

Case Report on Recombinant Coagulation Factor VIIa in the Treatment of Three Haemophilia A Patients with Inhibitors in Singapore

H J Ng,*^{MBBS, M Med (Int Med), MRCP (UK)}, L H Lee,**^{FAMS, MBBS, M Med (Int Med)}

Abstract

Introduction: We report the first experiences with use of recombinant coagulation Factor VIIa (rFVIIa) in the treatment of haemophilia A patients with inhibitors in Singapore and discuss observations in 3 patients. **Clinical Picture:** Case 1 bled on two separate occasions into his neck muscles and vocal cord. Case 2 had gross haematuria from bleeding in the renal calyces. Case 3 bled into the parotid muscles. **Treatment:** rFVIIa in doses, ranging from 50 ug/kg to 90 ug/kg, at different dosing intervals, were used. **Outcome:** Excellent responses were seen in doses of 70 and 90 ug/kg. **Conclusion:** rFVIIa is highly effective, both clinically and cost-wise, in the treatment of these patients.

Ann Acad Med Singapore 2002; 31:241-4

Key words: Bleeding, Cost-effectiveness, Dosing, Haemophiliacs, Response

Introduction

Development of inhibitors against factor VIII is one of the main complications in the treatment of haemophiliacs. Inhibitors block the procoagulant effects of factor VIII and prevent the successful arrest of bleeding episodes when administered to these haemophiliacs.

The prevalence of inhibitors ranges widely, from 18.4% to 28%, in prospective studies involving previously untreated patients.¹ Severe haemophiliacs are more likely to develop inhibitors than mild haemophiliacs. Among the 157 haemophilia A patients registered with the Haemophilia Registry in Singapore, 28 or 17.8% were known to have demonstrated inhibitors to factor VIII. Of these, 9 were high responders, 8 low responders and 11 had transient positive tests at some point in time. Haemophiliacs with inhibitors may be classified as low responders if they have inhibitor levels below 5 Bethesda units (BU) and when given factor VIII concentrates, do not present an anamnestic response. High responders have inhibitor levels above 10 BU and rise to very high levels anamnesticly, after infusion of factor VIII concentrates. Inhibitors have not been detected among the 21 haemophilia B patients in the Registry.

The treatment of bleeding episodes in these inhibitor-positive patients has always been a dilemma and challenge to the attending physician. Available treatment options include the use of by-passing agents or swarming with

massive amounts of factor VIII.² Prothrombin complex concentrates and activated prothrombin concentrates like FEIBA and Autoplex are bypassing agents available for use. Recombinant activated factor VII (rFVIIa; NovoSeven, NovoNordisk) has become available in Singapore and offers another option to this group of patients. Clinical experience since its introduction has suggested superior efficacy with low incidence of adverse events. rFVIIa will see wider usage as the preferred choice of treating patients with inhibitors against factor VIII and factor IX.

rFVIIa was first used on our patients in August 1999. To date, it has been given to 3 patients with haemophilia A for a total of 4 bleeding episodes. We describe here our experience with the use of rFVIIa in these haemophiliacs.

Case Reports (Table I)

Case 1

A 31-year-old Chinese man presented in August 1999 with acute bleeding bilaterally into the platysma and surrounding neck muscles. He was known to be a high responder with previous documented inhibitor levels reaching 1200 BU following use of factor VIII. Inhibitor level on admission was 8 BU. He was given rFVIIa at a dose of 3600 ug per day (90 ug/kg/day) as a single slow bolus dose for 2 days, followed by 2400 ug per day (60 ug/kg/day) on the subsequent 2 days. There was no further progression of bleeding after starting rFVIIa. He was

* Registrar

** Consultant

Department of Haematology

Singapore General Hospital

Address for Reprints: Dr Ng Heng Joo, Department of Haematology, Singapore General Hospital, Outram Road, Singapore 169608.

E-mail: ghenhj@sgh.com.sg

TABLE I: PROFILE OF 3 HAEMOPHILIA A PATIENTS TREATED WITH rFVIIa FOR BLEEDING EPISODES

Case no.	Race/Age (y)	Presentation	Inhibitor level	RFVIIa dosage and duration	Response
1 LSH	Chinese/31	1. Bilateral platysma and surrounding neck muscle haematoma	8 Bestheda units (BU)	3600 ug daily @ 90 ug/kg x 2 days followed by 2400 ug daily @ 60 ug/kg x 2 days (total: 4 doses)	Excellent
		2. Vocal cord haematoma	10 BU	3600 ug daily @ 90 ug/kg x 3 days (total: 3 doses)	Excellent
2 JH	Malay/36	Haematuria from haematoma in left renal calyces and pelvis	15 BU	3600 ug daily @ 50 ug/kg x 4 days, then *3600 ug 12 hourly @ 50 ug/kg x 4 days, followed by 3600 ug 8 hourly x 1 day (total: 15 doses)	Effective
3 CCB	Chinese/29	Right parotid region intramuscular bleed	4 BU	3600 ug daily @ 70 ug/kg x 1 day (total: 1 dose)	Excellent

* Subsequent administration after interruption by non-availability of rFVIIa

discharged the day after discontinuing rFVIIa.

One month later, he was readmitted for hoarseness secondary to vocal cord haematoma. rFVIIa at 3600 ug per day (90 ug/kg/day) was given as a slow bolus infusion daily for 3 days without further bleeding complications. He was discharged after a 3-day observation period.

Case 2

A 36-year-old Malay man was admitted for gross haematuria. Ultrasound imaging of the kidneys and ureters showed a dilated left ureter. An intravenous urogram also suggested haematomas in the left renal calyces with extension into the renal pelvis. He had inhibitor level of 15 BU on admission. The site of bleeding and his status as a high responder indicated the need for use of rFVIIa. This was given at 3600 ug per day (50 ug/kg/day) for 3 days with reduction in the severity of bleeding. There were, however, problems in obtaining further doses from the supplier in Singapore. Factor IX complex was given in place of rFVIIa. The haematuria persisted for the next 2 weeks with varying intensity. New stocks of rFVIIa eventually arrived and was given at 3600 ug (50 ug/kg) 12 hourly for 4 days, followed by 3600 ug (50 ug/kg) 8 hourly for 1 day. The haematuria stopped and this patient was discharged 3 days later.

Case 3

This was a 29-year-old Chinese man who bled into the muscles around the right parotid area. He was initially treated with factor IX complex but with only partial response. His haematoma worsened over the next few days and he developed a right conjunctival haematoma as well. Inhibitor level on admission was 4 BU but he had previously demonstrated high inhibitor response to factor VIII. rFVIIa as a single dose of 3600 ug (70 ug/kg) was given with no further progression of bleeding. He was discharged 3 days later.

Discussion

Recombinant human coagulation factor VIIa (rFVIIa) promotes coagulation by activating the extrinsic pathway of the coagulation cascade and is structurally similar to human plasma derived factor VIIa. When complexed to tissue factor, it activates factor X to factor Xa as well as factor IX to IXa. Normally, this path is rapidly inactivated by tissue factor protein inhibitor (TFPI) after a small amount of thrombin has been generated. By giving large doses of rFVIIa, the TFPI can be overcome and enough factor Xa generated. Factor Xa in combination with other factors then converts prothrombin to thrombin (Fig. 1). This facilitates the formation of a haemostatic plug by converting fibrinogen to fibrin and inducing local haemostasis.³ By activating factor X directly, this bypasses and dispense off the need for the pathway involving both factor VIII and factor IX. Further, rFVIIa binds with tissue factor at the site of vascular injury and initiates only local haemostasis. It has an overall efficacy rate of around 80%.⁴

The recommended dose of rFVIIa is 90 ug/kg every 2 hours until haemostasis is achieved or until treatment has been judged to be inadequate.⁵ The short recommended dosing interval is because of the short half-life of rFVIIa. Varying doses of between 35 and 120 ug/kg have, however, been used successfully in clinical trials with different administration intervals.⁶ The doses used on our patients were between 50 and 90 ug/kg with dosing intervals ranging from 8 hourly to daily. These dosages were derived from the use of an average of 3 vials of 1200 ug each for each patient without strict weight-based prescription. Dosing interval and duration of administration had been determined by the adjudged severity of bleeding and has been of relatively low intensity. The limited supply of rFVIIa made available to us for these patients and the very high costs of this agent made it not possible to use the dosages and dosing intervals as recommended.

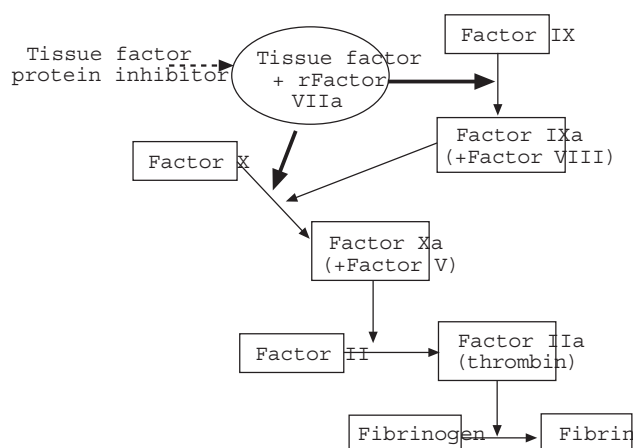


Fig. 1. Mechanism of action of recombinant coagulation factor VIIa (rFVIIa).

Observations and an analysis of our 3 patients' responses have yielded valuable information and lessons that will guide the subsequent use of rFVIIa in our local population of haemophiliacs with bleeding episodes.

In Case 1, the initial dose of 90 ug/kg was highly effective in arresting bleeding into his neck muscles and vocal cords. This dose initiated the rapid and effective formation of a haemostatic plug that arrested the bleed. Once effective haemostasis has been secured, further frequent doses may no longer be necessary. This assumption was put in practice in Case 3 where a single dose was given which effectively arrested bleeding. No further doses were given, unlike Case 1 who received additional doses over the subsequent days. These additional doses would be unnecessary in future patients with bleeds of similar severity and initial good response to rFVIIa. Case 3 also demonstrated that a lower dose of 70 ug/kg was effective in securing haemostasis.

In bleeding episodes of severity as in Case 2, a more intensive regimen would be required. This patient was unfortunate to have limited supplies of rFVIIa at his disposal at the time of his bleeding. Otherwise, a higher initiating dose of 70 to 90 ug/kg with more frequent dosing intervals may have successfully arrested his bleeding early and shortened his hospitalisation as well as reduced the overall number of doses used. The resumption of use of rFVIIa at the later stage of his hospitalisation at more frequent intervals was successful in securing full haemostasis. Frequent dosing of up to 2 hourly is recommended in major surgery, massive injuries or bleeding into the central nervous system in order to achieve continuous haemostasis till tissue injuries have recovered.

Cases 2 and 3 both demonstrated the superiority of rFVIIa over factor IX complex, which was used but did not adequately secure haemostasis in both patients. Indeed, the

limitation of factor IX complex is its unpredictable effects on haemostasis.

rFVIIa had been well tolerated by our 3 patients with no adverse events recorded in the 4 separate administrations. As rFVIIa is a potent activator of coagulation, thrombotic events are a concern and may be increased in patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury and septicaemia due to circulating tissue factor or predisposing coagulopathy. Very rarely have unwanted thrombotic complications been observed,^{7,8} but this should be less as compared to other by-passing agents. More common side effects that have been reported include fever, haemorrhage, decreased fibrinogen, haemarthrosis, hypertension, hypotension and allergic reactions.⁹ None of these were observed in our patients.

The clinical usefulness and efficacy of rFVIIa is clear but its cost remains a prohibitive factor against its widespread use. However, the potency of its action in achieving haemostasis may offset any cost disadvantage considering that it will shorten the duration of hospitalisation, avoid the use of large volume of factor VIII for swarming or use of other by-passing agents, which have more reported thrombotic episodes,¹⁰ and prevent the devastating long-term morbidity of an uncontrolled bleeding episode in an important organ. In patients where swarming with factor VIII was a viable option, rFVIIa can actually cost less. Case 3, for example, could have been swarmed and maintained for a few days with factor VIII for an estimated cost of approximately \$4300 (estimating swarming dose at 0.7 x 40 u/kg body weight x inhibitor levels, with maintenance dose to achieve factor VIII levels of 50% for 3 days). In comparison, the single dose of rFVIIa used costs about \$3500. Taking the various advantages into account, rFVIIa is more cost-effective than other available options for the treatment of this group of patients.

Given the favourable outcome of bleeding episodes treated with rFVIIa in our patients to date, it is set to gain a foothold as frontline treatment of bleeding episodes in our haemophiliacs with inhibitors. Determining the optimal dosages and dosing intervals for each individual bleeding episode shall become more precise as our experience with this therapeutic agent increases.

REFERENCES

1. Kreuz W, Escuriola-Ettingshausen C, Martinez-Sageur I, Gungor T, Kornhuber B. Epidemiology of inhibitors in haemophilia A. *Vox Sang* 1996; 70(Suppl 1):2-8.
2. Aledort L M. Inhibitors in hemophilia patients: current status and management. *Am J Hematol* 1994; 47:208-17.
3. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa).

- Transfus Sci 1998; 19:163-76.
 4. Negrier C, Lienhart A. Overall experience with NovoSeven. *Blood Coagul Fibrinolysis* 2000; 11(Suppl 1):S19-24.
 5. Hedner U. Dosing and monitoring of NovoSeven Treatment. *Haemostasis* 1996; 26(Suppl 1):102-8.
 6. Lusher J M, Roberts H R, Davignon G, Joist J H, Smith H, Shapiro A, et al. A randomised double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in person with haemophilia A and B, with or without inhibitors. RFVIIa Study Group. *Haemophilia* 1998; 4:790-8.
 7. Schmidt M L, Gamerman S, Smith H E, Scott J P, DiMichele D M. Recombinant activated factor VII (rFVIIa) therapy for intracranial haemorrhage in haemophilia A patients with inhibitors. *Am J Hematol* 1994; 47:36-40.
 8. Roberts H R. Clinical experience with activated factor VII: focus on safety aspects. *Blood Coagul Fibrinolysis* 1998; 9(Suppl 1):S115-8.
 9. Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis* 1998; 9:119-28.
 10. Lusher J M. Use of prothrombin complex concentrates in management of bleeding in hemophiliacs with inhibitors: benefits and limitations. *Semin Hematol* 1994; 31:49-52.
-