

# Recombinant Activated Factor VII (rFVIIa, NovoSeven®)

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## Abstract

Recombinant activated factor VII (rFVIIa, NovoSeven®) enhances haemostasis in individuals, with its predominant action limited to areas of injury, apparently without systemic activation of the coagulation cascade. rFVIIa is currently licensed in most countries worldwide, for its use in the treatment of bleeding episodes in patients with hemophilia and the presence of inhibitors. Recently in the European Union, rFVIIa, has been approved for use in congenital Factor VII deficiency and Glanzmann's thrombasthenia. Furthermore, a large number of case series studies and anecdotal evidences, from patients with different bleeding conditions, have now shown that rFVIIa is actually a very valuable general haemostatic agent. It has been reported to reduce bleeding in patients with liver disease, thrombocytopenia/thrombocytopenia, trauma, spontaneous intracerebral hemorrhage and in the reversal of anticoagulant overdosage or toxicity. A number of trials have been carried out, which have shown that it is a relatively safe and well tolerated drug with a few episodes of unwanted thrombosis. ©

## INTRODUCTION

Hemostatic challenges in patients with hemophilia A and B are treatable with highly purified plasma-derived and recombinant DNA-derived factor VIII and factor IX concentrates. However, a well recognized, and potentially life-threatening complication of hemophilia is the development of neutralizing antibodies against the missing factor. Up to 25 % of patients develop an inhibitor to factor VIII, and 3-5% to factor IX. This makes the management of bleeding episodes difficult and poses a challenge for elective or emergency surgical procedures.<sup>1</sup>

To date, therapeutic interventions in these situations have included overwhelming the inhibitors with large doses of factor VIII, but this is only feasible when the inhibitor titer is relatively low.<sup>2,3</sup> Other approaches have included the use of activated and non-activated prothrombin complex concentrates and porcine FVIII,<sup>4,5</sup> plasmapheresis with or without adsorption of antibody and, if time and resources permit, induction of immune tolerance.<sup>2</sup> All these interventions can have significant drawbacks including high cost, unpredictability of response, transmission of blood-derived infections, thromboembolic complications, and in the case of porcine FVIII, development of anti-porcine antibodies.

All these existing therapeutic caveats led to the development of rFVIIa as a potential solution for treating hemophilia patients with inhibitors. Apart from its usefulness in hemophilia and other bleeding disorders, data from several case reports and studies indicate that rFVIIa could be a valuable general haemostatic agent for non-hemophilic bleeding episodes. The purpose of this review is to explore and summarize the therapeutic status and safety profile of rFVIIa in diverse indications based on published case reports and early results from controlled randomized trials

## rFVIIa - CLINICAL PHARMACOLOGY

Recombinant FVIIa has an amino acid sequence identical to that of plasma-derived rFVIIa and is produced from a baby hamster kidney cell line, cultured in bovine albumin. As a recombinant product, it is not derived from human or animal plasma, thus eliminating the risk of human blood transmitted diseases. Although the mode of action is not completely clear, some studies suggest tissue factor dependant mechanisms and also emphasize the role of factors Xa and IXa on the surface of activated platelets. These studies relate thrombin generation on activated platelets to the high level of rFVIIa binding to the platelet surface. It acts by enhancing the natural coagulation pathway by activating formation of prothrombinase complex, and has a local action only in areas where tissue factor and/or phospholipid is exposed.<sup>6,7</sup> (Fig. 1). At pharmacological doses, rFVIIa bypasses conventional steps in coagulation cascade and directly generates a 'thrombin burst' on the

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activated platelets at the site of injury, leading to the generation of a fully stabilized tight fibrin clot. This has the advantage of limiting the extent of its activity to areas of injury and thus minimizing the risk for thromboembolic phenomena.

rFVIIa has a predictable, well-characterized pharmacokinetic profile (half-life of 2.7 hours).<sup>8</sup> Apart from its use in hemophilia rFVIIa has also been used to control bleeding in traumatic coagulopathies, thrombocytopathies, liver disease, liver transplantation, spontaneous intracerebral hemorrhage and patients undergoing cardiac surgery.

**Hemophilia with inhibitors :** rFVIIa has been used in a compassionate use programme in more than four hundred patients with Hemophilia A and B with inhibitors or with acquired inhibitors, involving over 1900 surgical and nonsurgical episodes.<sup>9,10</sup> It has been shown to be effective and well tolerated in majority of these patients with no evidence of an anamnestic response or of antibody formation against factor VII. The nonsurgical bleeding episodes included internal hemorrhage and joint and muscle bleeds.<sup>11</sup> Major and minor surgical procedures have been successfully undertaken in inhibitor patients treated with rFVIIa. Shapiro *et al.*<sup>1</sup> in their study found that a dose of 90 microgram/kg was highly effective for patients undergoing both major and minor surgical procedures, with between 83% and 100% of patients having satisfactory Haemostasis. Whether continuous infusion of rFVIIa would be more effective and drug sparing remains an issue to be addressed. The study also demonstrated a very low rate of clinically or laboratory defined adverse events. Current recommended dose of rFVIIa in hemophilia with inhibitors and acquired hemophilia is 90 mcg/kg IV bolus every 2 hours or until clinical hemostasis is achieved.<sup>12</sup>

**Factor VII deficiency :** FVII deficiency is a rare coagulation disorder, historically treated with prothrombin complex concentrates or plasma derived FVII concentrates. Mariani *et al.*<sup>13</sup> used rFVIIa very successfully while treating bleeding episodes in their FVII deficient patients. 27 spontaneous bleeding episodes were treated and 7 major and 13 minor surgical interventions were carried out using a mean dose of 22 - 26 mcg/kg. In all cases rFVIIa achieved excellent hemostasis. Other studies as well have shown the benefit of rFVIIa in FVII deficiency. The recommended dose of rFVIIa in Factor VII deficiency is 15-30 mcg/kg every 4-6 hours until hemostasis is achieved.<sup>12</sup>

**Glanzmann's thrombasthenia :** It is a rare inherited bleeding disorder due to deficiency or dysfunction of glycoprotein GP IIB-IIIa on platelets. The treatment in Glanzmann's thrombasthenia is a challenging issue, especially when repeated platelet transfusions have induced anti-glycoprotein GP IIB-IIIa or anti-HLA allo-immunisation. In an attempt to find an alternative

treatment regimen, d'Oiron *RD et al.*,<sup>14</sup> used rFVIIa as the first line therapy in 3 patients with Glanzmann's thrombasthenia and anti-GP IIB-IIIa iso-antibodies who were scheduled for surgery. The treatment resulted in excellent clinical efficacy in two out of three cases. Several other studies have shown the efficacy of rFVIIa in Glanzmann's thrombasthenia, The current recommended dose of rFVIIa in Glanzmann's thrombasthenia is 90 mcg/kg every 2 hours until hemostasis.<sup>12</sup>

## rFVIIa - EMERGING AS A GENERAL HEMOSTATIC

**Trauma and Surgery :** Coagulopathy is the major cause of bleeding-related mortality in patients who survive the operating room. Its association with hypothermia and metabolic acidosis is common and constitutes a vicious cycle. Virtually every aspect of the normal coagulation cascade is affected in the cold, acidotic, exsanguinating trauma patient. Early control of surgical bleeding and significant contamination, together with vigorous correction of hypothermia and continuous resuscitation, has improved the survival of these patients. Recently rFVIIa has been successfully used in moribund trauma patients in whom standard procedures failed to correct bleeding.<sup>15</sup> Investigators in one study successfully used rFVIIa to control hemorrhage in critically ill trauma patients.<sup>16</sup> In their study, five patients with diffuse coagulopathy and impending exsanguination were given rFVIIa in an effort to control life-threatening hemorrhage. Administration of rFVIIa contributed to the successful control of hemorrhage in three of five patients. Failure in two patients was most likely due to overwhelming shock and acidosis.

Successful use of rFVIIa to control bleeding in a 19-year old Israeli soldier with a high-velocity bullet injury has been earlier reported; when standard measures failed to restore hemostasis, administration of 60mcg/kg rFVIIa substantially reduced bleeding, and a second dose after 1 hour resulted in complete cessation of bleeding.<sup>17</sup> Subsequently, the compassionate use of rFVIIa for patients suffering from massive life-threatening bleeding as a result of surgery or trauma was approved by the Ethics Committee of the Israeli Ministry of Health.<sup>15</sup> In a series of seven critically ill hemorrhagic trauma patients, rFVIIa dose administered has ranged between 40 and 120mcg/kg to arrest bleeding;<sup>15</sup> four patients survived in this case series report while the nonsurvival in the rest was most likely due to the very unsalvageable nature of injury. In one of the largest prospective, randomized, multi-centric studies of rFVIIa, 301 patients with blunt or penetrating trauma were enrolled of whom 277 patients at the end of the study were analyzable. Three doses of rFVIIa (200mcg/kg, 100mcg/kg and 100mcg/kg) or placebo were administered IV bolus at entry, at 1 hour and 3 hours in addition to standard

measures of treatment. Study results were encouraging and showed a significant decrease in the number of RBC transfusions within 48 hours and a trend towards reduced multiple organ failure and acute respiratory distress syndrome in the rFVIIa-treated blunt trauma group.<sup>18</sup>

There are some reports demonstrating the efficacy of rFVIIa in controlling intraoperative bleeding during liver surgery, which is known to be associated with a higher level of blood loss than other types of surgery. One study has demonstrated that a single dose of rFVIIa (80mcg/kg) could reduce transfusion requirements in cirrhotic patients undergoing orthotopic liver transplant.<sup>19</sup> Another case of severe intra-abdominal bleeding three days after non-heart beating kidney transplantation, in a patient with concurrent severe coronary heart disease, in which 70mcg/kg of rFVIIa was successfully used with no safety concerns, has been recently reported.<sup>20</sup>

**Spontaneous intracerebral hemorrhage (ICH):** ICH is one of the most disabling types of stroke.<sup>21</sup> The current unmet medical need for a treatment of ICH is recognized by neurologists around the world as a serious medical emergency. The volume of bleeding into the brain is an important predictor of neurological and clinical outcomes after 30 days and it has been well documented that such bleeding continues over the early hours following symptom onset. Recently, one medical intervention ICH study, largest done to date, has reported encouraging results that early administration of rFVIIa is associated with reduced haematoma growth and improved clinical outcome with marginal risk of thromboembolic phenomena. The trial included 399 patients, all diagnosed by a CT scan within three hours of ICH onset. Patients were randomly assigned to receive placebo (N=96), 40 (N=108), 80 (N=92) or 160 (N=103) mcg/kg doses of rFVIIa within one hour of the baseline scan. The primary outcome measure was the percentage change in ICH volume at 24 hours after treatment. Clinical and neurological outcomes were assessed at 90 days after treatment. Compared to 29% growth in placebo arm, ICH volume growth in the 40, 80 and 160 mcg/kg arms was 16%, 14% and 11% respectively (corresponding to a relative reduction of 45%, 52% and 62%).<sup>21</sup> End-study findings were encouraging and included statistically significant reduction in haematoma growth and improvement in neurological and clinical outcome.

#### **rFVIIa – Safety Profile**

The mechanism of rFVIIa in initiating haemostasis has led to concerns that as well as acting locally at the site of vessel injury, more wide spread coagulation could be possible if tissue factor is in contact with plasma, e.g., when tissue factor is up regulated on the surface of circulating monocytes in the setting of gram negative septicemia/ endotoxemia resulting in DIC. Tissue factor is expressed within the lipid core of atherosclerotic plaques and is exposed at the sites of plaque fissure.

Administration of rFVIIa to those with fissured plaques could hypothetically generate an acute thrombus. Published data from the manufacturer documents more than 200,000 doses given worldwide to 7,500 hemophiliac patients with inhibitors to FVIII, with minor or major thrombotic complications occurring in only 35 cases.<sup>16</sup> In total, six cases of myocardial infarction and four cerebrovascular accidents occurred. The majority of these patients had age-related or other risk factors for atherosclerotic disease. This low incidence of events may be, however, falsely reassuring because many of the patients were young and were not expected to have atherosclerosis. There was a single case of pulmonary embolism, and five patients during clinical trials developed a mild consumptive coagulopathy. It is not known if there will be a similar low rate of unwanted thrombosis seen in hemorrhaging trauma patients, although none of significance has been reported to date. rFVIIa has an amino acid sequence identical to that of plasma derived rFVIIa and is produced from a baby hamster kidney cell line, cultured in bovine albumin. The product is purified with the use of mouse monoclonal antibodies. Hence rFVIIa should not be used in patients with a known hypersensitivity to mouse, hamster or bovine proteins. The half-life varies amongst individuals, but is approximately 2.7 hours after a single bolus dose in adults.<sup>22</sup> Whilst the PT and the APTT are shortened with pharmacological doses of rFVIIa, these do not appear to be direct correlates of its action. A major problem in the management of patients with rFVIIa therapy is that there is no consensus as yet on the most appropriate assay with which therapy can be monitored. The measurement of FVII clotting activity in the treatment of hemophiliac inhibitor related bleeding has led to the recommendation of a minimum level of 6-10 IU/ml FVIIC activity and peak levels of greater than 30-50 IU/ml when giving IV boluses.<sup>23</sup>

#### **rFVIIa – Future Prospects**

rFVIIa is currently approved for use in the treatment of bleeding episodes in patients with hemophilia and inhibitors and acquired hemophilia. Recently rFVIIa has also been approved for use in congenital FVII deficiency and Glanzmann's thrombasthenia in European Union. Furthermore, a large number of case series studies and anecdotal evidences, from patients with different non-hemophilic bleeding conditions, have now shown that rFVIIa may be a very valuable general haemostatic agent. It has been reported to reduce bleeding in patients with trauma, surgery, spontaneous intracerebral hemorrhage, and the spectrum of indications is fast expanding. Trials to date indicate that it is a relatively safe and well tolerated drug with a few episodes of unwanted thrombosis. Already clinicians in Israel<sup>15</sup> and US Army Institute of Surgical Research,<sup>24</sup> under the special approval on compassionate grounds, have been using rFVIIa to treat massive bleeding victims as per the rFVIIa

usage guidelines evolved by their respective regulatory bodies.

The cost/benefit ratio associated with the use of rFVIIa is currently not fully known. Although the drug itself is expensive (about 10,000 \$ per 100 mcg/kg dose in the USA), more rapid correction of traumatic coagulopathy will substantially reduce transfusion requirements and may impact ventilator days and the need for dialysis.<sup>25</sup> It is possible that an initial timely therapy with rFVIIa will ultimately reduce the economic burden associated with transfusion therapy, organ system support and critical care. Use of rFVIIa should be reserved for salvageable patients with coagulopathic bleeding that is unresponsive to existing medical therapies; definitive surgical control of accessible sites of hemorrhage is nevertheless a must-intervention. Recently the efficacy and safety studies for rFVIIa in trauma and intracerebral hemorrhage are successfully completed in the setting of randomized, controlled and double-blinded trials. Many new larger trials are further planned, and some already underway,<sup>26</sup> to establish rFVIIa as a safe and effective general hemostatic agent.

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