

# Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: A systematic review

Marcel Levi, MD; Marjolein Peters, MD; Harry R. Büller, MD

**Background:** Recombinant activated factor VII (factor VIIa) is a prohemostatic agent that can be used for patients with complicated coagulation disorders. Recombinant factor VIIa is, however, increasingly used for several other indications, including patients with a preexistent normal coagulation system but who experience serious bleeding, for example, after major surgery or trauma.

**Data Source:** We performed a systematic review of all published and unpublished clinical studies using MEDLINE (1966–2004) and all other sources available to assess the available evidence on the efficacy and safety of recombinant factor VIIa in patients with or without coagulation disorders.

**Study Selection:** We found 483 articles related to the pharmacologic use of recombinant factor VIIa, including 28 clinical trials, 124 case series, and 176 case reports, which were all considered for this review.

**Data Synthesis:** Recombinant factor VIIa is an effective and

relatively potent prohemostatic agent in approximately 90% of patients with hemophilia and inhibiting antibodies and other types of complex coagulation disorders. The application of recombinant factor VIIa in other patients who experience severe bleeding is promising, and although sound evidence from controlled clinical trials is only scarcely available so far, forthcoming trials are likely to provide more substantiation for this use. Recombinant factor VIIa appears to be relatively safe with a 1–2% incidence of thrombotic complications based on published trials.

**Conclusions:** More randomized controlled clinical trials are required to assess the efficacy and safety of recombinant factor VIIa for patients without a preexistent coagulation disorder and with severe bleeding. In the meantime, off-label use of recombinant factor VIIa may be considered in patients with life-threatening bleeding. (Crit Care Med 2005; 33:883–890)

**KEY WORDS:** bleeding; coagulation; factor VIIa; transfusion

**R**ecombinant factor VIIa (eptacog alpha activated, Novoseven) was introduced to clinical medicine in the 1980s as a prohemostatic agent (1). Based on the current insight into the function of blood coagulation *in vivo*, recombinant factor VIIa is thought to act locally at the site of tissue injury and vascular wall disruption, by binding to exposed tissue factor and generating small amounts of thrombin that are sufficient to activate platelets. The activated platelet surface can then form a template on which recombinant factor VIIa can directly or indirectly mediate further activation of coagulation, resulting in the generation of much more thrombin and, ultimately, fibrinogen to fibrin conversion (2, 3). Clot formation is stabilized by inhibition of fibrinolysis, due to factor VIIa-mediated activation of

thrombin-activatable fibrinolysis inhibitor.

Initially, recombinant factor VIIa was used in patients with congenital or acquired hemophilia and inhibiting antibodies toward factor VIII or IX, for which it has been licensed in the United States, Europe, and many other parts of the world (4). In recent years, the potential of recombinant factor VIIa to act as a prohemostatic agent in other categories of patients with coagulation defects or in patients with a preexistent normal coagulation system but who experience excessive bleeding, for example, as a result of trauma or surgery, has been explored (5). In this article, we systematically review the available evidence on the efficacy and safety of recombinant factor VIIa in various clinical situations.

## METHODS

**Search Strategy and Selection Criteria.** We searched MEDLINE (January 1966–July 2004) using the terms “recombinant factor VIIa,” “activated factor VII,” “Novoseven,” and “eptacog alpha” and the MESH term “factor VIIa,” including all subheadings. Based on the title and abstract of the publication, we retrieved English-language and non-English-

language articles containing clinical data on the use of recombinant factor VIIa for review. The references of all reports were cross-checked for other potentially relevant articles. We searched for both published and unpublished trials, contacting researchers and the manufacturer of recombinant factor VIIa.

All authors reviewed all articles, which were classified as clinical trial, case series, case report, or literature review. To be classified as a clinical trial, the report should consist of a prospective series of patients treated with recombinant factor VIIa in whom a predefined outcome was assessed, with or without a (placebo) control group. Reports describing the effect of the administration of recombinant factor VIIa in patients with various conditions were classified as case reports, whereas case series were defined as case reports in which more than three patients were reported. Articles on the use of recombinant factor VIIa that did not contain original clinical data or reported on previously published data were classified as other articles. Available data on setting, patient type, type of intervention, outcomes reported, and other findings as well as methodological quality of the publication (6) were independently extracted from the retrieved articles by all authors. It was envisaged that studies would be too heterogeneous to be combined for a formal meta-analysis, and therefore a narrative synthesis, mainly focusing on clinical trials, was undertaken.

From the Department of Vascular Medicine/Internal Medicine (ML and HRB) and Department of Pediatrics (MP), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

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## RESULTS

**Study Identification.** The literature search yielded 635 articles, of which 152 did not relate to the administration of recombinant factor VIIa to humans. Of the remaining 483 articles, there were 28 clinical trials, 124 case series, 176 case reports, and 155 other articles. The total number of patients reported in these publications was 1,854 (Fig. 1).

**Congenital and Acquired Hemophilia A and B.** We found 156 articles related to the use of recombinant factor VIIa in patients with hemophilia A or B and inhibiting antibodies toward factors VIII or IX, respectively. The first reports on the use of recombinant factor VIIa in hemophilia concern the efficacy of the agent in two bleeding patients with severe hemophilia A and a high-titer inhibitor against factor VIII and similar patients who underwent uncomplicated synovectomy of the knee covered by the administration of recombinant factor VIIa (1, 7). Hereafter, another 36 case reports and 66 case series (encompassing 408 patients) described the use of recombinant factor VIIa in patients with hemophilia and inhibiting antibodies. Virtually all reports claimed that recombinant factor VIIa was successful in stopping or preventing bleeding in these patients. A more systematic compilation of data comes from two international databases of patient data (8). The Compassionate Use Program included 195 patients with hemophilia and inhibiting antibodies and 36 patients with acquired hemophilia with >1,000 bleeding episodes, treated with recombinant factor VIIa usually at a dose of 90  $\mu\text{g}/\text{kg}$ . There was satisfactory hemostasis (i.e., success-

ful arrest of bleeding within 2–3 hrs and no need for transfusion) in 80–87% of serious bleeding episodes and in 91–94% of surgical bleedings. The Emergency Treatment Program included 253 bleeding episodes from 127 patients. Administration of recombinant factor VIIa (almost invariably 90  $\mu\text{g}/\text{kg}$ ) was effective in 93% of hemophilia patients and in 71% of acquired hemophilia patients.

In addition, there are 11 clinical trials with recombinant factor VIIa in 293 patients with hemophilia and inhibitors against factor VIII or IX, of which one study concerns the use of this agent in patients with bleeding, one trial was done in patients undergoing surgery, one trial specifically concerns patients with acquired hemophilia, four trials studied home treatment with recombinant factor VIIa, and four trials regard the continuous infusion of the drug (9–19). These trials are summarized in Table 1. All trials indicate that recombinant factor VIIa at a dose of 90  $\mu\text{g}/\text{kg}$  and an initial dosing interval of 2–3 hrs was effective in controlling active bleeding (9) or preventing blood loss during invasive procedures (10) in about 80–90% of the cases. This dose of recombinant factor VIIa corresponded to a plasma factor VII:c level of 20–30 IU/mL. Lower doses, resulting in a plasma concentration of factor VII:c of 10 IU/mL, were effective in only 50–60% of patients. An important factor in determining the efficacy of factor VIIa in bleeding patients appears to be the interval between the onset of bleeding and the administration of the agent. Therefore, a number of studies focused on home treatment with recombinant factor VIIa, al-

lowing initiation of treatment within 2–3 hrs after the onset of bleeding (12–15). The results of these four studies in 92 patients with 875 bleeding episodes indicated a somewhat higher treatment efficacy of 90% in most studies and a smaller number of injections with recombinant factor VIIa per bleeding episode. In case of surgery or invasive procedures, the effect of recombinant factor VIIa is immediate (i.e., the agent should be administered as briefly before the intervention as possible). The three trials on the use of continuous infusion of recombinant factor VIIa at a dose of 16.5  $\mu\text{g}/\text{kg}/\text{hr}$  after an initial bolus dose of 90  $\mu\text{g}/\text{kg}$  showed that the total daily dose of factor VIIa was indeed lower compared with repeated bolus injections; however, this approach was only moderately effective in controlling bleeding (50–80% of the cases). A subsequent study, using a continuous dose of 50  $\mu\text{g}/\text{kg}/\text{hr}$  of recombinant factor VIIa, showed that the attained plasma level of 30 IU/mL was associated with a better efficacy (88%) (19). However, with this dose regimen there was no saving in the total amount of factor VIIa used. There is no randomized comparison of repeated bolus injection vs. continuous infusion of recombinant factor VIIa.

**Other Coagulation Disorders.** The successful application of recombinant factor VIIa in patients with hemophilia and inhibitors prompted many clinicians to use this agent in other complicated coagulation disorders. We found 109 articles on the use of recombinant factor VIIa in 242 patients with coagulation disorders other than hemophilia A or B. Of these, 68 articles are case reports and 22 are case series, which virtually all claim that recombinant factor VIIa was effective in achieving hemostasis. The majority of these reports regard the use of recombinant factor VIIa in patients with platelet disorders. There are three clinical studies, one concerning the use of recombinant factor VIIa in patients with Glanzmann thrombasthenia, one in patients with severe thrombocytopenia, and one including patients with a congenital factor VII deficiency. The remaining 16 articles are other manuscripts.

Platelet defects represent a group of coagulation disorders that may be difficult to treat, in particular when trying to avoid the formation of allo-antibodies associated with platelet transfusion or when these antibodies are already present. Administration of recombinant factor VIIa was shown to result in satis-

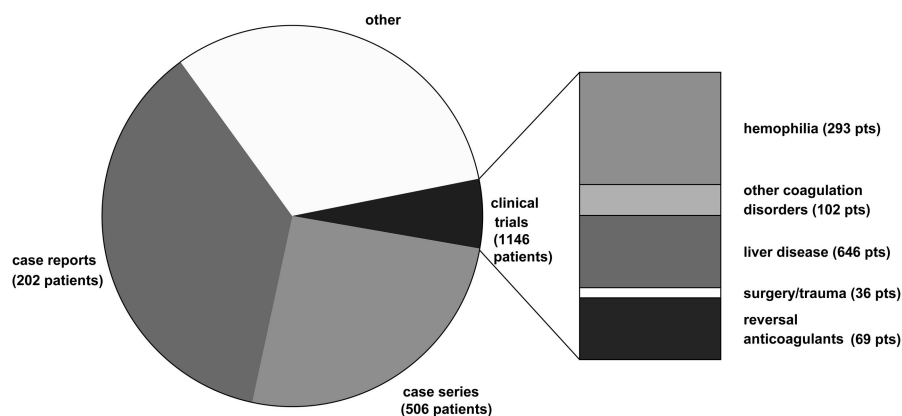


Figure 1. Published literature on recombinant factor VIIa until July 2004. The majority of publications regard case reports and case series (36% and 26%, respectively). There are 28 clinical trials (6%), 11 in hemophiliacs, three in patients (pts) with other coagulation defects, seven in patients with liver disease, one in surgical patients, and six concerning reversal of anticoagulation.

Table 1. Trials with recombinant factor VIIa in hemophilia

Study	Patients	Setting	No.	Bleeding Episodes	Dose	No. of Injections	Efficacy <sup>a</sup>
Bleeding/surgery							
Lusher et al. (9)	Hemophilia/inhibitors	Bleeding	84	179	Randomization 90 µg/kg or 35 µg/kg	3.1	Both doses: 91% effective or partially effective
Shapiro et al. (10)	Hemophilia/inhibitors	Surgery	29	—	Randomization 90 µg/kg or 35 µg/kg	42	71% fully effective 90 µg/kg: 100% effective first 48 hrs, 80–100% through day 5 35 µg/kg: 80% effective first 48 hrs, 40–70% through day 5
Hay et al. (11)	Acquired hemophilia	Bleeding	38	14 first line 60 salvage	90 µg/kg	28	First line: 100% Salvage: 75% good, 17% partial
Home treatment							
Ingerslev et al. (12)	Hemophilia/inhibitors	Bleeding	5	50	90 µg/kg	2	92%
Santagostino et al. (13)	Hemophilia/inhibitors	Bleeding	10	53	90 µg/kg	2	Fully effective: 79% Effective or partially effective: 90%
Laurian et al. (14)	Hemophilia/inhibitors	Bleeding	21	58	90 µg/kg	3	88%
Key et al. (15)	Hemophilia/inhibitors	Bleeding	56	614	90 µg/kg	2.2	92%
Continuous infusion							
Smith et al. (16)	Congenital/acquired hemophilia	Surgery	8	—	16.5 µg/kg/hr after bolus 90 µg/kg		38%
Santagostino et al. (17)	Congenital/acquired hemophilia	Bleeding/surgery	28	35	16.5 µg/kg/hr after bolus 90 µg/kg		80%
Chuansumrit et al. (18)	Hemophilia/inhibitors	Bleeding	5	9	16.5 µg/kg/hr after bolus 90 µg/kg		66%
Ludlam et al. (19)	Hemophilia/inhibitors	Orthopedic surgery	9	—	50 µg/kg/hr after bolus 90 µg/kg		88%

<sup>a</sup>Good efficacy is considered as excellent, complete, or satisfactory response.

factory hemostasis in patients with bleeding due to a wide spectrum of platelet defects, including Glanzmann thrombasthenia, Bernard-Soulier syndrome, myelodysplasia, and platelet-type von Willebrand disease (20, 21). In a small clinical study of four children with Glanzmann thrombasthenia, recombinant factor VIIa was given for 24 episodes of bleeding or invasive procedures (22). In 23 of 24 cases (96%), good hemostatic efficacy was achieved, although there was recurrence of bleeding in two cases. The dose of recombinant factor VIIa was 90 µg/kg every 2 hrs. For severe bleeding episodes, the median number of doses required was five (range, 1–18). An international survey of 59 patients with Glanzmann thrombasthenia showed efficacy of recombinant factor VIIa in 29 of 31 evaluable invasive procedures and in 77 of 103 bleeding episodes. Administration of recombinant factor VIIa was more successful at doses of >80 µg/kg and with repeated dosing (23). Recently, recombinant factor VIIa was licensed in Europe for use in patients with Glanzmann's disease. Based on the observation that high doses of recombinant factor VIIa could reduce blood loss in severely thrombocy-

topenic animals (24), initial clinical studies were performed in three patients undergoing bone marrow transplantation and severe thrombocytopenia. In two patients, a transient partial response after administration of recombinant factor VIIa was observed (cessation of bleeding at the initial site but recurrent bleeding at another site), and in one patient there was no effect on bleeding (25). In a prospective study, the administration of recombinant factor VIIa shortened the bleeding time in 52% of 74 patients with acute myeloid leukemia and thrombocytopenia (26). When a patient had a platelet count of  $>20 \times 10^9/L$ , recombinant factor VIIa was more effective. In six of eight patients with active bleeding in this trial, recombinant factor VIIa resulted in complete cessation of bleeding, whereas in two patients there was a partial response. A randomized placebo-controlled trial with recombinant factor VIIa in patients undergoing allogeneic stem cell transplantation is presently ongoing (27).

Factor VII deficiency is a relatively rare congenital coagulation disorder that in case of bleeding may be treated with plasma-derived factor VII concentrate. Recombinant factor VIIa was used in the

earlier mentioned Compassionate Use Program in 29 factor VII deficient patients and was shown to be effective in 89% (8). In a clinical study of 21 bleeding episodes in ten patients with factor VII deficiency, the efficacy rate of recombinant factor VIIa was 95% (28). Generally, the effective dose of recombinant factor VIIa used in patients with factor VII deficiency (10–30 µg/kg every 4–6 hrs) is lower than the dose used in patients with hemophilia A or B.

Other coagulation defects in which recombinant factor VIIa was shown to be effective include acquired von Willebrand disease, factor V deficiency, and factor XI deficiency (29).

**Liver Disease.** Liver disease is often associated with a coagulopathy, which may be a major contributor to morbidity and mortality of affected patients. Invasive procedures in patients with advanced liver disease are frequently complicated by bleeding. We identified 37 articles on the use of recombinant factor VIIa as a prohemostatic intervention in 684 patients with liver disease. Of these articles, 21 are case reports, seven are case series, and two are review articles. There are seven clinical trials with recombinant

factor VIIa in patients with liver disease (30–35).

A dose-finding study in ten cirrhotic patients with coagulation abnormalities showed a normalization of the prolonged prothrombin time (PT) in all subjects immediately after injection of recombinant factor VIIa at a dose from 5 to 80  $\mu\text{g}/\text{kg}$  (30). It should be mentioned, however, that normalization of the PT does not automatically imply correction of the hemostatic defect, since the PT (which is based on incubation of plasma with tissue factor) is extremely sensitive for factor VIIa. Hence, the effect on the PT may be an *ex vivo* effect rather than reflecting *in vivo* correction of hemostasis. A second study in ten patients with cirrhosis and bleeding from esophageal varices confirmed the correction of the PT by a single injection of recombinant factor VIIa (80  $\mu\text{g}/\text{kg}$ ) but also showed immediate bleeding control in all patients (31). Of note, it is not clear whether patients were also treated endoscopically in this trial, and also the absence of a placebo control makes proper interpretation of the results difficult. Based on the results from these two studies, a placebo-controlled trial in 245 patients with liver cirrhosis and portal hypertension, presenting with upper gastrointestinal bleeding, was performed (32). In this study, the administration of recombinant factor VIIa at a dose of 100  $\mu\text{g}/\text{kg}$  in addition to endoscopic and pharmacologic treatment resulted in a two-fold reduction of the proportion of patients in whom variceal bleeding could not be controlled (7.9% in the recombinant factor VIIa groups compared with 15.4% in the placebo group). This effect was only seen in patients with Child B-C cirrhosis and not in those with Child A cirrhosis. Further evidence on the efficacy of recombinant factor VIIa in liver disease comes from a randomized dose-ranging study in 71 patients undergoing laparoscopic liver biopsy (33). In this uncontrolled study, complete hemostasis within 10 mins was observed in 74% of patients at doses between 5 and 120  $\mu\text{g}/\text{kg}$ , administered immediately before the procedure, with no clear dose-response relationship. Additionally, 20% of patients were given a rescue dose of recombinant factor VIIa (80  $\mu\text{g}/\text{kg}$ ), which was successful in all patients. None of the patients required transfusion or surgical intervention. Another area where the administration of recombinant factor VIIa might be effective is liver transplantation. An initial open-label pi-

lot study in six patients undergoing orthotopic liver transplantation showed a strong reduction in transfusion requirements in patients who received a single dose of recombinant factor VIIa (80  $\mu\text{g}/\text{kg}$ ) compared with historic matched controls (34). However, an unpublished randomized placebo-controlled trial in liver transplantation did not show a reduction in transfusion requirements by administration of recombinant factor VIIa (80  $\mu\text{g}/\text{kg}$ ). Last, the efficacy of recombinant factor VIIa to prevent blood loss and transfusion requirements was studied in a randomized placebo-controlled trial in 204 patients undergoing partial hepatectomy. Administration of recombinant factor VIIa at a dose of 80  $\mu\text{g}/\text{kg}$  resulted in reduced blood loss compared with placebo, and the proportion of patients receiving postoperative blood transfusion decreased from 37% to 25% ( $p = .05$ ) (35).

**Surgery and Trauma.** Surgery and trauma, associated with major blood loss, may be another potentially interesting area for recombinant factor VIIa. This is illustrated by 21 case reports, 12 case series, and 14 other articles regarding the use of recombinant factor VIIa for this indication (84 patients); however, there is only one randomized placebo-controlled trial (36). In this trial, 36 patients undergoing abdominal prostatectomy, which is associated with major blood loss, were randomized to a single injection of recombinant factor VIIa (20 or 40  $\mu\text{g}/\text{kg}$ ) or placebo during the operation. Administration of recombinant factor VIIa (40  $\mu\text{g}/\text{kg}$ ) at the beginning of the operation resulted in a 50% reduction of blood loss compared with placebo and eliminated the need for blood transfusion, which was required in about 60% of placebo-treated patients. Patients who received 20  $\mu\text{g}/\text{kg}$  recombinant factor VIIa showed a smaller (35%) but still significant reduction in blood loss, and of these patients 38% needed a blood transfusion. This relatively small study was the first to show that administration of recombinant factor VIIa in patients with a preexistent normal coagulation system could reduce blood loss and transfusion requirements in major surgery.

Bleeding is one of the leading causes of death in patients with severe trauma. Several case reports and case series indicate that recombinant factor VIIa may potentially be effective in reducing excessive blood loss and transfusion requirements in these patients (37, 38). Experi-

ments in hypothermic coagulopathic swine (but not in noncoagulopathic swine) with severe liver injury showed a reduction in blood loss by recombinant factor VIIa (39, 40). A large placebo-controlled trial of recombinant factor VIIa (400  $\mu\text{g}/\text{kg}$  in three doses) in 301 patients with severe blunt and/or penetrating trauma, aiming to achieve a reduction in transfusion requirements, has recently been completed. A preliminary report regarding this study showed a significant reduction of red cell transfusion in patients with blunt trauma and a trend toward a reduced incidence of multiple organ failure and acute respiratory distress syndrome in patients receiving recombinant factor VIIa. Mortality in blunt trauma patients receiving recombinant factor VIIa was 25% in comparison to 30% in the placebo group (not significant) (41).

**Reversal of Anticoagulant Therapy.** There are 28 articles on reversal of anticoagulant therapy with recombinant factor VIIa, of which six are clinical trials (total 106 subjects). In healthy volunteers who were treated with the vitamin K antagonist acenocoumarol, the prolongation of the international normalized ratio (INR) above 2.0 was normalized with the administration of recombinant VIIa at doses between 5 and 320  $\mu\text{g}/\text{kg}$  (42). The duration of the INR correction was dependent on the dose of recombinant VIIa, whereby doses of rVIIa >120  $\mu\text{g}/\text{kg}$  resulted in an INR normalization that lasted >24 hrs. As mentioned previously, normalization of the INR or the prothrombin time does not automatically imply reversal of the anticoagulant effect or an adequate prohemostatic response. Nevertheless, five case reports and ten case series claimed effective arrest of bleeding by administration of recombinant factor VIIa to patients who were treated with vitamin K antagonists or the ability to safely perform invasive procedures in warfarin-treated patients by administration of recombinant VIIa (43). A series of six patients with central nervous system bleeding due to treatment with vitamin K antagonists showed successful reversal of anticoagulation, arrest of bleeding, and uncomplicated surgical drainage of the hematoma in all patients after administration of 40  $\mu\text{g}/\text{kg}$  recombinant factor VIIa (44). A recent study demonstrated that reversal of warfarin anticoagulation by recombinant factor VIIa (15–90  $\mu\text{g}/\text{kg}$ ) in a series of 13 patients undergoing invasive procedures re-

sulted in a normalization of the prothrombin time and prevented bleeding in all subjects (45). It should be mentioned, however, that the duration of the effect of recombinant factor VIIa is rather short (2–3 hrs) in comparison with prothrombin complex concentrates (about 8 hrs) and that prothrombin complex concentrates have the advantage that not only a deficiency of factor VII but also the deficiency of other vitamin K proteins is corrected. In addition, recombinant factor VIIa is more expensive than prothrombin complex concentrates.

Of interest, recombinant factor VIIa seems effective in blocking the anticoagulant effect of various new anticoagulant agents for which no alternative antidote is available. In two randomized placebo-controlled crossover studies in volunteers treated with the pentasaccharide fondaparinux or its very long-acting analogue idraparinux, a single injection with rVIIa (90  $\mu\text{g}/\text{kg}$ ) normalized the prolonged activated partial thromboplastin and PT and reversed the decrease in markers for thrombin generation (46, 47). These results suggest that recombinant factor VIIa might be useful to reverse the anticoagulant effect of pentasaccharides in case of serious bleeding complications, although there is no report on the efficacy of rVIIa in a patient with bleeding during treatment with pentasaccharides. Similarly, recombinant factor VIIa was shown to reverse the anticoagulant effect of a new anticoagulant aimed at inhibition of tissue factor (48). It is less clear whether recombinant factor VIIa can be used as an antidote for the new direct thrombin inhibitor (xi)melagatran. In a recently conducted controlled clinical study in healthy subjects, the melagatran-induced effects on activated partial thromboplastin, thrombin generation, and platelet activation were not affected by the administration of recombinant factor VIIa at a dose of 90  $\mu\text{g}/\text{kg}$  (49). However, since in this study recombinant VIIa was able to increase thrombin precursor protein concentrations, it might be that higher doses of recombinant VIIa will have some effect in this situation, but this needs to be studied in future experiments.

*Excessive or Life-Threatening Bleeding.* We identified 33 articles specifically dealing with the use of recombinant factor VIIa in 37 patients with excessive and/or life-threatening bleeding. There are no clinical trials on the use of recombinant factor VIIa in these patients,

which is no surprise in view of the heterogeneous patient group and the difficulty of performing a sound study in this situation. Twenty-one case reports and five case series report on the effective use of recombinant factor VIIa in this situation, in most cases resulting in a rapid reduction of blood loss or decrease in transfusion requirement. Most cases deal with excessive blood loss after surgery, in which all other therapeutic measures had failed. A recent retrospective analysis of ten patients with excessive blood loss and massive transfusion showed cessation or reduction of bleeding in 60% of patients treated with recombinant factor VIIa but no effect on overall survival in comparison with patients who had not received recombinant factor VIIa (50). Since the decision to administer recombinant factor VIIa was not random, this result is difficult to interpret.

A specific situation is represented by patients with spontaneous intracranial hemorrhage. Preliminary results from a recently completed, yet unpublished, placebo-controlled dose-finding trial (400 randomized patients) indicate that administration of recombinant factor VIIa (in doses from 40 to 160  $\mu\text{g}/\text{kg}$ ) results in a reduction of hematoma size on repeated computed tomography scan of the brain and a 35% reduction in mortality as well as an improved disability score at 90 days follow-up (51).

*Adverse Events.* The hemostatic system is responsible for the delicate balance between clot formation (e.g., if disruption of the vessel wall causes bleeding) and maintaining fluidity of the blood in the circulation (thereby guaranteeing an adequate blood supply). Any intervention in the coagulation system aimed at each of these two functions may simultaneously affect the other function. Hence, the prohemostatic properties of recombinant factor VIIa may theoretically have a downside in the form of potential thrombotic complications associated with its use (52). In particular, clinical conditions that are mediated by tissue factor exposure to the circulation may theoretically carry the risk of adverse thrombotic reactions upon the administration of recombinant factor VIIa. An example of such a condition may be the patient with a semiruptured atherosclerotic plaque that is known to contain abundant tissue factor. In this situation, recombinant factor VIIa may hypothetically precipitate an acute thrombotic event, such as a myocardial infarction. Another condition that

is associated with systemic tissue factor exposure to the circulation is disseminated intravascular coagulation (DIC), due to exposure of tissue factor on circulating mononuclear cells (53), whereby administration of recombinant factor VIIa could theoretically lead to a more severe coagulopathy and aggravate systemic microvascular thrombosis.

In patients with hemophilia, the estimated incidence of serious adverse events due to administration of recombinant factor VIIa, including thrombotic complications, was about 1%. In 664 patients with hemophilia A or B participating in clinical trials with recombinant factor VIIa, there were seven thromboembolic events (1%) (54). In addition, there are case reports of myocardial infarction in six patients with hemophilia (three congenital and three acquired), of which five patients were known to have coronary artery disease (55, 56). A recent article estimated that the incidence of thrombotic events associated with the use of recombinant factor VIIa is 24.6 per  $10^5$  infusions compared with a rate of 8.2 per  $10^5$  infusions of activated prothrombin complex concentrate (57). DIC appears to be a very infrequent complication during treatment with recombinant factor VIIa (only five patients reported) and was mostly considered not to be attributable to this agent. In fact, all reports on DIC in association with recombinant factor VIIa are related to patients who already had DIC or were at high risk to develop DIC (e.g., septic patients). In our literature search, there were 15 patients in whom recombinant factor VIIa was used for severe bleeding, despite the concomitant presence of DIC. These cases concern patients with (acquired) hemophilia or severe liver failure, most with infectious problems complicated by DIC. Remarkably, recombinant factor VIIa was reported to be effective in 14 of these 15 patients, and in none of these patients were there signs of escalation of the DIC.

Pooling of all reported cases in which a coagulation defect other than hemophilia was treated with recombinant factor VIIa results in an estimated incidence of thromboembolism in 1.4% of patients (upper limit 95% confidence interval, 1.9%). When the recently completed placebo-controlled trials are included in this analysis, the incidence of adverse events is likely to be even lower, although the full data of these studies have not yet been published. In virtually all cases, there are other factors that may at least

be partially responsible for the occurrence of thrombosis, such as the simultaneous use of activated prothrombin complex concentrates or the presence of sepsis and an associated systemic inflammatory response. Also, in a considerable number of thrombotic complications, the temporal relationship between the administration of recombinant factor VIIa (which has a half-life of 2–3 hrs) and the thrombosis (often several days later) makes a causal relationship more difficult. Similar data come from studies and reports on the use of recombinant factor VIIa in surgery and trauma. In the earlier mentioned prostatectomy trial, in which 36 patients with a normal coagulation system were included, patients were daily monitored for arterial or venous thrombotic complications, but no adverse events occurred during the study (36). One patient developed a myocardial infarction outside the study but 11 days after the administration of a low dose (20 µg/kg) of recombinant factor VIIa. Also here, the long interval between infusion of recombinant factor VIIa and the myocardial infarction made a causal relationship less likely.

Together, the available evidence tentatively indicates that the risk of thromboembolic complications due to factor VIIa is low, although safety data from placebo-controlled studies with recombinant factor VIIa are scarce. Nevertheless, a more precise safety profile of recombinant factor VIIa is required to more accurately assess its place in prevention and treatment of excessive bleeding. The ongoing placebo-controlled trials will be helpful in that respect.

## DISCUSSION

It may be concluded from the available evidence that recombinant factor VIIa is a potent prohemostatic agent that can be used in patients with serious and complicated coagulation defects to arrest or to prevent bleeding. In particular in patients with hemophilia and inhibiting antibodies toward coagulation factor VIII or IX, the available evidence in several hundreds of patients indicates that recombinant factor VIIa is an effective agent and may have fewer side effects than alternative treatment strategies, although there are no clinical studies directly comparing recombinant factor VIIa with, for example, activated prothrombin complex concentrates. Therefore, recombinant factor VIIa may be considered as first line treat-

ment to stop or prevent bleeding in specific subsets of these patients, for example, those with high-titer inhibitors. Early treatment with recombinant factor VIIa, for example, by self-administration at home, seems to be more effective than delayed treatment or salvage treatment. Based on the current understanding of the mechanism of action of recombinant factor VIIa, it is not surprising that repeated bolus injections are more effective than continuous administration, in particular for severe bleeding or major surgery.

In view of its apparently potent prohemostatic effect, recombinant factor VIIa is a promising agent for application in other patients who suffer from major bleeding, albeit that clinical database is much smaller than in hemophilia. Initial reports in these categories of patients show encouraging results but need confirmation in methodologically sound clinical trials. In particular, the use of recombinant factor VIIa in patients with liver disease and active bleeding or those undergoing invasive procedures is promising. Also, in patients with major trauma, where the proper management of bleeding may be critical for survival in a substantial proportion of patients, there is a large need for potent adjunctive prohemostatic treatment, and recombinant factor VIIa may be able to fulfill that requirement. For both indications, ongoing controlled clinical trials will provide the answer in the near future.

It is interesting to note that administration of recombinant factor VIIa was shown to generate a prohemostatic response in subjects treated with new generation anticoagulants, for which no other antidotes exist. Despite the fact that specific antidotes for anticoagulated patients are infrequently used (58), the absence of a suitable strategy to reverse anticoagulant therapy that is complicated by major bleeding, in particular concerning long-acting agents, may hamper the clinical use of the agents (59). The efficacy of recombinant factor VIIa as a potential agent to reverse the anticoagulant effects may be helpful in this respect, although so far the evidence is based on laboratory results and limited clinical observation.

The application of recombinant factor VIIa in patients with life-threatening bleeding, in whom all other hemostatic treatments have failed, is also attractive, and its potential is illustrated by a number of case reports. However, the risk of

**R**ecombinant factor VIIa is a promising potent prohemostatic agent that can be used for treatment and prevention of severe bleeding in patients with complex coagulation disorders but probably also in a number of other clinical conditions that are dominated by serious blood loss.

publication bias should be taken into consideration here. It is feasible that successful use of a new agent or a dramatic effect in a severely ill patient is more likely to generate enthusiasm with authors to report the case and with editors to publish these reports.

It is not clear at what stage recombinant factor VIIa should be administered. Since the efficacy and safety of recombinant factor VIIa have not been characterized in randomized controlled studies, it may be argued that the safest approach is to administer the agent only if all other treatment has failed. However, if the agent is given too late, ongoing bleeding and transfusion may have resulted in such a derangement of the coagulation system that the drug is less effective. There are studies comparing early vs. late administration of recombinant factor VIIa in this situation.

The safety of recombinant factor VIIa is an important issue that deserves attention. Rather surprisingly, the incidence of thrombotic and other serious adverse events is relatively low. Here, the effect of publication bias may actually be little, since in view of the fear of thrombotic complications but the perceived safety of the agent, it can be hypothesized that authors and editors are willing to report adverse events with recombinant factor VIIa. Also, the safety data from the clinical trials are reassuring. Nevertheless, it is important that the safety of recombinant factor VIIa be adequately and sys-

tematically assessed for each clinical situation in which it is used. While we await such systematic safety data, the use of recombinant factor VIIa in these circumstances should—in our view—be restricted to life-threatening situations.

A last remark concerns the cost of recombinant factor VIIa. A single 90 µg/kg dose of this agent to a 80-kg person costs US\$4,500, and in some patients repeated dosing is necessary. These costs should obviously be offset against the cost of the management of severe bleeding, including costs of blood transfusion. It is conceivable that systematic cost-effectiveness analyses regarding the use of recombinant factor VIIa will be part of the decision making on the use of this agent in various clinical situations.

## CONCLUSIONS

Recombinant factor VIIa is a promising potent prohemostatic agent that can be used for treatment and prevention of severe bleeding in patients with complex coagulation disorders but probably also in a number of other clinical conditions that are dominated by serious blood loss. Administration of recombinant factor VIIa is relatively safe. Appropriately controlled clinical trials will definitively assess the place of recombinant factor VIIa for these conditions.

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