

# TRANSFUSION MEDICINE UPDATE



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## Off-label use of Recombinant Factor VIIa (rFVIIa)

Suzanne Bakdash, M.D., M.P.H., *Transfusion Medicine Fellow, Institute For Transfusion Medicine & University of Pittsburgh School of Medicine, Department of Pathology*

Franklin A. Bontempo, M.D., *Medical Director, ITxM Coagulation Laboratory & Associate Professor of Medicine, University of Pittsburgh School of Medicine, Division Of Hematology/Oncology*

### INTRODUCTION

Recombinant activated factor VII (rFVIIa) (NovoSeven, Novo Nordisk, Denmark) is a non-human glycoprotein concentrate similar to human plasma-derived activated coagulation factor VII.

rFVIIa is FDA approved for the treatment of bleeding in hemophilia A or B patients with inhibitors (to factor VIII or IX, respectively), patients with acquired hemophilia and patients with congenital factor VII deficiency. It is also approved for prevention of bleeding during surgery or invasive procedures in the same patient population.

### MECHANISM OF ACTION

Tissue factor (TF) is expressed in areas of vascular injury. The TF/rFVIIa complex activates the coagulation cascade, which, in the presence of activated platelets, leads to thrombin generation and fibrin clot formation. Superphysiologic levels of rFVIIa can also lead to increased thrombin generation independent of TF. Replacing coagulation factors (including fibrinogen) and platelets remains necessary to achieve hemostasis in coagulopathic patients even if a high dose of rFVIIa is used. The theoretical benefit of localizing clot formation to areas of vascular injury and TF expression has led to increasing off-label use of rVIIa in a broad range of clinical settings<sup>1</sup>.

### CLINICAL STUDIES OF OFF-LABEL USE

A recent review<sup>2</sup> of a limited number of randomized controlled clinical trials (RCTs) did not demonstrate any statistically significant advantage or disadvantage to the off-label prophylactic or therapeutic use of rFVIIa as compared to placebo. However, one study with results strongly in favor of rFVIIa for treatment of intracerebral hemorrhage could not be included in the combined statistical analysis. Overall, there were non-statistically significant trends in favor of prophylactic off-label rFVIIa decreasing the number of required transfusions and therapeutic off-label rFVIIa decreasing mortality. There were also non-statistically

significant trends of off-label prophylactic and therapeutic rFVIIa increasing adverse thrombo-embolic events.

Use of rFVIIa within 3 - 4 hours of onset of acute intracerebral hemorrhage was shown to limit expansion of the hematoma, reduce mortality and improve functional neurologic outcomes at 90 days. However, it was also associated with a small increase in the risk of serious thromboembolic events<sup>3</sup>. Recent guidelines for management of spontaneous intracerebral hemorrhage in adults assigned this use a recommendation class of IIb, pending confirmation by phase III clinical trials<sup>4</sup>.

rFVIIa has also been used off-label for rapid reversal of warfarin anticoagulation in over-anticoagulated patients who are actively bleeding, or at high risk of it, when traditional treatments such as plasma or prothrombin complex concentrates are unavailable, contraindicated, or likely to take too long.

Major bleeding in patients with the hereditary platelet defect of Glanzmann thrombasthenia, have been successfully treated with rFVIIa in case reports. Such patients can develop refractoriness to platelet transfusion and the use of rFVIIa may provide an alternative hemostatic avenue for them. This indication for rFVIIa is approved in Europe.

Other off-label uses for rVIIa include trauma, uncontrolled surgical bleeding, and cardiac surgery. Although more RCTs are needed to get a better sense of the risks, benefits, and dosing of rVIIa in these settings, a number of reports show some benefit in certain situations. rFVIIa is currently considered in salvageable trauma and surgical patients with massive bleeding that persists despite surgical intervention, appropriate replacement of coagulation factors and fibrinogen with plasma and cryoprecipitate, replacement of platelets and red blood cells, correction of acidosis and hypothermia, and administration of anti-fibrinolytic agents if needed<sup>5,6</sup>.

rFVIIa has been used off-label in a number of pediatric settings of uncontrolled bleeding, including trauma, surgery, and coagulopathy. Case reports suggest that it may enhance hemostasis without increased adverse events, but these are based on small numbers. No pediatric RCTs have yet been reported<sup>7</sup>.

## **DOSAGE AND MONITORING**

The half-life of rFVIIa is about 2-3 hours. For off-label use, no more than 3 doses are usually administered. The standard dose in hemophiliacs with inhibitors is 70 - 90 µg/kg. There is no consensus regarding off-label dosing, although 40 - 50 µg/kg is probably most often recommended. rVIIa is available in 1.2 mg (1200 µg), 2.4 and 4.8 mg vials, at an average cost of \$1 per µg (\$3,600 - \$ 4,800 for an average dose).

Although it acts through the extrinsic (PT) coagulation pathway, no good correlation exists between the effect of rFVIIa and the shortening of the prothrombin time (PT) or INR. Clinical monitoring of bleeding and overall hemostasis is necessary to monitor efficacy of rVIIa therapy. Continued replacement with standard blood products may also be required.

## **CAUTIONS & ADVERSE EVENTS**

Use of rVIIa is associated with a risk of thromboembolic complications. More than half of these are arterial, including stroke and myocardial infarction. Deep venous thromboses, pulmonary embolism and device-associated thrombi have also been described. These complications appear to be of more concern in non-hemophiliacs and warrant caution in rFVIIa use, particularly in patients already at high risk for thromboembolic events, until further evidence is available<sup>8</sup>. rFVIIa is contraindicated in patients with known hypersensitivity to mouse, hamster or bovine proteins.

## **SUMMARY**

Moderate evidence exists to support the early use of rVIIa in patients with acute intracerebral hemorrhage. However, while the concept of a universal hemostatic agent is appealing, there is insufficient evidence at this time to warrant wide-spread prophylactic or therapeutic off-label use of rFVIIa. A number of additional RCTs are underway to help clarify the advantages and disadvantages of rFVIIa in various settings.

Many institutions have assigned transfusion medicine physicians or hematologists to act as consultants for off-label rFVIIa requests, for a variety of reasons including uncertain efficacy, high cost and risk of serious thromboembolic events. Such consultants can provide specialized knowledge of hemostasis and coagulation, suggest alternative therapies and assist with dosing recommendations until more uniform standards and guidelines become available.

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Editor: Donald L. Kelley, MD, MBA: [dkelley@itxm.org](mailto:dkelley@itxm.org).

For questions about this TMU, please contact:

Franklin A. Bontempo, MD at: [fbontempo@itxm.org](mailto:fbontempo@itxm.org)  
412-209-7320.

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