinical trials involving 277 patients with blunt or penetrating trauma, rFVIIa significantly controlled bleeding by decreasing the need for RBC transfusion without increasing the incidence of adverse events, including thromboembolic events. There was a trend toward fewer complications such as multiorgan failure and ARDS.¹⁰ In several case reports of liver lacerations related to blunt injury, rFVIIa,

in addition to conventional medical and surgical interventions, was found to be effective.

Reducing surgical blood loss: In a double-blind, randomized placebo-controlled trial involving 36 patients, a single dose of rFVIIa 20 or 40 µg/kg prior to retropubic prostatectomy reduced blood loss and need for transfusion compared to placebo.¹¹

Pediatric use: In 6 preterm infants with gestational age less than 33 weeks and prothrombin time greater than 48 seconds during the first 7 days of life, rFVIIa 80 µg/kg reduced prothrombin time more effectively than FFP without evidence of side effects. There are multiple case reports of spontaneous and surgical bleeding in preterm infants responding to rFVIIa after failing conventional treatment.¹²

Complications: The incidence of thromboembolic complications has ranged from 1-2% and was more likely when rFVIIa was used in combination with other coagulation agents. An increase in thromboembolic events was reported when rFVIIa was used to treat of intracranial hemorrhage.¹⁸ DIC is rarely reported as a result of rFVIIa use.^{8,9}

Current use patterns: rFVIIa has been used off-label to prevent bleeding primarily in procedural manipulations and for treatment of bleeding. Coagulopathy was present in the majority of these patients, and about 1 in 7 patients

in the prevention group bled within 6 hours of administration, whereas about 1 in 2 patients in the treatment group stopped bleeding within 6 hours of administration.¹³

Special considerations: Since rFVIIa acts on the patient's own clotting mechanism, administration should be considered after blood component therapy has achieved the following: fibrinogen of 50 mg/dL (preferably 100 mg dL); platelet of 50,000/µL (preferably 100,000/µL); and the pH corrected to 7.2. rFVIIa is active in hypothermia. However, restoring physiologic body temperature should be attempted.¹⁴

Conclusion: The benefit of rFVIIa in the treatment of hemophilia patients with inhibitors is well established. Reported off-label indications include prophylaxis and treatment of patients with and without underlying coagulopathy, life-threatening hemorrhage, cerebral hemorrhage, liver failure, rapid reversal of anticoagulants and qualitative and quantitative platelet disorders. Most of the off-label use is based on anecdotal evidence and small studies. Further studies to better define these indications would be helpful.

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APPROVED INDICATIONS IN THE U.S.:

- Hemophilia A or B patients with inhibitors to Factor VIII or Factor IX
- Congenital FVII deficiency

OFF-LABEL USAGE:

Uncontrolled bleeding in:

- Blunt and penetrating trauma
- Intracranial hemorrhage
- Rapid correction of drug-induced coagulopathy
- Qualitative and quantitative platelet disorders
- Temporary control of coagulopathy in liver failure
- Surgical blood loss, including children and preterm infants with coagulopathy
- Postpartum hemorrhage
- Religious objection to blood products

ADVERSE REACTIONS:

- Thromboembolic events, including MI
- High D-dimer levels and consumption coagulopathy
- Hypersensitivity reactions