

Evidence Supporting the Use of Recombinant Activated Factor VII in Congenital Bleeding Disorders

Pär I Johansson¹ and Sisse R Ostrowski²

1. Medical Director; 2. Consultant, Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, University of Copenhagen

Abstract

Recombinant activated factor VII (rFVIIa) [NovoSeven] was introduced in 1996 for the treatment of haemophilia patients with inhibitors (HPIs) to factor VIII or IX. This article reviews the evidence for the use of rFVIIa in congenital bleeding disorders. English-language databases were searched in September 2009 for reports of randomised controlled trials (RCTs) evaluating the effect of rFVIIa on haemostasis in congenital bleeding disorders. Eight RCTs comprising 256 HPIs were identified. The evidence for the use of rFVIIa in HPIs in terms of dose, clinical setting, modes of administration, efficacy and adverse events was weak, given the limited number of patients included and the heterogeneity of the RCTs. Overall, the haemostatic efficacy of rFVIIa varied from 25 to 100% in the studies reviewed; <1% of the patients receiving rFVIIa developed a thromboembolic adverse event. The authors suggest that the addition FVIIa therapy to HPIs should be based on the patient's ability to generate thrombin and form a clot, rather than being based on weight alone. Assays reflecting thrombin generation, such as whole-blood thrombelastography, have the potential to significantly improve the treatment of these patients.

Keywords

Recombinant activated factor VII (rFVIIa), haemophilia, randomised controlled trials (RCTs), bleeding, monitoring, thrombelastography

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Correspondence: Pär I Johansson, Medical Director, Section for Transfusion Medicine, Capital Region Blood Bank, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E: per.johansson@rh.regionh.dk

Patients with haemophilia are subject to recurrent bleeding episodes. Those with severe haemophilia have a reduced life expectancy, with liver disease/hepatocellular carcinoma and intracranial haemorrhage being the primary causes of death.¹ Some patients with haemophilia develop antibodies against the replaced coagulation factors, commonly denoted inhibitors, because they inactivate the biological activity of the replaced factors.² This is a major cause of morbidity and mortality in these patients.³ Surgery is avoided where possible as the presence of inhibitors makes it difficult to secure peri-operative haemostasis, although those with low-titre inhibitors face fewer clinical problems since haemostasis can usually be achieved by saturating the inhibitor with higher doses of the deficient factor.

However, in patients with high-titre inhibitors other treatment modalities must be used (plasmapheresis, immunoabsorption, immune tolerance induction) and/or their activity bypassed.

Factor Eight Inhibitor Bypassing Activity

Factor eight inhibitor bypassing activity (FEIBA), an activated prothrombin complex concentrate, has been used as a haemostatic bypassing agent in patients with high-responding inhibitors for decades.⁴ Recombinant activated factor VII (rFVIIa) [NovoSeven] was introduced as a haemostatic bypassing agent in 1996. It was initially used for the treatment of bleeds in patients with inhibitors, with a recommended dosing schedule of 90µg/kg rFVIIa every two to three hours until haemostasis was achieved.⁵ In 2007, the European Medicines Agency (EMA) approved the use of single-dose rFVIIa

270µg/kg for the treatment of mild-to-moderate bleeds in haemophilia patients with inhibitors.⁶ rFVIIa is currently a first-line treatment for bleeding episodes in patients with congenital haemophilia A and B with inhibitors and is used to treat patients with acquired haemophilia.^{7–9} In Europe, rFVIIa therapy has also been approved for the treatment of patients with congenital FVII deficiency or Glanzmann's thrombasthenia refractory to platelet transfusions.

The administration of pharmacological doses of rFVIIa (90µg/kg) induces haemostasis in the absence of FVIII or FIX. It probably does this by enhancing thrombin generation on the surface of the activated platelet leading to clot formation, with a stable near-normal fibrin clot network forming a strong haemostatic plug.⁵ rFVIIa also inhibits fibrinolysis *in vitro* in haemophilia A by induction of thrombin-activatable fibrinolysis inhibitor (TAFI) activation, improving clot stability.¹⁰ This article presents the evidence for the use of rFVIIa in congenital bleeding disorders.

Methods of the Studies Included

English-language databases were searched, including MEDLINE, ScienceDirect, CINAHL and Blackwell Science, for reports of randomised controlled trials (RCTs) that tested the effect of rFVIIa on haemostasis in patients with congenital haemophilia A and B, congenital FVII deficiency or Glanzmann's thrombasthenia. The inclusion criteria were prospective RCT, use of rFVIIa and presence of a control group. End-points investigated were the achievement of haemostasis and the development of thromboembolic complications.

Table 1: Randomised Clinical Trials Concerning Recombinant Activated Factor VII in Haemophilia Patients with Inhibitors

Study	Type	Intervention	Treated (n)	Response to Treatment	Thrombotic AE
Shapiro et al., 1998 ¹¹	Double-blind RCT	rFVIIa 35 versus 90µg/kg prior to incision, then every 2 hours or as needed for 48 hours, then every 2–6 hours for 3 days, thereafter 90µg/kg as needed	29	Treatment successful: low dose 67% versus high dose 93%, being significant from day 3 post-operatively; p<0.05	1 in the 35µg/kg group
Lusher et al., 1998 ⁸	Double-blind RCT	rFVIIa 35 versus 70µg/kg to treat joint, muscle and mucocutaneous bleedings	66	Treatment rated excellent in 61% (35µg/kg group) versus 57% (70µg/kg group); p=NS	None
Santagostino et al., 2006 ¹²	Multicentre open-label cross-over RCT	rFVIIa 270 versus 90µg/kg within 6 hours of joint bleed every 3 hours. If not haemostasis at 9 hours continue 90µg/kg up to 24 hours, then other options	18	Haemostasis at 9 hours 25% (high dose) versus 31% low dose; p=NS. Number of boluses needed in the high-dose (n=1) versus standard-dose (n=3) groups; p=0.0001	None
Kavakli et al., 2006 ¹³	Multicentre double-blind cross-over RCT	rFVIIa 270µg/kg + 0 + 0 at 3-hour intervals versus 3x90µg/kg at 3-hour intervals at first and second joint bleeding or <i>vice versa</i>	22	65% (270µg/kg) versus 70% (3 x 90µg/kg) achieved haemostasis; p=NS	None
Astermark et al., 2007 ¹⁴	Multicentre open-label cross-over RCT	1 dose FEIBA (75–100IU/kg) versus 2 doses rFVIIa 90–120µg/kg	48	FEIBA (80.9%) and rFVIIa (78.7%) exhibit similar effects on joint bleeds; p=0.059	None
Konkle et al., 2007 ¹⁵	Double-blind cross-over RCT	rFVIIa 270 versus 90µg/kg daily prophylaxis for 3 months compared with 3 months pre- and post-prophylactic period	22	Reduced bleeding frequency by 45% (90µg/kg) and 59% (270µg/kg), both p<0.001. No difference between dose groups	None
Pruthi et al., 2007 ¹⁶	Open-label multicentre RCT	Pre-operative bolus 90µg/kg and then BI every 2 hours during surgery to POD 5 and then every 4 hours to POD 10 versus CI 50µg/kg/hour to POD 5 and then 25µg/kg/hour to POD 10	24	Haemostatic efficacy was 73% in BI versus 75% in CI; p=NS	1 in the BI group
Young et al., 2008 ¹⁷	Multicentre double-blind cross-over RCT	270µg/kg + 0 + 0 every 3 hours versus 3x90µg/kg versus 75IU/kg FEIBA at time 0	27	Rescue medication needed within 9 hours was 8.3% (rFVIIa 270µg/kg), 9.3% (3x90µg/kg) and 36.4% (FEIBA), respectively. rFVIIa 270 and 3x90µg/kg versus FEIBA; p=0.032 and p=0.069, respectively. No difference between rFVIIa dose groups	None

AE = adverse event; BI = bolus infusion; CI = continuous infusion; FEIBA = factor eight inhibitor bypassing agent; NS = not significant; POD = post-operative day; RCT = randomised controlled trial; rFVIIa = recombinant activated factor VII.

Results of the Studies

Eight RCTs involving 256 haemophilia patients with inhibitors receiving rFVIIa were identified (see *Table 1*). Shapiro et al.¹¹ performed a RCT comparing rFVIIa (3,590 versus 90µg/kg) during and after elective surgery. Patients received rFVIIa immediately prior to incision: intra-operatively as needed, every two hours for the first 48 hours and every two to six hours for the following three days. Intraoperative haemostasis was achieved in 28 out of 29 patients. All high-dose patients and 12 out of 15 low-dose patients had satisfactory haemostasis during the first 48 hours. One patient, who had received the 35µg/kg dose, developed thrombosis of the right internal jugular vein after central venous catheter placement. A statistically significant difference was reported in efficacy from days three to five post-operatively in favour of the high-dose group compared with the low-dose group.

Lusher et al. investigated the effect of rFVIIa 35 versus 70µg/kg on haemostatic efficacy in patients with and without inhibitors having joint, muscle and mucocutaneous bleeds.⁸ This RCT demonstrated no significant difference between groups.

Santagostino et al.¹² reported on a multicentre, randomised, open-label cross-over trial comparing the efficacy and safety of standard (90µg/kg every three hours as needed) and high-dose (single dose of 270µg/kg) rFVIIa for home treatment of haemarthroses. Eighteen haemophiliacs

with inhibitors were included and similar success rates for standard- and high-dose regimens were reported.

A similar study was performed by Kavakli et al.¹³ Study compared one high dose of rFVIIa + two placebo doses with 3 medium doses of rFVIIa. In this multicentre RCT, patients were randomised to treatment of a first joint bleeding episode with one 270µg/kg rFVIIa dose followed by two doses of placebo at three-hourly intervals. Treatment of a second joint bleed was with three single doses of 90µg/kg rFVIIa at three-hourly intervals. The results showed a similar efficacy for both regimens.

Astermark and colleagues¹⁴ compared one dose of FEIBA (target dose, 85IU/kg) or two doses of rFVIIa (target dose, 105µg/kg x two), with the second dose of rFVIIa administered two hours after the first dose. The haemostatic effect of the treatment was evaluated by the patients up to 48 hours after administration. No significant differences were identified between groups. Efficacy at six hours – the primary outcome measured – was 80.9% in FEIBA patients versus 78.7% in the rFVIIa group (p=0.059).

Konkle et al.¹⁵ conducted a RCT using rFVIIa for secondary prophylaxis in inhibitor patients. Twenty-two patients were randomised 1:1 to receive daily rFVIIa prophylaxis with either 90 or 270µg/kg for three months. Bleeding frequency was reduced by 45 and 59% during

prophylaxis with 90 and 270µg/kg rFVIIa, respectively (both $p < 0.0001$). Patients reported significantly fewer hospital admissions and days absent from work/school during prophylaxis compared with the pre-prophylaxis period.

Pruthi et al.¹⁶ investigated the efficacy of bolus infusion (BI) versus continuous infusion (CI) of rFVIIa in inhibitor patients undergoing major surgery. All patients received an initial bolus of 90µg/kg rFVIIa and were then randomly assigned to BI ($n=12$) or CI ($n=12$). The BI group received 90µg/kg rFVIIa every two hours during surgery through day five, then every four hours for days six to 10. The CI group received 50µg/kg/hour rFVIIa through day five, then 25mg/kg/hour for days six to 10. The haemostatic efficacy of rFVIIa was similar in the BI and CI arms (73 and 75%, respectively).

Young et al.¹⁷ evaluated rFVIIa and FEIBA for controlling joint bleeds in a home treatment setting. Patients received each of three treatments in one of six possible sequences: 270µg/kg rFVIIa at hour 0 plus placebo at three and six hours, 90µg/kg rFVIIa at 0, three and six hours, and 75IU/kg FEIBA at 0 hours. Efficacy was assessed as the need for rescue treatment within nine hours of administration of the trial drugs. The percentage of rFVIIa 270µg/kg patients requiring additional haemostatics within nine hours was lower than for the FEIBA group (8 versus 36%, $p=0.032$).

No RCT conducted in patients with Glanzmann's thrombasthenia, Bernard-Soulier syndrome or in patients with acquired FVII deficiency were identified.

Discussion

This article found eight randomised clinical studies evaluating the haemostatic efficacy of rFVIIa in patients with haemophilia A and B with inhibitors. These studies included a total of 256 patients, with the majority of studies enrolling <30 patients. This limits conclusions on the efficacy and safety of rFVIIa in these patients.

Haemostatic Efficacy

When comparing studies evaluating the haemostatic efficacy of rFVIIa in patients undergoing surgery, Shapiro et al.¹¹ reported the effect of rFVIIa at 35 and 90µg/kg, where the high-dose patients had 93% haemostatic efficacy versus 67% in the 35µg/kg dose group. The results were significantly different from day three post-operatively. This study concluded that 90µg/kg was appropriate for surgical interventions. This thinking was recently challenged by Obergfell et al.¹⁸ who reviewed published data on elective orthopaedic surgical procedures in haemophilia patients with inhibitors. These authors found that increasing the dose or administering an extra dose, i.e. related to the inadequate amount of rFVIIa, could resolve most bleeding complications.

Therefore, they concluded that the optimal rFVIIa bolus dose for orthopaedic surgery might be higher than 90µg/kg. A minimum initial dose of 120µg/kg, followed every two hours by a similar dose or a 90µg/kg dosing regimen for BI was suggested.¹⁸

Four RCTs have been reported in the home-treatment setting. The percentage of patients reporting a successful response to rFVIIa treatment varied from 31 to 66%, which is well below the 80–90% efficacy rating often reported in the literature from non-randomised trials.^{7,19} The reason for this discrepancy is unclear, since RCTs and

observational studies in general are expected to yield similar efficacy.^{20,21} However, the higher haemostatic efficacy of rFVIIa reported from the non-randomised observational studies may be due to the fact that observational studies can include a wide spectrum of disease severity, with treatment tailored to the individual patient thereby introducing confounding by indication. Furthermore, the low number of subjects included in the RCTs^{8,12,13,17} may also explain the finding of broader, and hence less precise, efficacy ranges compared to the larger observational studies.^{7,19}

No significant differences in haemostatic efficacy following rFVIIa treatment^{12,13,17} and/or need for rescue medication^{13,17} were found between repeated standard dosing versus single high-dose rFVIIa administration in the RCTs reported here. Based on the evidence, high-dose rFVIIa (270µg/kg) was approved by the EMEA in 2007.

However, it should be noted that the three RCTs performed to date only involved 67 patients in total. This makes it difficult to exclude the possibility that a clinically significant difference between the treatment regimes may actually exist.

In terms of CI of rFVIIa versus BI doses, data indicate that CI at a dose of 50µg/kg/hour after a standard BI dose of rFVIIa results in acceptable haemostatic efficacy. These results suggest that it may be beneficial to consider adjunctive treatment with tranexamic acid, although a RCT is warranted.

When comparing the haemostatic efficacy of a standard dose (90µg/kg) of rFVIIa infused two¹⁴ or three times¹⁷ versus a single dose of FEIBA at 75–100IU/kg, different results emerge. Astermark et al.¹⁴ reported similar haemostatic efficacy (81% for FEIBA versus 79% for rFVIIa); whereas Young et al.¹⁷ reported a successful response in only 54% of the FEIBA-treated patients compared with 91–92% in the rFVIIa patients.

The difference in rFVIIa response between the two studies may, at least in part, be explained by different dosing schedules. The patients in the study by Young et al.¹⁷ received three doses at three-hourly intervals compared to only two doses in the Astermark study.¹⁴ With an estimated half-life of approximately 120 minutes for rFVIIa, three doses would result in a higher peak thrombin generation, maintaining a high thrombin generation for a longer period of time, compared with only two doses.

However, the different haemostatic responses to FEIBA reported in the two studies reviewed is less obvious.^{14,17} When comparing efficacy between rFVIIa and FEIBA, it could be argued that since the standard recommended dose of FEIBA is 50–100IU/kg every four to six hours and that of rFVIIa is 90µg/kg every two to three hours until haemostasis is achieved, the dose in the FEIBA and rFVIIa arms were markedly unmatched. This is a strong argument because it is assumed that the treatment efficacy depends on the dose of FEIBA administered at each infusion.²² This was illustrated in a study of six haemophilic patients with inhibitors experiencing 61 bleeds treated with FEIBA. There was definite cessation of bleeding in 93% of cases with a cumulative median dose of 205IU/kg per event.²²

One study evaluated the effect of rFVIIa in two doses (90 versus 270µg/kg) for secondary prophylaxis. This study demonstrated that bleeding frequency was halved during the three months of

prophylaxis treatment with rFVIIa in both treatment groups compared to the three-month pre-prophylaxis period. The median target joint bleeds before and during prophylaxis were respectively 11.5 versus 4 at 90µg/kg and 9 versus 2.5 at 270µg/kg (both $p < 0.001$).¹⁵

Secondary prophylaxis appears to be a promising alternative to on-demand therapy in haemophilia patients without inhibitors.^{23,24} Despite this, apart from the RCT included in this review,¹⁵ the scientific level of evidence using such therapy in secondary prophylaxis compared with on-demand treatment is low.

As outlined above, there is considerable difficulty in evaluating rFVIIa in haemophilia patients with inhibitors due to the apparent lack of standardisation in how haemostatic efficacy should be evaluated. In the home-treatment studies, efficacy was evaluated by the patients themselves^{12–14,17} or by the investigators.⁸ Different time-points for evaluation of haemostatic efficacy were used as primary end-points in the studies. There was also considerable heterogeneity in how haemostatic efficacy should be assessed and at what time-points haemostasis was assessed between RCTs and non-randomised studies.^{7,18,19,22,25–31} Obviously, this constitutes a significant problem for the interpretation and comparison of results from studies of haemophilia patients.

Risk of Thromboembolic Events

Concern in terms of the potential risk of developing thromboembolic events secondary to administration of rFVIIa has been raised.^{32,33} In the studies reviewed herein there are two reports of thromboembolic events.^{11,16} Shapiro et al.¹¹ reported that one patient in the 35µg/kg group developed thrombosis of the right internal jugular vein on the second day following central venous catheter placement. In the study by Pruthi et al.,¹⁶ one patient in the BI group developed thrombosis of the popliteal vein and proximal peroneal vein on day 10 after surgery.

Two reviews have reported 55 thromboembolic events in approximately 1.5 million standard doses (90µg/kg for a 40kg individual),³⁴ which must be considered low. Consequently, the administration of rFVIIa in haemophilia inhibitor patients appears safe, with lower incidences of thromboembolic events than reported for other clotting factor concentrates.^{34,35}

Safety and Efficacy in Congenital Platelet Disorders

No RCTs reporting on the safety and efficacy of rFVIIa in patients with congenital platelet disorders exist. A number of reports suggest that administration of rFVIIa to patients with Glanzmann's thrombasthenia and Bernard-Soulier syndrome may be beneficial, whereas other observations do not support its use.³⁶ Taking into account that in patients with congenital platelet disorders rFVIIa administration is only considered when other treatment options fail, this may justify its use despite the lack of scientific evidence.

Use of Assays

The cell-based model of haemostasis was introduced in 1994, emphasising the importance of tissue factor in initiating coagulation

and the importance of platelets for intact haemostasis.^{37,38} Furthermore, it was recognised that the kinetics of the thrombin burst has a separate influence on the strength and stability of the clot compared with the cleaving fibrinogen to fibrin. Thrombin also activates FXIII to XIIIa and TAFI to TAFIa in a concentration-dependent manner.³⁹

It is well recognised in the scientific community that the coagulopathy of haemophilia relates to impaired thrombin generation. It is therefore surprising that assays only reflecting the first 2–3% of the patient's ability to generate thrombin, such as activated partial thromboplastin time and prothrombin time, are employed. This is despite the fact that such assays have consistently been shown to correlate poorly with clinical bleeding conditions.^{40–49}

Whole-blood viscoelastic assays, such as thrombelastography (TEG) and thromboelastometry (ROTEM) have been consistently shown to be superior to conventional plasma-based coagulation assays in predicting the need for blood transfusion in actively bleeding patients. They have also provided guidance for treatment with plasma and platelets in non-haemophilia patients.^{44–47,50–61} The scientific rationale for this superiority was delineated by Rivard et al.⁶² who demonstrated a correlation between total thrombus generation over time, as evaluated by TEG, and the concentration of generated thrombin-antithrombin (TAT) complexes.

Coagulation factor deficiency and/or thrombocytopenia/pathy may result in impaired thrombin generation and, hence, impaired clot generation with reduced clot stability, as evidenced by an abnormal TEG tracing.^{44–47,50–60,63,64} Given this, it seems rational to monitor haemostasis in haemophilia patients with inhibitors using TEG or ROTEM, as suggested by Yoshioka et al. more than 10 years ago⁶³ and Sørensen et al. more recently.⁶⁴ This view is supported by Bassus et al.,⁶⁵ who found that administration of FVIII concentrate in patients with haemophilia A correlated linearly with increased FVIII activity, as evaluated by activated partial thromboplastin time. Thrombin generation and maximal clot strength, evaluated by thrombin generation test (TGT) and TEG, showed no such correlation. Instead, substituting whole-blood samples *ex vivo* with 1U/ml FVIII resulted in maximal haemostatic effect of FVIII, as evaluated by both TGT and TEG maximal clot strength. It also became evident that 30% FVIII activity was sufficient to produce >90% of the maximal thrombin generation and maximal clot strength and that FVIII substitution up to a plasma activity of >90% did not further enhance the haemostatic effect.

Furthermore, in terms of inhibitor patients, Trowbridge et al.⁶⁶ reported on the successful use of TEG to guide the administration of rFVIIa in haemophilia patients who were difficult to manage.

Conclusion

In conclusion, the systematic use of viscoelastic whole-blood assays may have the potential to significantly improve the treatment of haemophilia patients with inhibitors. Instead of administering rFVIIa in doses related to patient weight, an individual dosing regimen based on the amount rFVIIa needed to establish maximal thrombin generation and, hence, clot strength and stability seems reasonable. ■

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