

## When all else fails to stop massive bleeding from trauma

ARTHUR R. THOMPSON

Puget Sound Blood Center and the University of Washington, Seattle WA, USA

**To cite this article:** Thompson AR. When all else fails to stop massive bleeding from trauma. *J Thromb Haemost* 2005; 3: 638–9.

See also Martinowitz U, Michaelson M on behalf of the Israeli Multidisciplinary rFVIIa Task Force. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. This issue, pp 640–8.

Recombinant factor VIIa (FVIIa) was Food and Drug Administration (FDA)-approved in the United States for the treatment or prevention of excessive bleeding in patients with hemophilia and inhibitors in 1996 [1,2], following 7 years of clinical trials. Recently, there has been increasing off-label use as a hemostatic concentrate, often in life-threatening bleeding and frequently with dramatic results [2]. Unfortunately, there are no clear guidelines for either indications or dosing in patients without an inhibitor and most reports are anecdotal. To address its use in massive bleeding from trauma, Martinowitz and Michaelson summarize 5 years of multicenter experience in Israel where 57 consecutive, young adult trauma victims received recombinant FVIIa treatment.

Their analysis is based on 36 subjects, excluding those who died acutely and those whose trauma was limited to the head and brain. Of these, 26 responded with marked decrease in blood loss and 10 failed to respond; nine of the latter group died within 15 h. Recombinant FVIIa was administered after critical attempts to stabilize blood pressure, correct acidosis and hypothermia. Furthermore, all subjects were given blood components prior to FVIIa in an attempt to increase platelet counts to at least 50 000 (preferably  $> 100\,000\ \mu\text{L}^{-1}$ ) and fibrinogen levels to above 50 (preferably  $> 100\ \text{mg dL}^{-1}$ ).

Data from eight of the 10 subjects who failed to respond showed higher mean initial prothrombin and partial thromboplastin times than those 26 who responded. Curiously, after FVIIa the prothrombin time decreased in six of the eight and was at least near normal in four, whereas it became at least near normal in all 26 who responded. Meanwhile, the pre- and post-partial thromboplastin times decreased in responders but began at a somewhat higher mean clotting time in non-responders and remained elevated after FVIIa [3]. It would be useful to know, in those who failed to correct their partial thromboplastin times, whether an antithrombin effect was

excluded (heparin contamination of sample or very high levels of D-dimer; a thrombin time would help). Was either of the two non-responders with the highest prothrombin times the one that had the lowest initial fibrinogen of 23? Was cryoprecipitate subsequently given and did it raise that individual's level to a hemostatic range? In the acute setting, however, it is noteworthy that testing results represent only a single moment when drawn and where several subjects undoubtedly had at least some ongoing consumption of platelets and fibrinogen. Thus, it is difficult to assess if hemostasis had been corrected and if so, for how long.

Dosing is another issue and, although relatively high doses are recommended and there was a 'trend' for those given higher doses to respond better, there was a wide range used. Were the lower doses given to those with less severe ISS scores or to non-responders? Did doses vary and increase during the course of study? Using the hemophilic inhibitor model, 90 and more recently up to  $270\ \mu\text{g kg}^{-1}$  doses [4] have been tried, but these do not necessarily apply to trauma victims without inhibitors. For warfarin overdose [5] or congenital FVII deficiency [6], it may be that only  $20\text{--}30\ \mu\text{g kg}^{-1}$  are needed. There may be a tendency, as often seen in medicine, to increase doses to achieve more responses whereas there may be some threshold beyond which one is only increasing the risk of thrombosis. It is noteworthy that there are limited data on how low is the risk of thrombosis when recombinant FVIIa is used in individuals without inhibitors [2,7]. Although the age range was 14–65 years, the median was 19.5, such that most of these subjects in this trauma series were young adults and teenagers. As age is in itself a thrombotic risk factor, the absence of overt thrombotic events in this study's survivors of massive trauma is of limited value in estimating this overall risk to older individuals.

There are clearly many variables that were beyond control of these investigators, but further details might help their recommendations to be evaluated. One can assume that the frequencies and intervals of laboratory testing varied as well as the degree of cardiovascular stabilization and hemostatic correction at the time of FVIIa therapy. Nevertheless, this series indicates that judicious use of recombinant FVIIa in the

Correspondence: Arthur R. Thompson MD, PhD, Puget Sound Blood Center, 921 Terry Avenue, Seattle, WA 98104, USA.

Tel.: + 1206 2926570; fax: + 1206 2928030; e-mail: arthomps@u.washington.edu

setting of acute trauma where bleeding cannot be controlled by conventional measures to improve hemostasis and correct acidosis can have dramatic effects to stop or slow hemorrhage in the majority of patients treated.

Recently, a series from the Shock Trauma Center in Baltimore included 46 trauma victims without brain injury who received recombinant FVIIa over a 2.5-year period [8]. Again, about three-quarters responded with an acute decrease in blood loss. Only 20 survived, however, and this may be due at least in part to their older age, where the median was 38 years (range 15–78). Although ISS scores were comparable, there are several other variables that might also impact response. These include differences in the timing of administration of FVIIa or other blood component usage. Furthermore, pH data were not analyzed in the US series.

Due to its cost and concern for inappropriate usage, several institutional pharmacies or transfusion services are attempting to establish guidelines for the use of recombinant FVIIa. There is a developing consensus [9] supported by the results in trauma victims that FVIIa be withheld until it is shown that hemorrhage persists despite hemostatic levels of platelets, fibrinogen and other factors, corrected with traditional blood components and that the bleeding is not typical of a larger vessel that can be approached surgically or by embolization. In the acute trauma setting, however, and especially if laboratory confirmation of response to hemostatic components may be delayed, it may be prudent to use FVIIa when generalized or significant hemorrhage persists despite a therapeutic trial of blood components. It seems unlikely that placebo-controlled trials will be implemented to address efficacy. However, trials

where the clinical and laboratory status are carefully monitored and documented in subjects randomized to different doses could establish guidelines for use in massive bleeding from trauma.

## References

- 1 Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost* 2004; **2**: 899–909.
- 2 Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 2004; **104**: 3858–64.
- 3 Martinowitz U, Michaelson M, on behalf of the Israeli Multidisciplinary rFVIIa Task Force. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 2005; **3**: 640–8.
- 4 Kenet G, Lubetsky A, Luboshitz J, Martinowitz U. A new approach to treatment of bleeding episodes in young hemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven®). *J Thromb Haemost* 2003; **1**: 450–5.
- 5 Deveras RA, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Int Med* 2002; **137**: 884–8.
- 6 Ziedins KB, Rivard GE, Pouliot RL, Butenas S, Gissel M, Parhami-Seren B, Mann KG. Factor VIIa replacement therapy in factor VII deficiency. *J Thromb Haemost* 2004; **2**: 1735–44.
- 7 Hay CRM. Thrombosis and recombinant factor VIIa. *J Thromb Haemost* 2004; **2**: 1698–9.
- 8 Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM. Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 2004; **57**: 709–18.
- 9 Goodnaugh LT, Lublin DM, Zhang L, Despotis G, Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion* 2004; **44**: 1325–31.