Recombinant activated clotting factor VII (rFVIIa) in the treatment of surgical and spontaneous bleeding episodes in hemophilic patients

Heng Joo Ng
Lai Heng Lee

Department of Haematology, Singapore General Hospital, Singapore

Abstract: Inhibitors against replacement clotting factors occur in approximately 30%–40% of patients with hemophilia A and 1.5%–3% of patients with hemophilia B. In this group of patients, bleeding events are best treated with bypassing agents. Recombinant activated factor VII (rFVIIa) has become the first-line agent in treating surgical and non-surgical bleeding in many centres with efficacy at standard 90 μg/kg doses approaching 90%. The greater efficacy is associated with early initiation of treatment, as well as, possibly larger doses of rFVIIa. A higher concentration appears to be essential in initiating an adequate thrombin burst, which results in a stable clot. Higher dosage regimens, home therapy and continuous infusion regimens are continuously evolving as we strive to define optimal dosing strategies in hemophilia patients. rFVIIa has been a remarkably safe agent for hemophiliacs but with high dosages being advocated and older patients being given such doses outside a trial setting, thromboembolic events remain a concern.

Keywords: recombinant activated factor VII, hemophilia, inhibitors, bleeding.

Introduction

The development of alloimmune antibodies against factor VIII has been recognized since the early treatment of hemophilic patients with blood product transfusion many decades ago (Munro and Jones 1943). Highly effective treatment and prophylaxis of bleeding episodes with increasingly purified factor VIII containing products over the years have been negated by development of inhibitors in approximately 30–40% of patients with severe hemophilia A (Ehrenforth et al 1992; Scharrer et al 1999; Kreuz et al 2002). Similar inhibitors have been developed, between 1.5–3% of hemophilia B patients receiving factor IX concentrates (Warrier and Lusher 1998).

To circumvent their devastating effects against replacement factor concentrates, treatment strategies for bleeding episodes are based upon the premise of either saturating inhibitors with excess of clotting factors or bypassing the factor requirement altogether (von Depka 2005). The first strategy can only be attempted in patients with low inhibitor levels (<5 Bethesda Units). Bleeding episodes in patients with high responding inhibitor levels pose a considerable challenge to clinicians and requires the use of bypassing agents such as prothrombin complexes and recombinant activated factor VIIa (rFVIIa, Novo Seven). Hemostasis is not assured despite the use these agents and responses vary between individual patients, with overall costs being potentially prohibitive for many patients (Allen and Aledort 2006).

rFVIIa is the latest among the limited range of currently available bypassing agents. Successful use of plasma derived FVIIa in hemophilia A patients with inhibitors was first reported about 2 decades ago (Hedner and Kiesel 1983). Experience with its recombinant form in hemophiliacs began in the late 1980's (Hedner et al 1988) and represented a major advance in the treatment of patients with inhibitors (Hedner 1990). The US Food and Drug Administration (FDA) approval for use in both hemophilia A

Correspondence: Heng Joo Ng
Department of Haematology, Singapore General Hospital, Outram Road, Singapore 169608, Singapore
Email ng.heng.joo@sgh.com.sg

and B patients with inhibitors, was attained in 1999. In Europe, the regulatory approvals have been extended to other indications such as acquired hemophilia, factor VII deficiency and Glanzmann's thrombasthenia. The current understanding of its hemostatic action suggests that pharmacologic doses of rFVIIa enhance the thrombin-generating potential of activated platelets and facilitate full activation of thrombin-activatable fibrinolytic inhibitor (TAFI) and factor XIII. The sum result of these processes is the formation of a stable hemostatic plug, which is resistant to premature lysis (Hedner 2006). rFVIIa has a short half-life of 2.9 hours and dosing at intervals of 2–3 hours is necessary to maintain hemostasis (Lindley et al 1994). Significantly faster clearance has been observed in children compared to adults (Villar et al 2004).

In the following sections, we will review various aspects and issues concerning the use of rFVIIa in treating and prophylaxing against bleeding episodes, among both hemophilia A and B patients. Medline and EMBASE electronic databases were comprehensively searched using the following terms: recombinant FVIIa, recombinant activated factor VII, NovoSeven, eptacog alfa and haemophilia/hemophilia. Unless otherwise stated, the studies and reports mentioned include both hemophilia A and B patients with inhibitors

Efficacy of rFVIIa in non-surgical and surgical bleeding

Following the first reported treatment success with rFVIIa (Hedner et al 1988), many case reports and case series were published, reporting mostly successful control or prevention of bleeding in hemophiliacs with inhibitors (Levi et al 2005). Further suggestions of efficacy came from compilation of data and reports derived from the databases of the Compassionate Use Program and later, the Emergency Treatment Study (Bech 1996; Rice and Savidge 1996; Arkin et al 1998; Scharrer 1999; Arkin et al 2000; Ludlam 2002). Under the first program, 260 patients received rFVIIa for more than 1000 bleeding episodes over 8 years. Doses of 60–90 μg/kg were used with efficacy reported to be between 80%–87% in serious bleeds and 91%–94% in surgical bleeding. In the Emergency Treatment Study, 253 acute bleeding episodes in 127 patients were treated with rFVIIa at 90 μg/kg, repeated 2-hourly until bleeding stopped. An efficacy rate of 93% was reported. The compassionate use program and emergency use study were however not subjected to the rigorous standards and monitoring of a clinical trial; hence, a potential for biased and unreliable reporting.

There were, however, two randomized, double blind, multi-center dose-finding trials that assessed control of bleeding in non-surgical and surgical bleeding respectively. In the non-surgical trial (Lusher et al 1998), 84 patients were treated with either 35 μg/kg or 70 μg/kg of rFVIIa given 2–3 hourly, for joint, muscle and mucocutaneous bleeding. Both doses were considered to be equally efficacious with excellent or effective response in 71% of patients. The second randomized trial (Shapiro et al 1998) compared a dose of 35 μg/kg against 90 μg/kg in the initiation and maintenance therapy for bleeding during and after surgery. Intra-operative hemostasis was achieved in 28 of 29 patients. All 14 high dosed patients and 12 of 15 low-dosed patients had adequate hemostasis during the first 48 hours. The higher dose was adjudged to be more effective.

Accumulated evidence over the years has mostly shown rFVIIa to be effective in the management of bleeding episodes. Alternative bypassing agents are largely preparations of prothrombin complexes in activated or non-activated forms. Evidence of efficacy for these alternatives is best described for FEIBA (factor eight bypassing activity), an activated prothrombin complex. In a double blind comparison with a non-activated prothrombin complex, effective non-surgical hemostasis was achieved in 64% vs 52% of hemophilia A patients, in favor of FEIBA (Sjamsoedin et al 1981). More recent reports suggest an efficacy rate closer to 80% in both surgical and non-surgical bleeding (Negrier et al 1997; Hilgartner et al 1990). A randomized multi-center equivalence study comparing the efficacy of rFVIIa against FEIBA (FENOC) has also recently been published in abstract form (Berntorp et al 2005). Sixty-six hemophilia A patients were randomized to either one dose of FEIBA or two doses of rFVIIa for bleeding episodes. At 6 hours, 76.1% of FEIBA treated patients reported cessation of bleeding, in comparison to 65.2% receiving rFVIIa (confidence intervals for equivalence –2.7%, 24.5%). Equivalence could not be concluded for response at 6 hours though they were determined to be of similar efficacy at 24 and 48 hours. Despite these inconsistencies, it appears that the two products may have similar efficacy.

Optimal dosing strategy

Early experience and dose finding trials of rFVIIa have suggested that a dose of 90–120 μg/kg confers adequate hemostatic effect for most surgical and non-surgical bleeding. The initial dose should be high enough to maintain a plasma level of FVII-coagulant activity (FVII:C) of >6 U/mL for

several hours (Hedner 1996). Dosing intervals of 2 hours are recommended, until hemostasis is achieved, irrespective of bleeding etiology or location. Higher doses of rFVIIa which, supposedly, ensure the generation of a full thrombin burst, have been touted to be more efficacious (Cooper et al 2001). A full thrombin burst is necessary for the formation of a stable hemostatic plug with a tight fibrin structure, and decrease susceptibility to fibrinolysis (Blomback et al 1994). Besides plasma concentration, early administration of rFVIIa is also important for effective control of bleeding (Lusher 2000). Strategies targeting these two areas have been studied to optimize treatment.

Megadose rFVIIa

Incremental doses of rFVIIa have been investigated by various workers to determine if such a strategy leads to better control of bleeding without a significant increase in cost (Table 1). Kenet and colleagues compared an augmented versus a standard protocol of rFVIIa administration in a small study population. Initial bolus doses were doubled from 90 μg/kg to 180 μg/kg with an increase in infusion rates from 15 μg/kg/h to 30 μg/kg/h and a reduction in total infusion duration from 12 to 6 hours (Kenet et al 2000). Shorter response time and duration of therapy was demonstrated in the augmented protocol. These two protocols were subsequently compared

Table 1 Efficacy of rFVIIa at different bolus dose regimens for the treatment of acute non-surgical bleeding in hemophilia A and B patients with inhibitors

Study	Type of bleeding	Number of episodes (no. of patients, where available)	Dose (μg/kg)	Number of doses used per bleed	Effective response (%)
Lusher et al 1998[RCT]	Joint/muscle/ mucocutaneous	Joint–59 Muscle–15	35	Joint–2.7 Muscle–3.5	71 53
Lusher et al 1998[RCT]	Joint/muscle/ mucocutaneous	Joint–85 Muscle–14	70	Joint–3.1 Muscle–3.6	71 72
Bech 1996[a]	Joints/muscle	494(111)	60–120	11–65	Joints–79 Muscle–65
Rice and Savidge 1996[a]	Central nervous system (CNS)	29 (21)	80–100	2–332	84
Arkin et al 1998[a]	Intracranial	13 (12)	90	96.9	83
Scharrer 1999[a]	Joints and other sites	45(23)	90	46.8	69
Kenet et al 2003	Joints and others	114 (3)	300	1	83[b]
Parameswaran et al 2005	Joint/muscle/ mucocutaneous	146 154 136 119	<100 100–150 150–200 >200	4.3 5.2 3.4 2.3	85 84 84 97
Santagostino et al 2006[RCT]	Joints	36(18)	270	1	64[b]
Kavakli et al 2006[RCT]	Joints	20(20)	270	1	65[b]

[a] Studies include non-hemophilic patients and were part of the Compassionate Use Program and Emergency Use Study.
[b] Results of efficacy was analyzed after single dose of rFVIIa (as allowed by protocols).
Abbreviations: RCT, randomized controlled trials.

with a megadose protocol using a single dose of 300 μg/kg (Kenet et al 2003). Pain relief and response was fastest with the megadose protocol and most preferred by patients. However, it consumed more rFVIIa per bleed than the standard protocol, but less than the augmented protocol. No serious safety issues were observed. The greater efficacy of high dose rFVIIa was also suggested by a retrospective analysis of data from the Haemophilia and Thrombophilia Research Society Registry (Parameswaran et al 2005). Bleeding episodes were grouped according to the bolus rFVIIa dose used (Table 1). The highest efficacy was achieved in the group given >200 μg/kg (97%, compared with 84% in the 3 lower dose groups, $p < 0.001$). Doses as high as 346 μg/kg were used without apparent safety issues.

Two multi-center prospective randomized trials have compared the use of high dose rFVIIa against standard doses for home treatment of hemarthroses. The first study was open-labeled and compared a standard dose of 90 μg/kg (repeated every 3 hourly if necessary) against a single dose of 270 μg/kg in a total of 68 bleeding episodes (Santagostino et al 2006). Success rates were identical at all time points (66% for standard dose vs 64% for high dose at 48 hours) as was the total dose of rFVIIa used. The second study was double blinded and used either 3 single doses of 90 μg/kg or a dose of 270 μg/kg with two placebo doses, given at 3-hour intervals (Kavakli et al 2006). No significant difference in efficacy was found (65% for high dose versus 70% for standard dose). Both studies did not identify significant safety issues with the high dose regimen. The authors of both papers surmised that high dose treatment may be preferred by patients because of the convenience of single administration, without a significant increase in consumption of rFVIIa. The data on megadosing are, however, immature and need to be further investigated.

Home treatment

Early treatment of bleeding episodes in hemophiliacs is generally accorded with a greater rate of success and a reduction in damage cause by the bleeding. Analysis of experiences from the compassionate use program, dose finding trials as well as the US home treatment study, showed that the highest rate of efficacy and lowest dose requirement of rFVIIa was found in the home treatment group (Lusher 1998). An efficacy rate of 92% with a mean of 2.3 doses was achieved, which was superior to rates achieved when late treatment was given. The interval between the onset of bleeding and administration of rFVIIa appears crucial and various trials have studied early treatment with rFVIIa at home (Ingerslev et al 1998; Key et al 1998; Laurian et al 1998; Santagostino et al 1999; Santagostino et al 2006; Kavakli et al 2006).

Four studies have investigated home treatment with rFVIIA at a standard dose of 90 μg/kg given repeatedly every 2–4 hours, if necessary, for up to 12 hours (Ingerslev et al 1998; Key et al 1998; Laurian et al 1998; Santagostino et al 1999). Treatment was safe and effective in 79%–93% of bleeding episodes. Santagostino et al demonstrated that the risk for partially effective or ineffective response was smaller for treatment started within 6 hours of the onset of bleeding than for those started later (OR 0.24, 95% CI, 0.09–0.63) (Santagostino et al 1999). Early treatment was also significantly associated with lower rFVIIa usage (median 1.5 doses vs 3, $p = 0.07$). A significant improvement in response rate and reduction in doses used was associated with early treatment in all the 4 studies.

Continuous infusion

Continuous infusion (CI) regimens theoretically offer the advantage of avoiding the repeated bolus dosing needed to maintain adequate plasma FVII: C concentrations, with a potential for reduction in overall rFVIIa requirement. Surgical patients could derive most benefit because rFVIIa needs to be given for a few days after surgery. Since the first feasibility study by Schulman and colleagues (1996), there have been various studies on CI of rFVIIa at different infusion rates for surgical procedures and bleeding episodes (Mauser-Bunschoten et al 1998; Montoro et al 1998; Kenet et al 2000; Smith et al 2001; Mauser-Bunschoten et al 2002; Ludlam et al 2003). Several studies use an initial bolus dose of 90–120 μg/kg followed by CI at a rate of 16.5–18 μg/kg/h, with subsequent adjustments aiming to achieve a FVII: C level of >10 U/ml (Mauser-Bunschoten et al 1998; Montoro et al 1998; Kenet et al 2000; Mauser-Bunschoten et al 2002). Results have however been inconsistent. Higher infusion rates and augmented regimens to achieve a higher FVII: C level have therefore been investigated. Kenet et al (2000) used an initial dose of 180 μg/kg followed by an infusion of 30 μg/kg/h. This was 100% effective in securing hemostasis for surgical intervention and 72% effective for non-surgical bleeding. Ludlam et al (2003) reported on a regimen using 90 μg/kg as an initial dose, followed by 50 μg/kg/h for major orthopedic surgery. This achieved a FVII: C of 30 U/mL and appears to provide good hemostatic control. Such augmented dosing may however use substantially more rFVII than conventional CI, standard repeated boluses or even megadosing (Kenet et al 2003).

Despite theoretical advantages, the place of CI therapy and its optimal delivery and cost-effectiveness remains controversial. CI may be considered for surgery, complicated bleeding or delayed treatment, where prolonged therapy may be required (Abshire and Kenet 2004). The current concept which places importance on an adequate thrombin burst to achieve effective hemostasis, will further cloud this picture, as this phenomenon is better achieved with the high plasma concentration of rFVIIa that follows the administration of large bolus doses.

Specific approaches in surgery

RFVIIa has allowed thousands of inhibitor patients to undergo otherwise high risk elective and emergency surgeries successfully. Both bolus (Ingerslev et al 1996; Lusher et al 1998; Shapiro et al 1998; Hvid and Rodriguez-Merchan 2002) and CI regimens (Schulman et al 1996; Mauser-Bunschoten et al 1998; Montoro et al 1998; Kenet et al 2000; Smith et al 2001; Mauser-Bunschoten et al 2002; Ludlam et al 2003) have been studied in patients undergoing surgery. Lusher et al (1998) analyzed data on 103 surgical procedures with most patients given an initial dose of 90 μg/kg (range 60–120 μg/kg). Responses were rated as excellent in 81% of major surgical procedures, 86% of and minor procedures and 92% of dental procedures. In a study by Shapiro et al (1998), bolus doses of 90 μg/kg were repeated every 2 hours for 48 hours, followed by 2- to 6-hour intervals for the next 3 days, and all patients had satisfactory control of bleeding at 48 hours. This regimen was superior to the comparative regimen of 35 μg/kg and is the most commonly used bolus regimen dose. A recent consensus meeting on inhibitor management strategies in surgeries made the following recommendations (Rodriguez-Merchan et al 2004). For minor procedures, a bolus dose of 90–120 μg/kg given 2 hourly for up to 4 doses, followed by 3- to 6-hour redosing for 24 hours is recommended. For major surgeries, a starting dose of 120 μg/kg (150 μg/kg for pediatrics), followed by 90–120 μg/kg 2 hourly for the first day, is recommended. Subsequent dosing intervals are 3 hourly for day 2, 4 hourly for days 3–5, and 6 hourly thereafter as necessary.

Rates for continuous infusion are less well defined with limited evidence for more specific recommendations. The same consensus meeting recommended infusion rates ranging from 15–50 μg/kg/h for up to 14 days. There has also been no direct comparison between bolus dosing regimens against continuous infusion protocols.

Safety issues in hemophiliacs

Thrombotic concerns are understandable with a pro-hemostatic agent such as rFVIIa and thrombogenic potentials of alternative agents such as FEIBA and other prothrombin complexes have been well described (Kohler 1999, Ehrlich et al 2002). Thrombotic events related to the use of rFVIIa in hemophiliacs and other bleeding conditions have however been low since its first introduction. This is largely attributed to its action on activated platelets at sites of bleeding only, and not systemically. Abshire and Kenet (2004) reviewed 25 reported thrombotic events in hemophiliacs and found that a predisposing cause was found in 15/18 (83%) spontaneously reported cases and 5 of 7 (71%) clinical trial patients. Eleven of the 25 patients had received concomitant therapy with activated prothrombin complexes or antifibrinolytic agents. This is consistent with our experience of a young patient developing deep vein thrombosis following sequential use or rFVIIa and prothrombin complexes (Ng et al 2004).

A recent review of adverse events reported to the FDA suggests that most thromboembolic events are associated with use of rFVIIa for "off-label" indications, with serious morbidity and mortality (O'Connell et al 2006). Pre-existing risk factors for thromboembolic events were strongly associated with these events. In the most compelling evidence of possible thromboembolic risk associated with rFVIIa, serious thromboembolic event rates of 7% (mainly myocardial and cerebral infarction) were reported in a randomized placebo controlled study of rFVIIa for intracerebral hemorrhage involving 399 patients (Mayer et al 2005). This was in comparison to 2% in patients receiving the placebo ($p = 0.12$). While the characteristics of patients with respect to underlying medical conditions were not well defined, it is likely that the subjects (median age in study groups between 64–68 years) in this study represent an "at risk population". Furthermore, the incidence of these events, expressed as a percentage of the number of patients in each study group, was highest (10%) in those receiving 160 μg/kg, the highest dosage used. Using data from the FDA pharmacovigilance program, thrombotic events after rFVIIa have also been compared against FEIBA and appear to be more frequent for rFVIIa (incidence rate ratio, 2.98; CI 1.71–5.52) (Aledort 2004).

As larger doses and more intensified regimens are being studied for hemophiliacs, thrombotic risks with rFVIIa need to be better characterized. It remains to be defined what a "safe" dosing regimen will be, especially for older patients.

Antigenicity

As with the use of clotting factor replacement in the hemophilias, there have been concerns about the possibility of inhibitor development against rVIIa in patients receiving this therapy. This has so far proved unfounded among the hemophiliacs. Nicolaisen followed up a series of 267 patients given rFVIIa, (including 238 hemophiliacs) for over 9 years with no evidence of inhibitor development (Nicolaisen et al 1998). In contrast, antibodies to rFVIIa have been isolated among 6 patients with hemophilia A and B with high responding inhibitors (Astermark et al 2002). Because of multiple exposure to other bypassing and blood products, causality with use of rFVIIa could not be assigned. Other studies and ongoing experience have not unveiled significant development of inhibitors against rFVIIa among hemophiliacs. At this juncture, the potential for development of inhibitors against rFVIIa in hemophiliacs have not been conclusively disproved and vigilance, as in patients with factor VII deficiency, must continue.

Conclusion

As a bypassing agent, rFVIIa does not fully replicate the effectiveness of pure factor replacement therapy for bleeding episodes in hemophiliacs without inhibitors, nor allow prophylaxis against spontaneous bleeding events. Responses, while impressive, are less than universal and remain unpredictable. It has, nonetheless, advanced the treatment of this unfortunate group of patients and allowed them to benefit from many elective and emergency surgical procedures. rFVIIa's success with hemophiliacs has been extrapolated to an increasing number of "off-label" indications. Exciting work is currently taking shape for these new indications with more randomized well-controlled trials being conducted. Rather than diverting attention away from hemophiliacs, these studies have produced valuable data with respect to many unresolved issues in hemophiliacs, such as improved dosing strategies and safety data. rFVIIa, in combination with normal clotting factor replacement, may even play a role in better controlling difficult bleeding situations in hemophiliacs without inhibitors.

For the present, outstanding issues that can be surmised from this review are as follows: (Table 2)

- Optimal dosing strategies remain inadequately defined. While the trend is towards higher bolus and CI doses, it is likely that the chosen optimal dose will need to be tailored to the individual patient and clinical situation, for this strategy to be cost effective. There will be a limit on the quantum of rFVIIa that can be given, after which no further significant benefit can be derived and safety and cost effectiveness becomes compromised.
- Objective and easily obtainable measures of adequate response, which may be based on thrombin generation, thromboelastography, plasma concentrations, or combinations of these and other surrogate markers, need to be further developed for this issue of optimal dosing to be resolved.
- For a treatment that is extremely expensive, cost-effectiveness remains of utmost importance and must form part of the equation in any true "optimal dosing". A greater role for FEIBA in this aspect cannot be ignored.
- There is a place for both bolus dosing and continuous infusion strategies but CI protocols need to be better defined. Efforts should also continue to develop more user-friendly and effective early home treatment strategies, which can provide better outcomes.
- While remarkably safe so far, safety concerns will likely feature more prominently once this agent is extended to a wider spectrum of patients. Current studies that dispel concerns about thromboembolic risks with incremental doses were confined to young subjects. As this dosing strategy becomes more accepted, it is likely that older patients with significant thromboembolic risk factors will be included and challenge this notion of safety.

Table 2 Unresolved issues with recombinant activated factor VII use in hemophiliacs

- Optimal dosing strategies
- Modalities for measuring and monitoring response
- Cost-effectiveness
- The place for continuous infusion
- Thrombotic risks

Finally, with these shortcomings, we should continue our search for the ideal bypassing agent – one that is universally effective, cheap, easily administered, has a long half-life, suitable for prophylaxis strategies, uniform in dose requirement and, ultimately, safe.

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