Reprint from

Volume 78
Number 6
Pages 1463–1467
December 1997

ISSN 0340-6245

Thrombosis and Haemostasis

Journal of the International Society on Thrombosis and Haemostasis

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The Treatment of Bleeding in Acquired Haemophilia with Recombinant Factor VIIa: A Multicentre Study

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Summary

Recombinant factor VIIa was used to treat 38 patients with acquired haemophilia participating in the Novoseven compassionate-use program. 19 were male, median age 59, range 2-89 years. The median pre-treatment anti-human (H) and anti-porcine (P) inhibitor titre was H 43 BU/ml (range 1-4500) and P 4.5 BU/ml (range 0-1600). Recombinant factor VIIa was used as first-line therapy for 14 bleeding episodes and as salvage-therapy for 60 episodes which failed to respond to blood-product therapy given for a median of four days (range 1-21 days) prior to treatment with rVIIa. Pre-rVIIa treatment was not reported for four episodes. The indications for treatment were 7 haemarthroses, 40 muscle haematomas, 20 urinary or GI haemorrhages and 3 surgical interventions. The median starting dose of rVIIa was 90.4 ug/kg (range 45-181). A median of 28 doses (range 1-541) were given per episode, over a median 3.9 days (range 0-43).

Efficacy was assessed clinically 8 and 24 h after the start of rVIIa and at the end of treatment. A good response was obtained in all 14 bleeds for which rVIIa was used as first-line therapy. The response after 24 h of rVIIa salvage-therapy for 60 bleeds was good in 75%, partial in 17% and poor in 8%. Efficacy was unreported in 4 cases. The median prothrombin time (PTT) shortened from 12 s (range 9.3-20) pre-treatment to 8.8 s (range 6-14) during treatment. The clinical response did not correlate with the dose of rVIIa used, the type of bleed or the degree of shortening of the PTT following rVIIa infusion.

Three patients died from haemorrhagic complications of acquired haemophilia. This mortality of 7.9% is lower than previously reported for this condition. Although one patient developed DIC during treatment with rVIIa, this was probably attributable to hypovolaemic shock, massive transfusion and the use of PCCs. This study demonstrates that rVIIa is a safe, useful and effective treatment for bleeding in patients with acquired haemophilia.

Introduction

Acquired haemophilia is a severe bleeding diathesis caused by autoimmune depletion of factor VIII with an incidence in excess of 1 per million of population per year (1-3). Although classically associated with pregnancy, autoimmune disease and malignancy, it arises most commonly in elderly patients who lack any associated disease (1-6). Bleeding is often severe, occurring spontaneously or in relation to minor trauma, and occurs in up to 87% of patients (3). Soft tissue haematomas, bruising, muscle bleeds and gastrointestinal and urinogenital bleeding are frequent, in contrast with congenital haemophilia where haemarthroses are the principal manifestation. Bleeding may be life threatening, particularly during the first few weeks after presentation, resulting in a mortality of between 13 and 22% (2, 3).

The dual objectives of the treatment of acquired haemophilia are the elimination of the auto-antibody and the treatment of haemorrhage. Immunosuppression with prednisolone alone may be associated with complete remission in 32% (3, 4) and the addition of cyclophosphamide increases the overall response to 70% (3, 4, 6-9). The factor VIII inhibitor titre commonly declines slowly, over a period of weeks or months, following immunosuppression during which time the patient may bleed repeatedly.

Various blood products have been used to secure haemostasis, none of which are universally effective or free from side-effects. Although acquired haemophilia is usually refractory to human factor VIII, most patients respond well to porcine factor VIII to which their inhibitor auto-antibodies usually have little cross-reactivity (10). The side-effects of this product include an occasional anamnestic rise in inhibitor titre affecting 4% of patients with acquired haemophilia (10), a post infusion decline in platelet count which is usually transient and dose-related, and transfusion reactions which are also most commonly associated with intensive therapy (11, 12). These side-effects limit its use in some patients. FEIBA and other activated prothrombin complex concentrates (PCCs and APCCS) may also be used and are effective in 50-70% of bleeding episodes (13-15). Thrombosis, myocardial infarction and DIC have all been reported with the use of high doses of these products (13-15) leading some authorities to recommend a maximum dose of 200 u/kg/day (16). Given these limitations, there is clearly a need for a safer and more effective haemostatic agent for the management of haemorrhage in acquired haemophilia.

Recombinant VIIa (rVIIa, Novoseven, Novo Nordisk, Denmark), has been reported to be clinically effective and relatively free from side-effects, in patients with haemophilia A and B with inhibitor antibodies (17-20). We report the use of rVIIa for severe bleeding in acquired haemophilia between 1990 and 1995 from the Novoseven compassionate use program.

Methods

The diagnosis of acquired haemophilia was based upon the demonstration of a reduced plasma factor VIII level and a factor VIII auto-antibody in a patient with no previous history of bleeding or blood-product replacement. Anti-human and anti-porcine inhibitor titres were measured locally using the Bethesda method (21). Only inhibitor titres measured immediately prior to treatment with rVIIa are reported.

It was planned, according to the Novoseven compassionate-use protocol, to administer rVIIa to patients with acquired haemophilia for the treatment of serious bleeding *when other treatment modalities had failed.* This was initially administered by 2 h i.v. bolus. The choice of dose, dose-interval and length of

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treatment with Novoseven were adjusted according to the clinical response, at the discretion of the managing clinician.

Clinical efficacy was assessed eight and 24 h after the beginning of treatment with rVIIa and at the end of treatment. This was categorised by the supervising physician as effective, partial response, or ineffective, based on clinical examination of the bleed, careful monitoring of vital signs and the full blood count, and ultrasonography or CT scanning where appropriate.

The prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen level and platelet count were monitored using local methods. Some participating centres also monitored plasma D-Dimers and antithrombin.

All adverse events occurring within two months of the end of the treatment with rVIIa were reported.

Data retrieval, study monitoring, and drug monitoring were conducted by Novo Nordisk to Food and Drug Administration (FDA) or good clinical practice (GCP) standards. Background data on underlying illnesses associated with acquired haemophilia and response to immunosuppressive therapy was not recorded since the primary objective of data-collection was to facilitate a product license application.

Summary statistics were calculated using Minitab statistical software. The difference in duration of treatment with rVIIa, and with blood products prior to treatment with rVIIa, between those with an effective response and those with a partial or absent response was analysed using a Mann-Whitney u-test.

Results

Thirty-eight patients with acquired haemophilia were treated with rVIIa for a total 78 bleeds. These patients were managed in 32 centres from Europe, Canada, the USA, Australia and Malaysia between 1990 and 1995. Nineteen were male and 19 female. Their median age was 59 years, range 2-89. The median anti-human (H) and anti-porcine (P) inhibitor titre, immediately pre-treatment, was H 43 BU/ml, range 1-4500 and P 4.5 BU/ml, range 0-1600.

Indications for Treatment and Dosage of rVIIa

The indications for treatment with rVIIa included 40 muscle haematomas, 4 urinogenital haemorrhages, 16 gastrointestinal bleeds, 7 haemarthroses, and 3 surgical operations.

The median starting dose of rVIIa was 90.4 μg/kg (range 45-181). This was initially administered to each patient by bolus at 2 h intervals, although the interval between doses was lengthened progressively up to 6 h when a satisfactory clinical response had been obtained. The dose varied little during the course of a bleeding episode. A median of 28 doses, range 1-541 was given per episode, over 3.9 days (range 0-43).

Treatment prior to rVIIa

Immunosuppressive and haemostatic therapy given prior to treatment with rVIIa was reported for 35 of 38 patients and for 71 of 78 bleeding episodes. Immunosuppressive therapy was used in 27 of these 35 patients. Twenty three used prednisolone, supplemented with intravenous immunoglobulin (IVIgG) in five, cyclophosphamide in 8, and both immunoglobulin and cyclophosphamide in a further 4. One patient was treated with IVIgG combined with cyclophosphamide and two were treated with IVIgG alone. No other immunosuppressive agents were used.

Contrary to the protocol, recombinant VIIa was used as first-line haemostatic treatment in combination with tranexamic acid in 6 patients for 14/71 bleeding episodes for which information on pre rVIIa haemostatic therapy was provided. These data are included in this report.

Table 1 Number of bleeds treated with different blood-products or combinations of blood products prior to treatment with rVIIa

BLOOD-PRODUCT THERAPY OF BLEEDS	HUMAN VIIIC	PORCINE VIIIC	PCC OR APPC
HUMAN VIIIC	31	18	12
PORCINE VIIIC	18	30	15
PCC OR APPC	13	15	33
HUMAN AND PORCINE VIIIC	18	18	8
NO BLOOD PRODUCTS 14 BLEEDS	-	-	-

Recombinant VIIa was used as second-line or salvage-therapy for the remaining 57/71 bleeding episodes in 29 patients when they had failed to respond to conventional blood product replacement therapy. These patients had been treated with a median of 2, range 0-3 blood products for a median of 4 days, range 1-21 days. These blood products included human VIIIC, porcine VIIIC or prothrombin complex concentrates (PCCs) (Table 1). Antifibrinolytic therapy was used for 33 bleeding episodes and DDAVP for 5.

Efficacy

Efficacy was reported for 74 of 78 bleeds treated. Recombinant factor VIIa was used as first-line therapy for 14 bleeding episodes in six patients and as salvage therapy for 60 episodes in 29 patients for which efficacy was reported.

The efficacy of rVIIa used as first-line therapy for 14 bleeds was judged to be good in all cases at 8 and 24 h after the start and at the end of treatment.

The efficacy of rVIIa used as salvage therapy for 60 bleeds is shown in Figure 1. The response to treatment usually occurred rapidly, within 8-24 h. The clinical response to treatment after 8 h was good in 36 episodes (60%), partial in 17 (28%) and poor in 7 (12%); after 24 h was good in 45 (75%), partial in 10 (17%), and poor in 5 (8%); and at the end of treatment was good in 45 (75%), partial in 10 (17%), and poor in

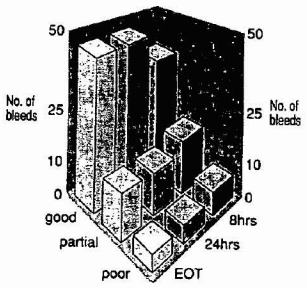

Fig. 1 Number of bleeds with a good, partial or poor response to treatment with rVIIa as salvage-therapy, assessed at 8 and 24 h and at the end of treatment (EOT)

5 (8%). Two bleeding episodes with a good response at 8 and 24 h responded partially overall, and a further two with a partial response at 8 and 24 h responded well overall.

There was no difference in the number or type of blood-product used prior to rVIIa between those with a good or sub-optimal response (partial and no response) to rVIIa. The length of time for which the patient was treated with blood products prior to treatment with rVIIa was shorter in responders than in partial or non-responders to rVIIa (median 4 vs. 8 days, $p = 0.058$), but this failed to achieve statistical significance. Although the median duration of treatment with rVIIa was significantly shorter for bleeding episodes which responded well compared with those with a partial or poor response (3.9 vs. 7 days, $p = 0.05$), there was no difference between the two groups in the intensity of rVIIa therapy.

No non-responders and only five of ten partial responders were treated with concomitant antifibrinolytic therapy. Of the fifteen bleeds in which the response was classified as partial or ineffective five were gastrointestinal, six were muscle bleeds, one was urinogenital and three were post-traumatic.

The median prothrombin time (PTT) shortened from 12 s (range 9.3-20) pre-treatment to 8.1 s (range 6-14) during treatment. There was no difference in the PT or the degree of shortening of the PTT between bleeds which had an effective response and those who had a partial or ineffective response.

Mortality and Adverse Events

Four patients died from haemorrhage, all after discontinuation of treatment with rVIIa. One responded well to rVIIa but died suddenly from a ruptured aortic aneurism, unrelated to acquired haemophilia, on the day after treatment with rVIIa finished. Two responded partially to rVIIa. One of these died from uncontrolled gastrointestinal bleeding 24 h after rVIIa discontinuation of rVIIa, and the second died from a new intracerebral bleed which occurred seven days after discontinuing rVIIa. The final patient failed to respond to rVIIa and died from retroperitoneal haemorrhage seven days after treatment with rVIIa had been discontinued.

One patient developed probable disseminated intravascular coagulation (DIC). This 56 year old female presented with an inhibitor of H 4500 BU/ml and P 1600 BU/ml and gastrointestinal bleeding which initially failed to respond to PCCs, aminocaproic acid and conjugated oestrogen. She was treated with rVIIa, without concomitant antifibrinolytic therapy. This was initially given by two hourly bolus injection. This resulted in slowing of bleeding, and so the interval between boluses was gradually increased. The dose-rate of administration of rVIIa (expressed as μg/kg/h, for the sake of clarity) was reduced from 50 μg/kg/h on the first day to 25 μg/kg/h on the tenth day of treatment. Her rVIIa dose-rate, APTT, PTT, fibrinogen and platelet count are illustrated in Fig. 2. These haemostatic variables were relatively stable until the tenth day of treatment with rVIIa when her gastrointestinal bleeding became much more severe and the patient developed hypovolaemic cardiovascular collapse requiring resuscitation. She was rapidly infused with ten units of blood, ten units of platelets, 2 l of fresh frozen plasma and 3000 units of Konyne (PCC). The dose of rVIIa was not increased, at this point, and was discontinued later on that day. Successful resuscitation was accompanied by a precipitous fall in fibrinogen and platelet concentration and prolongation of her APTT and PTT. No change was observed in the D-dimers, which remained <500 ng/ml. Despite the absence of elevated plasma D-dimer levels, in the absence of significant hepatic failure, these haemostatic changes were taken to indicate DIC. The fibrinogen, platelet count APTT, PTT and the gastrointestinal bleeding gradually improved over the subsequent five days.

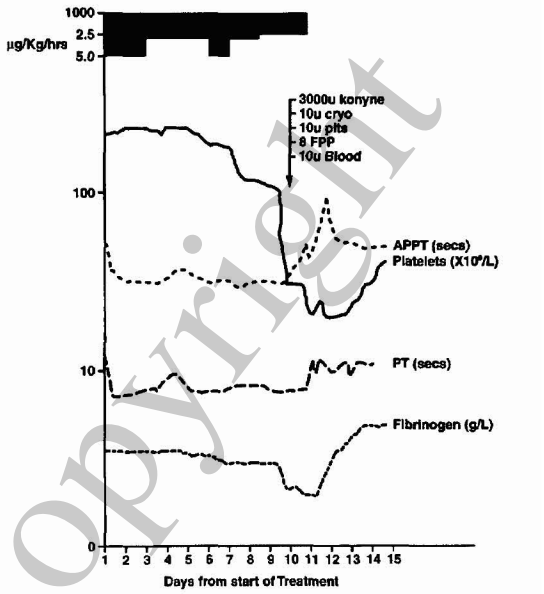

Fig. 2 RVIIa dose-rate and haemostatic parameters (on a logarithmic scale) in a 56 year old female treated with rVIIa for ten days for severe gastrointestinal bleeding. RVIIa was administered by iv bolus given every two to six hours. The dose-rate is expressed in μg/kg/h for clarity

Minor side-effects included slight fever in one and nausea in three patients following treatment with rVIIa. No other significant adverse events were reported.

Discussion

This study shows that rVIIa (Novoseven, Novo, Denmark) is an effective salvage therapy for bleeding in patients with acquired haemophilia who have failed to respond to blood-product therapy. A good or partial response to treatment was observed in 88% of bleeding episodes after 8 h and in 92% after 24 h of treatment with rVIIa. This response rate is similar to that described in patients with congenital haemophilia and inhibitors treated with rVIIa (17, 18, 20). The response to treatment was usually rapid and the response after eight and 24 h was generally predictive of the overall response.

This is superior to the 50-70% response-rate reported for PCCs (13, 14) and is comparable with the initial response to treatment of acquired haemophilia with porcine VIIIC (10). The design of this study also permits a limited direct comparison with alternative treatment modalities since these patients had already failed to respond to a median of two blood-products, including human and porcine factor VIII and PCCs or APCCs, given over a median of four days. Selection bias limits this comparison, since the failure of conventional therapy was an entry criterion for the study. A randomised trial would theoretically offer the firmest basis for comparison of these alternative treatments, but the logistics of such a study are prohibitive. It might also be argued that porcine factor VIII should have been used in a higher proportion of these patients since several patients in whom this product was not used had low-level antiporcine inhibitors or had no assessment of their inhibitor

with porcine factor VIII. Nevertheless, rVIIa was the most effective haemostatic agent used in these patients. The response to rVIIa used as salvage therapy was superior to that previously reported for conventional blood product therapy when used as first-line treatment (10-12, 14).

Efficacy may be greater when rVIIa is used as first-line therapy, since it was always effective in the sub-group treated in this way. It is also plausible that rVIIa may be more effective if used early, since non-responders had been treated with blood-products for twice as long as responders prior to the introduction of rVIIa although this difference was not significant.

The relatively low haemorrhagic mortality observed in this study may be an indication of improved haemostatic control compared with earlier series. Only 7.9% of our subjects died from haemorrhage attributable to acquired haemophilia and none were being treated with rVIIa when they died. This compares favourably with the 13-22% incidence of haemorrhagic death reported in earlier series (2, 3). Although this difference should be interpreted with caution, the prognosis may have been improved by treatment with rVIIa, particularly amongst those treated for potentially life-threatening haemorrhage which had failed to respond to conventional blood-product therapy.

Efficacy was unrelated to the dose of rVIIa in this study. Dose-ranging studies of rVIIa using single doses of 17.5, 35 and 75 μg/kg demonstrated a correlation between the dose used and both efficacy and recurrent bleeding (18). A recently reported trial of surgery in which patients were randomised to receive either 35 or 90 μg/kg of rVIIa 2 h showed the 90 μg dose to be clearly superior (22). Although some of our patients may have been treated with unnecessarily large doses of rVIIa, none were treated with doses less than 45 μg/ml and the median dose used was 90 μg/kg. These observations suggest that the optimal dose of rVIIa probably lies between 35 and 90 μg/kg, but this remains to be established and the optimal dose may vary with the clinical circumstances. Further dose-ranging studies are required.

No correlation could be demonstrated between efficacy and the degree of shortening of the PTT following infusion of rVIIa, in keeping with previous reports. Clinical response may be predicted by the plasma concentration of rVIIa, a possibility currently under investigation. If this is the case, interpersonal variation in factor VII half-life may be responsible for much of the variation in dose-response observed (23, 24).

Anti-fibrinolytic therapy may enhance the haemostatic effect of rVIIa which was used in only one of the five cases who failed to respond to treatment and five of the ten who obtained only a partial response.

One patient developed probable DIC during treatment with rVIIa. Although it cannot be excluded as a risk-factor for DIC in this case, it is unlikely to have been the cause, since DIC developed after 10 days treatment with rVIIa uncomplicated by coagulopathy when the dose rate of rVIIa had been reduced to half the starting rate and ten days after antifibrinolytic therapy had been discontinued. Furthermore, DIC developed during massive transfusion for cardiovascular collapse and following treatment with PCCs. These are all more-likely precipitants of DIC than rVIIa. One other case of DIC arising in during rVIIa therapy has been described. This patient with severe haemophilia A developed DIC following surgery for a massive abscess in the thigh and Salmonella septicaemia (19). Again, it developed after several days of uncomplicated reducing therapy with rVIIa and in the presence of other potent risk factors for DIC. These included systemic sepsis and massive blood transfusion. It must, therefore, remain doubtful that rVIIa causes DIC. This is a considerable advantage over PCCs and APPCs which are well recognised to cause DIC, thrombosis and myocardial infarction, particularly when used in large doses, in elderly patients with additional risk-factors such as liver disease and established arterial disease (13-15). These risks-factors for DIC and myocardial infarction with PCCs are particularly common in patients with acquired haemophilia most of whom will be elderly and many of whom will have established atherosclerosis.

RVIIa was otherwise associated with only very minor side-effects such as fever and nausea, and has not been reported to cause serious transfusion reactions, in contrast with the blood-product therapy (10, 11, 12). Blood products, including porcine VIIIc, PCCs and APCCS, may all also cause an anamnestic rise in inhibitor titre, a side-effect not associated with the use of rVIIa (17-19). This relative absence of significant side-effects is a major advantage of rVIIa over conventional treatment of factor VIII inhibitors with blood-products (10-14). One further advantage of rVIIa over plasma products is that it should not transmit blood-born viral infection since it uses no human plasma products either in manufacture or as an excipient and stabiliser.

All treatments for bleeding in patients with factor VIII inhibitors are costly, and rVIIa is no exception. The price of rVIIa was established with reference to the treatment of serious bleeding in inhibitor patients with prothrombin complex concentrates based on an international survey conducted on behalf of the manufacturer (25). RVIIa was calculated to cost slightly more, per treatment episode, than prothrombin complex concentrates (25). A direct comparison with the cost of human or porcine factor VIII is impossible since the cost of treatment with these products varies widely depending on the inhibitor titre and the development of an anamnestic response.

RVIIa is effective both as first-line and as salvage-therapy. It appears to be safe and is largely free from the risks and side-effects associated with alternative blood-product therapy. Further studies are required to establish effective laboratory monitoring of rVIIa treatment and continuous infusion procedure for this product so that treatment-cost may be minimised without loss of efficacy (26).

Acknowledgement

We are grateful to the following for contributing data to this series:

J. Alperin, University of Texas, Galveston, USA; E. Briët, Akademisches Ziekenhuis, Leiden, Netherlands; R. Bona, St. Francis Medical Center, Hartford, USA; N. Soo Chin, Subang Jaya Medical, Petaling Jay, Malaysia; B. Ewenstein, Brigham Womens Hospital, Boston, USA; L. Fiora, Dept. of Veterans Affairs, Boston, USA; J. Gill, Great Lakes Haemophilia Foundation, Wauwatosa, USA; M. F. X. Glyn, General Hospital Toronto ii, Canada; D. Green, Northwest University Medical Centre, Chicago, USA; J. Jacobson, West Roxbury VA, Boston, USA; G. Lucas, Manchester Royal Infirmary, Manchester, UK; L. Lyckholm, University of Iowa Hospital, Iowa City, USA; G. Macik, Duke University Medical Centre, Durham, N. Carolina, USA; B. A. McVerry, St. James' Hospital, Leeds, UK; M. Makris, Royal Hallamshire Hospital, Sheffield, UK; Martinez, Thomas Jefferson University, Philadelphia, USA; E. Meili, University of Zurich, Zurich, Switzerland; S. Oswald, E Army Medical Centre, Fort Gordon, USA; J. Owen, Bowman Grey School, Winston Sale, USA; M. Phillips, Gulf State Haemophilia Center, Houston, USA; O. Ratnoff, University of Cleveland, Cleveland, USA; H. Roberts, Chapel Hill, N Carolina, USA; G. Savidge, St. Thomas' Hospital, London, UK; E. Scheibel, University of Copenhagen, Copenhagen, Denmark; S. Schulman, Karolinska Hospital, Stockholm, Sweden; R. Streiff, Shands Hospital, Jacksonville, USA; J. Teitel, St. Michaels Hospital, Toronto, Canada; L. Tengborn, Sahlgrenska Hospital, Goteborg, Sweden.

We also thank Novo Nordisk for their assistance in making this data available.

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Received March 21, 1997 Accepted after resubmission July 17, 1997