

How we manage requests for recombinant factor VIIa (NovoSeven)

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Novel transfusion products present interesting and new challenges to transfusion medicine professionals. Hospitals and clinicians often rely on the transfusion medicine physician or hematologist for advice and in some cases permission to use these products. Use of a specific service as a gatekeeper is controversial but would be more appropriate in situations where the products represent extremely expensive options that are being used “off label” (i.e., for situations in which they have not been approved by the US Food and Drug Administration [FDA]). Recombinant factor (F)VIIa is such a product that clearly has important uses, but in many cases its use is controversial.¹ We present an approach to the management of requests for this product based on the combined input of clinicians who treat patients with bleeding disorders and physicians who manage transfusion services.

RECOMBINANT FVIIa

Recombinant FVIIa (rFVIIa; NovoSeven, Novo Nordisk, Princeton, NJ) is a recombinant form of FVIIa produced by cloning of the human FVII gene, which is then expressed in baby hamster kidney cells, secreted into the culture media, and proteolytically converted to the two-chain active form. It is identical to the human molecule except for minor differences in glycosylation. As a recombinant product, it avoids the risks of a human pooled plasma product. The mechanism of rFVIIa in hemostasis is the subject of research and debate. A currently accepted hypothesis is that supraphysiologic doses of FVIIa allow the intrinsic pathway of coagulation to be bypassed and

sufficient thrombin to be generated to lead to stable clot formation. The sites of activation are the tissue factor-FVIIa complex on damaged endothelium as well as rFVIIa acting directly on thrombin-activated platelet (PLT) surfaces.² rFVIIa interacts in the tissue factor-VIIa complex and can directly activate FX.^{3,4}

At the current price of approximate \$1000 per milligram, this product represents a significant cost burden. The standard dose is generally 90 µg per kg given every 2 hours, for the FDA-approved indication viz. hemophilia patients with inhibitors. Therefore, it would cost approximately \$6300 for a single dose for a 70-kg male, which when repeated every 2 hours could cost a fortune for a single episode of bleeding. rFVIIa is also currently approved by the FDA for use in patients with congenital FVII deficiency at a lower dose of 15 to 30 µg per kg. After the initial report of an Israeli soldier with massive bleeding being successfully resuscitated with rFVIIa, there have been increasing reports of its use for surgical and nonsurgical life-threatening bleeding.⁵ We have also seen life-saving results of rFVIIa used at our institution.⁶⁻⁸

A growing number of prospective, randomized trials have been published.⁹⁻²⁰ Most of these have small numbers of subjects; several specifically deal only with anticoagulation reversal. Not all of the studies were able to demonstrate a positive effect of rFVIIa administration.^{9-11,17,20}

SAFETY PROFILE

Initially, the rFVIIa safety profile was thought to be very good with less than 1 percent of doses resulting in an adverse event, usually a thrombotic complication. Many of those who had an adverse event were elderly with existing atherosclerotic disease. The adverse event could have been a result of return to the “status quo” hemostatic profile in an individual with risk factors for thrombosis who had been previously anticoagulated. The FDA, however, has collected adverse event reports related to FVIIa.²¹ The reports are particularly prominent in off-label uses of the factor. They involve arterial and venous thromboembolic events with a frequent fatal outcome (this is likely increased by reporting bias). Half of them occurred in the first 24 hours after the last rFVIIa dose. Underlying medical conditions existed in some but not all of the cases. In 71 percent of reports, the reporter felt that there was a

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causal relationship.²¹ Although rFVIIa still appears to be relatively safe,²²⁻²⁵ concerns about patient safety have been heightened and therefore would lead to a more cautious approach in the use of the product in off-label situations.

OUR APPROACH

Hospital control of drugs and biologicals may range from unlimited access (for example, most antibiotics), to strict control and tracking of use (as for certain blood products). For drugs that are extremely expensive or prone to misuse, “gatekeepers” are sometimes established. Some institutions establish strict criteria for product use, and the ordering physician must demonstrate to a gatekeeper that the patient meets established criteria. At our institution, we use a less formal system of content experts. Only physicians familiar with the risks, benefits, and indications for the drug are allowed to order it from the pharmacy. Initially, only one hematologist had this privilege. As more physicians have gained experience with the drug, this has expanded to several hematologists, transfusion medicine experts, and surgeons with an interest in hemostasis. A clinical service contemplating the use of rFVIIa will usually request a consultation from the content expert with whom they are most familiar or be referred by pharmacy to an appropriate content expert. Because of the unique challenges of the use of an off-label drug in the pediatric population, rFVIIa is only issued after consultation with a pediatric hematologist with expertise in this area. Institutional use is monitored in the event that more oversight may be needed in the future.

There is an obvious division between those rFVIIa uses that are approved indications (those that involve patients with congenital coagulation factor deficiency) and indications that are considered off-label. Use of rFVIIa for approved indications typically involves very specific patient populations and therefore it is only ordered by hemophilia or other coagulation specialists. It is the off-label use that provides challenges for blood banks and pharmacies (see below).

Control of rFVIIa for use in congenital factor deficiency and in patients with inhibitors

1. In patients with hemophilia and inhibitors.

Patients with hemophilia are best managed at a center specializing in the treatment of bleeding disorders and with an appropriate coagulation laboratory. Therefore, the first step that should be taken is to determine whether such a treatment site is available and, if not, to assure that there is adequate coagulation and specialist support. Our institution houses the only Hemophilia Treatment Center in the state of New Mexico; both pediatric and adult patients with hemophilia, von Willebrand disease (VWD), and other bleeding disorders are evaluated and diag-

nosed, and individualized management plans are developed. Additionally, we have a state-of-the-art special coagulation laboratory that is available 24/7 to run laboratory tests that may be critical in the management of the individual patient. The use of rFVIIa in patients with hemophilia is directed by an adult or pediatric hematologist at the center.

rFVIIa is appropriate for management of acute bleeds in hemophilia patients with high-titer inhibitors (>5 BU).²⁴ For minor bleeding, rFVIIa is typically given in 90 µg per kg doses every 2 hours until hemostasis is achieved or until the treatment is judged to be unsuccessful. Many times, management of minor bleeding in these patients is done as an outpatient, thereby decreasing hospital costs. For major bleeding, the patient is usually hospitalized, the pharmacist in house is alerted of the particular patient, and the transfusion medicine team is made aware of this patient (in case of the need for blood product support). A plan is then devised for dosing and duration of rFVIIa in collaboration with the service to which this patient is admitted. This plan is partially dependent on the patient’s previous responses to rFVIIa. Furthermore, if this patient is already on another bypassing agent such as FEIBA (the only other agent available for these patients to control bleeding) then this would be the first agent of choice. Recombinant FVIIa has been found to be efficacious in joint, muscle, and mucocutaneous bleeding in hemophilia patients with inhibitors, as well as when these patients have other types of severe bleeding.²⁶ In hemophilia patients with high-titer inhibitors, rFVIIa treatment may be considered as a first line of treatment for bleeding. Being comfortable with its use, we have, at times, administered doses as high as 270 µg per kg, with dosing every 3 to 4 hours, for severe, uncontrollable bleeding in patients with inhibitors that did not respond to lower doses.

There is good evidence as well for the use of rFVIIa in surgery for patients with hemophilia.^{24,27,28} High-quality evidence comes from prospective randomized trials with a significant difference in efficacy favoring rFVIIa treatment. Multicenter open-labeled compassionate-use trials have similarly shown positive results. Thus, rFVIIa can open the possibilities for elective surgery in patients with hemophilia and inhibitors who might otherwise not be able to receive surgical repairs (e.g., joint replacements). Anecdotal reports support the use of rFVIIa in central nervous system bleeding in hemophilia patients with inhibitors and in the control of bleeding during immune tolerance induction.²⁸ There are also reports supporting the use of continuous infusion rather than boluses. Use of continuous infusion in management of these bleeds is controversial, however, given that a burst of thrombin may be required for achieving hemostasis (as seen after a bolus infusion). At our institution, we use bolus infusions predominantly, with continuous infusion used only as part of

a clinical trial. Dosing of rFVIIa in our hemophilia patients undergoing surgery is based on whether the surgery is minor (e.g., tooth extraction) or major (e.g., tonsillectomy, port placement, joint replacement, trauma). For major surgery, we use 90 to 120 μg per kg for surgery, given every 2 hours for the first 48 hours, and decrease the dose to every 4 hours on the third or fourth postoperative days and then to every 6 hours for another week. Orders for rFVIIa are written by the pediatric or adult hematologist on service. The exact dosage is based on knowledge of the available vial sizes of rFVIIa (1.2-, 2.4-, and 4.8-mg vials). We round the prescribed dose to the nearest vial size, so no factor is wasted—most often rounding *up*.

Achievement of clinical hemostasis is the marker we use to monitor dosing, duration, efficacy, and adverse events of rFVIIa. There are no good laboratory markers for monitoring the efficacy of rFVIIa, although recently some centers are studying the use of the thromboelastograph.²⁹ We use the trend of the quantitative D-dimer levels as a marker to monitor clot formation and fibrinolysis *in vivo*, along with the blood counts and fibrinogen level. We do not routinely rely on the clotting times (prothrombin time [PT]/aPTT) to monitor hemophilia patients. The primary patient care service usually leaves the management of medical hemostasis to the hematologists or transfusion medicine specialists. rFVIIa has clearly filled an important therapeutic niche in patients with hemophilia who have high-titer inhibitors and who have not responded well to other therapies.

2. Use in congenital FVII deficiency. There is only midlevel (case series and low level anecdotal) evidence for the use of rFVIIa in congenital FVII deficiency, but this is an FDA-approved use of the drug. Given the small number of patients available for study, more evidence may be difficult to obtain. In a report on seven patients, all but one tolerated the therapy with good clinical results. The mean dose was 22 to 26 μg per kg (doses ranged from 30 to 112 $\mu\text{g}/\text{kg}$). The one patient who had problems developed antibodies 4 to 5 weeks after a very high dose. Two other case reports of rFVIIa use during cranial hemorrhage and dental surgery also showed good results.²⁸

The only other options for patients with congenital FVII deficiency currently available in the United States are fresh-frozen plasma (FFP; which has the problem of volume limitation) and activated prothrombin complex concentrates, both of which give unneeded coagulation factors. Therefore, it would appear that in the management of these patients, rFVIIa should be made available for clinical use in bleeding problems as well as for surgical prophylaxis. The FDA-approved dose for congenital FVII deficiency is 15 to 30 μg per kg, given every 6 to 12 hours as needed to achieve hemostasis. At our institution, we do not have many patients with congenital factor deficiency, and the ones we have are mild ones. When these patients show up in the emergency room or are admitted for sur-

geries, the primary service consults with the hematology or transfusion medicine team, and together we plan for their management. We use the smallest vial required for these patients, with a dose of 15 to 30 μg per kg, administered every 6 to 12 hours, monitored by the PT. Administration of rFVIIa rapidly corrects the PT and since it is deficiency of FVII that is the issue, the PT serves as an adequate marker for the administration of rFVIIa in these situations. Correction of PT appears to correlate well with achievement of clinical hemostasis (the ultimate marker) for administration of rFVIIa in patients with deficiency. We rarely, if ever, need FFP for these patients to achieve hemostasis.

Control of rFVIIa when used for off-label indications

Preliminary guidelines for off-label use of rFVIIa were proposed in 2004.¹ Recently, a consensus panel of distinguished experts has evaluated the data for off-label use of rFVIIa in adults.³⁰ Our institutional content experts rely on similar data when consulting on the appropriate use of rFVIIa. The consensus panel related the use of rFVIIa as appropriate in a limited set of circumstances:

1. In cardiac, thoracic, aortic, and spinal surgery; in hepatic resection; in hysterectomy; or for cases of postpartum bleeding where intense traditional clotting factor replacement has failed.
2. For severe, multiple trauma in cases where surgery and substantial blood replacement have been ineffective.
3. For nontraumatic intracranial bleeding if it has been less than 4 hours since onset of symptoms or for cases of anticoagulated patients with expanding hematomas.

Doses of 41 to 90 μg per kg were recommended in adults for all scenarios, except that a lower dose of 20 to 40 μg per kg was recommended for nonemergent anticoagulation reversal.³⁰

The use of rFVIIa in pediatric patients also holds potential and has been reviewed by Mathew and coworkers.^{8,27,28} Guidelines for use have also been reported by the Israeli Multidisciplinary rFVIIa Task Force.³¹ These echo the recommendation above for use in “any salvageable patient” suffering from massive, uncontrolled hemorrhage that fails to respond to appropriate surgical measures and blood component therapy.³¹ Correction of the pH value to greater than 7.2 is recommended due to markedly decreased activity of rFVIIa in acidosis.³² The recommended dose in these multitrauma patients is 100 to 140 μg per kg with a repeat dose of 100 μg per kg if hemorrhage persists. A third dose is not given before careful reevaluation. At our institution, we generally use these as guidelines, augmented by our experience in the management of these patients. A few scenarios are highlighted below.

1. Liver disease. There is no high-level evidence for use in treatment of bleeding in liver disease—only small case series or case reports.³⁰ In two cases, children were treated with rFVIIa before liver transplantation with a good outcome. In other cases, bleeding slowed but other blood components had also been given. With minimal data, rFVIIa should not be used as standard therapy during bleeding in patients with liver disorders, but should be used either as part of a clinical trial or with compassionate use in a desperate situation where there is a possibility of appropriate therapy if life-threatening bleeding can be stopped. In the latter situation, data should be kept. These patients sometimes have *acquired* FVII deficiency (as monitored by the PT and FVII levels). At our institution, the transfusion team and/or hematology service is usually consulted after the traditional treatment options have been exhausted (administration of FFP, red blood cells [RBCs], PLTs). We then decide if rFVIIa is appropriate in this patient by evaluating seven points:

1. the clinical scenario;
2. the underlying disorder;
3. blood gases (if available—to ensure that the patient is not severely acidotic and has a pH > 7.2);
4. the amount of blood products the patient has received thus far;
5. the salvageability of the patient;
6. whether the patient has an inherent thrombotic tendency (e.g., atherosclerotic heart disease, previous myocardial infarction, strokes, etc.); and
7. whether we believe the patient will benefit from rFVIIa.

Once we believe that the benefit exceeds the risk, we inform the admitting service as well as make a personal phone call to the pharmacist regarding issuing and dosing of rFVIIa. The primary service then discusses this drug option with the family members and the patient (if capable of consenting) and also the potential risks and benefits, including thrombotic risks. For liver disease patients, we typically use a dose of 15 to 30 μg per kg, but may use a dose of 90 μg per kg, if the bleeding is severe. We monitor the PT in these patients, and the second dose is administered if the PT is still prolonged or if bleeding has not stopped, in 6 hours. A third dose is rarely given.

2. Use after cardiac surgery. The evidence for use after cardiac surgery is low level, consisting of case reports. In children, there have been no adverse events.³⁰ Given the potential in this scenario for thrombotic episodes especially in the elderly, rFVIIa use should be considered experimental and done either as part of a clinical trial or only in a situation where traditional transfusion support has failed. When we are consulted about these patients, we follow the same thought processes as described above, weighing benefit versus risk, as well as failure of standard therapies, including administration of

other blood products, vitamin K, and so forth. If intra- or postoperative bleeding is excessive, we use one dose of 90 to 120 μg per kg. We may give a second dose if the first dose has shown a response, but has not slowed the bleeding sufficiently; if the surgical field is wet with oozing blood; or if the patient is exsanguinating in the operating room. Rarely do we use more than three doses of rFVIIa. In those cases where the bleeding may be related to an acquired FVII deficiency, we have been able to achieve hemostasis with the lower dose of 15 to 30 μg per kg, rounded off to the nearest vial, usually with one or two doses.

3. Preterm and term infants. The efficacy of rFVIIa is difficult to determine in preterm and term infants even though most treated infants appear to make an uneventful recovery.^{27,28} There is one report of midlevel evidence and a few low-level evidence reports. In these patients, use should be limited to clinical trials or for adjunctive situations that are desperate in nature and where life-saving cessation of bleeding could lead to appropriate therapy.²³ We have not used rFVIIa in preterm infants as of yet. We have been managing these patients with standard blood component therapy for their bleeding (FFP, RBCs, PLTs, cryoprecipitate). One of the issues to keep in mind with the use of rFVIIa in these patients is that the smallest vial size of rFVIIa is 1200 μg . For a 1.5-kg preterm infant, this would give an extremely high dose of 800 μg per kg if one were to use the entire vial. For these patients, we would normally split the vial into four or six parts in the pharmacy and use one part at a time, trying to use the entire vial over a 24-hour period (even though the manufacturer does not recommend this). We have used this strategy effectively in some of our smaller term babies, with the PT as a rough guide to time the dosing of the subsequent doses. Again, rFVIIa is dispensed only after standard hemostatic therapy has been given or, alternatively, in certain babies where there is risk of volume overload with FFP. Approval from the pediatric hematologist is obtained by the pharmacy.

4. Use in qualitative PLT disorders. Based on the ability of pharmacologic doses of rFVIIa to enhance the rate of thrombin generation on activated PLTs, rFVIIa has been employed for management of bleeding in qualitative PLT defects. Midlevel evidence and case reports exist.²⁸ In Glanzmann's thrombasthenia, there have been a number of reports in which major bleeding has been treated with rFVIIa with good results. A report of 33 episodes in seven children found that in 60 percent of cases the response was excellent if treated within 12 hours of the onset of bleeding.³³ All five surgical procedures performed under the cover of rFVIIa showed a good response, but no overall reduction in transfusion requirements could be demonstrated. Based on studies including those by Poon and associates,³⁴ rFVIIa has been approved for use in Europe for Glanzmann's thrombasthenia. There are also case reports of a good response in other thrombocytopathies.

Under a single case report, two patients with Type II VWD and high-titer inhibitors to von Willebrand factor showed good response.²⁸ There has also been good response reported in uremic bleeding. In all of these instances, the paucity of evidence suggests that use in these cases should remain investigative: either as part of a controlled clinical trial or, where there are very small numbers of patients, as a highly controlled clinical case study with the data carefully maintained and only as an adjunctive therapy when other approaches have failed.

We have used rFVIIa in some of our Glanzmann's thrombasthenia patients for surgical prophylaxis and excessive menstrual bleeding. The use of rFVIIa was dictated by the fact that one of our patients had history of alloimmunization to previous PLT transfusions; in another, the desire to reserve PLT transfusion for a major bleeding episode. These patients received first-line rFVIIa treatment under the care of the pediatric hematologist, because use of rFVIIa was considered appropriate. In these situations, doses of 90 to 120 μg per kg were used with successful achievement of hemostasis.

5. Use in trauma. Since the successful report of the use of rFVIIa for trauma in an Israeli soldier and a subsequent report on 19 critically ill trauma patients, the use of rFVIIa in blunt or penetrating trauma in cases where conventional hemostatic measures have failed has attracted great interest.³⁰ There are many case reports of successful use of rFVIIa, including one from our institution in children with injuries to the juxtahepatic veins—one of the most challenging and deadly forms of hepatic trauma.⁶ It would appear that rFVIIa is a promising addition to the therapeutic armamentarium for patients with trauma who fail conventional hemostatic measures. In this area, there are sufficient patients to allow for a well-controlled clinical trial. Getting approval for conducting prospective studies on severely injured patients is difficult in some countries due to the challenge of obtaining informed consent. In the meantime, the use of rFVIIa in these scenarios should still be considered experimental therapy, to be used only adjunctively when other forms of therapy have failed.^{31,35}

At our institution, the trauma surgeon usually calls the hematologist or the transfusion medicine team before the patient goes to the operating suite or calls from the operating room. In these situations, rFVIIa is used up front after an initial course of standard blood component therapy. This may be to prevent the patient from requiring a major liver surgery (as in patients with liver injuries) or to treat patients in which surgical hemostasis has been thought to be achieved but that still have continued bleeding in spite of extensive blood component therapy. In the latter case, usually a dose of 90 to 120 μg per kg is given, followed by a second similar dose or half the dose about 2 hours later. Rarely is a third dose given. Thus, unlike patients with hemophilia with severe bleeding that may

require rFVIIa every 2 hours for multiple days, in these off-label situations, we rarely use more than three doses at a time.

6. Use in intracranial hemorrhage. A recent report in intracranial hemorrhage in adults showed that rFVIIa was able to control the expansion of intracranial hematomas in elderly patients, thereby improving their neurologic outcome and significantly decreasing mortality. Serious thromboembolic events, however, were higher in the treated groups (7% vs. 2% for placebo).¹⁶ For nontraumatic intracranial bleeding, if it has been less than 4 hours since onset of symptoms or for cases of anticoagulated patients with expanding hematomas, rFVIIa has been found beneficial.³⁰ Further trials are under way at this time.³⁶ We have not used rFVIIa for this indication as of yet, but in such a patient, we would use a dose of 80 to 90 μg per kg as a single dose, preferably after radiologic confirmation of an intracranial bleed.

7. Other off-label conditions. Various other conditions involving severe hemorrhage have also been treated with rFVIIa. In some cases, rFVIIa has been used because of religious objections to transfusion.³⁷ In a group of 10 children with various coagulopathies, there were positive responses in all, with no adverse effects.²⁷ There is another report of 3 patients in which this agent was used for the rapid correction of coagulopathy before neurosurgical procedures. All of these patients also received FFP. In 3 patients with post-marrow transplant pulmonary hemorrhage, there was transient clinical benefit, but renewed bleeding subsequently led to discontinuation of rFVIIa therapy. In cases such as these, the use of rFVIIa should be regarded as adjunctive and experimental.

SUMMARY

Recombinant FVIIa has demonstrated great potential in achieving hemostasis in patients refractory to traditional treatments.²⁴ Owing to the significant cost and uncertain benefit in many clinical situations, however, it should not be used indiscriminately. For off-label use in the setting of serious bleeding refractory to standard hemostatic therapies, a maximum of two doses may be considered appropriate, with further doses being given only after additional expert consultation.³¹ We believe that it is appropriate for the transfusion service or pharmacy to control the use of rFVIIa for release in patients. Content experts with experience in hemostasis are appropriate gatekeepers for this type of therapy. In patients with hemophilia and inhibitors, this therapy is effective and safe and should be available for treatment by physicians experienced in therapy of bleeding disorders. In FVII deficiency, given the small number of patients and the labeled indication, the therapy should be available for use by physicians appropriately experienced in treating this condition. In some cases, where patients are in remote hospitals without specialists,

it could be released under guidance from a specialist via telemedicine or telephone consultation.

In acquired bleeding complications and inherited PLT disorders, it is impossible to claim robust efficacy or safety based on the data that are available. Obvious advantages of rFVIIa include rapid onset of action, low-volume dosing, the recombinant nature of the product alleviating infectious disease transmission potential, and generally, a low risk of thrombogenicity. There must be a caveat, however, that there are increasing cases being reported of thromboembolic manifestations—particularly after the drug is stopped.

Disadvantages include the substantial cost, the risk of thrombosis, the variability of current recommended dose and dosing intervals, the short half-life (particularly in children), limited data pertaining to safety and efficacy, and problems with monitoring its efficacy. Shortening of the PT does not completely reflect the *in vivo* effect of rFVIIa on the coagulation process and therefore is not reliable as a monitoring parameter. Newer methods of monitoring (thromboelastography, thrombin generation) are being used—but studies to validate these instruments in the monitoring of rFVIIa efficacy are still in the early stages.

Randomized controlled studies would be ideal and are badly needed. In the situation where rFVIIa must be used for relief of life-threatening bleeding in patients who do not respond to other forms of therapy, the use of an international registry (already available for pediatrics²⁸) should be encouraged.²⁷ Specialist physicians should be consulted in these situations and should release the drug on a case-by-case basis, evaluating the total picture and attempting to capture as much data from the treatment as possible. Careful analysis should assure that surgical bleeding has been fully addressed and that conventional hemostatic therapies have been optimized before rFVIIa is used.

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