Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors

A multi-centre, randomised, double-blind, cross-over trial

Khan Kavakli[1], Mike Makris[2], Bulent Zulfikar[3], Elizabeth Erhardtsen[4], Zvi S. Abrams[4], Gili Kenet[5] for the NovoSeven® trial (F7HAEM-1510) investigators

[1]University of Ege, Izmir, Turkey
[2]Royal Hallamshire Hospital, Sheffield, United Kingdom
[3]Istanbul University, Istanbul, Turkey
[4]NovoNordisk A/S, Bagsvaerd, Denmark
[5]Sheba Medical Centre, Tel-Hashomer, Israel

Summary

The aim was to evaluate the efficacy and safety of two recombinant factor VIIa (rFVIIa) dose regimens for treating haemarthroses in patients with congenital haemophilia A or B and inhibitors. This was a multicentre, randomised, cross-over, double-blind trial. Patients were randomly allocated to treat a first joint bleeding episode with one 270 μg/kg rFVIIa dose followed by two doses of placebo at 3-hour intervals and a second joint bleed with three single doses of 90 μg/kg rFVIIa at 3-hour intervals, or *vice versa*. Efficacy was evaluated using a novel and robust treatment response-rating scale based on patient-assessment of pain and joint mobility. Outcome was rated at different time-points, and an effective or ineffective treatment response was determined. Treatment "preference" was defined as effective treatment with one regimen and ineffective with the other. Patients with equally effective or ineffective treatments had no "preference". Treatment was rated as effective for 65% of patients using the 270 μg/kg dose versus 70% for the 90 μg/kg × 3 regimen. An equal "preference" was noted for the two regimens (21% for each; p=0.637); most patients (58%) had no "preference". 37/42 bleeding episodes (88%) were successfully treated with rFVIIa; additional haemostatic medications were administered for five episodes. No safety issues were identified. Administration of rFVIIa as a single 270 μg/kg dose to treat haemarthroses in patients with haemophilia and inhibitors was at least as efficacious and safe as the 90 μg/kg × 3 regimen.

Keywords

Recombinant FVIIa, haemophilia, inhibitor, high-dose, home treatment

Thromb Haemost 2006; 95: 600–5

Introduction

Recombinant activated coagulation factor VII [rFVIIa (NovoSeven®), Novo Nordisk A/S, Bagsvaerd, Denmark] is currently a first-line treatment of bleeding episodes in patients with congenital haemophilia A and B with inhibitors, and is used to treat patients with acquired haemophilia (1–3). In Europe, rFVIIa therapy has been approved for the treatment of patients with congenital FVII deficiency and those with Glanzmann's thrombasthenia refractory to platelet transfusions as well.

Effective haemostasis may be obtained in up to 92% of mild or moderate bleeding episodes following treatment with 90 μg/kg rFVIIa intravenous (i.v.) injections every 2–3 hours. Nonetheless, an average of 2.2 injections is required to achieve haemostasis in patients with haemophilia and inhibitors. It is well accepted that there is substantial interindividual variation in thrombin generation following rFVIIa administration (4): in some individuals 90–120 μg/kg rFVIIa may be the lower dose-limit required to produce sufficient thrombin, while in others, this dose may be below the "normal" lower dose-limit. The clearance

Correspondence to:
Dr. Gili Kenet
Pediatric Coagulation
National Hemophilia Center
Sheba Medical Center
Tel-Hashomer 52621, Israel
Tel.: +972 3530 2120, Fax: +972 35351 8065
E-mail: gili.kenet@sheba.health.gov

Financial support:
This study was sponsored by Novo Nordisk A/S, Bagsvaerd, Denmark.

Received July 21, 2005
Accepted after resubmission February 13, 2006

Prepublished online March 17, 2006 DOI: 10.1160/TH05–07–0510

rate of rFVIIa also varies (5–8). A preliminary trial in children less than 15 years of age indicates that clearance may be 50% higher in children compared with adults (9), suggesting that the use of higher doses in paediatric patients could be justified. Reducing the frequency of dosing by administering a single higher rFVIIa dose may also be beneficial for patients with restricted venous access, and may therefore be a more convenient alternative for some haemophilia patients with inhibitors.

Several reports suggest improved efficacy of rFVIIa when given as a single dose of greater than 90 μg/kg (10–13). A specific high initial dose of 300 μg/kg rFVIIa has been shown to be effective and safe for the treatment of haemarthrosis in patients with haemophilia and inhibitors (14).

In the home setting, a single dose regimen provides the most convenient way of managing a bleeding episode. Home treatment also enables early intervention, which is closely related to faster and more efficient haemostasis (15, 16) and a decrease in the number of days spent in hospital (17).

Previous studies using a higher dose of rFVIIa did not report any serious adverse events or thromboembolic complications (14). However, a controlled trial was needed to accurately assess the efficacy and safety of single doses of rFVIIa doses greater than 90 μg/kg compared with the repeated dose regimen. We conducted a randomised, double-blind, cross-over trial, to evaluate the efficacy and safety of a single dose of 270 μg/kg rFVIIa followed by two placebo doses versus three doses of 90 μg/kg rFVIIa administered at 3-hourly intervals. The aim of the trial was to demonstrate that a single dose of 270 μg/kg rFVIIa is at least as effective and safe as the 90 μg/kg × 3 dose regimen.

Materials and methods

Trial design

This was a multicentre, randomised, cross-over, double-blind trial (F7HAEM-1510) to compare the efficacy and safety of treating haemarthroses in patients with haemophilia and inhibitors with two rFVIIa regimens in a home-treatment setting. Eligible patients were symmetrically randomised to treat the first joint bleed with three consecutive 90 μg/kg rFVIIa injections at 3-hourly intervals and a second episode with an injection of 270 μg/kg rFVIIa followed by two placebo injections at 3-hourly intervals, or *vice versa*.

The selection of the repeated dose regimen was based on good clinical practice. Key, et al. (17) reported that to achieve adequate haemostasis an average of 2.2 doses of 90 μg/kg was required, followed by administration of an additional dose to maintain haemostasis. Based on these data, a regimen of three consecutive doses of 90 μg/kg rFVIIa at 3-hourly intervals was chosen. The decision to use a single dose of 270 μg/kg rFVIIa was based on the fact that it is equivalent to the total dose administered using the triple dose regimen.

Two separate joint bleeding episodes per patient were treated during the trial. Episodes of joint bleeding were treated with rFVIIa, which was administered at home within 1 hour from the onset of bleeding. Patients assessed each haemorrhagic event for at least 9 hours after administration of the first injection and recorded the results in a patient diary. Patients attended the clinic for a screening visit and for a follow-up visit within 7 days of each bleeding episode.

The trial was conducted in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki (18) and was approved by the local independent Ethics Committees of participating institutions. A blinded Novo Nordisk Safety Committee performed ongoing safety surveillance. In addition, an independent blinded expert reviewed data on pain and joint mobility and judged the responses to treatment as positive or negative based on a scoring system developed for this trial. This evaluation was performed after the last patient had received the last dose.

Patients

To be included in the trial, patients were required to: have a history of three or more haemarthroses during the preceding 12 months; have adequate venous access; and demonstrate, during the screening visit, the appropriate techniques for reconstituting and injecting the trial product. Patients also needed to be judged as capable of assessing the haemorrhagic event. Patients on immune tolerance therapy who developed break-through bleeding could be included in the trial.

The exclusion criteria included: receipt of any investigational drug within the 30 days prior to screening; joint bleeding within 7 days prior to screening; receipt of any treatment for bleeding episodes within 5 days prior to screening; clinically relevant coagulation disorders other than congenital haemophilia A or B; and a history of end-stage liver disease (Child-Turcotte classification C). Patients were withdrawn from the trial 12 months after randomisation if two bleeding episodes had not been reported within this timeframe.

Drug preparation and administration

Recombinant FVIIa was administered i.v. by a slow 2-minute injection. rFVIIa can not be diluted further than the prescribed reconstitution volume, hence to maintain blinding, an equal total volume/kg body weight of the trial product in an equal number of syringes was supplied to all patients irrespective of treatment group, by using concomitant placebo solution.

Efficacy and safety assessments

At the screening visit, information regarding the patient's demographics, medical history, concomitant illnesses, and medication was collected. In addition, the patient's vital signs, weight and height were measured and a full physical examination, including joint mobility assessment and measurement of the elbow and knee circumference at the midpoint of the joint at extension, was performed. Blood and urine samples were taken and used for the following analyses: complete blood count, blood chemistry, coagulation status (including coagulation factor levels and inhibitor status) and urinalysis.

No objective, versatile methods for continuously evaluating haemarthroses are available for daily clinical use. To date, clinical assessment of the range of joint movement and the patient's perception of pain have been used to determine any improvement in joint bleeding. In this study, efficacy was evaluated using two methods: i) the percentage of patients for whom haemostatic control was achieved without the need for additional haemostatic

Table 1: Global response scoring system.

Time after first injection	Pain			Mobility		
	More	No difference	Less	More	No difference	Less
1 h	N	P	P	P	P	N
3 h	N	P	P	P	P	N
6 h	N	N	P	P	N	N
9 h	N	N	P	P	N	N

N: negative; P: positive; ≥ 6P: global treatment effective; < 6P: global treatment ineffective.
For the primary efficacy analysis, pain was defined as negative if pain had increased ('more') at any of the timepoints, or not changed ('no difference') after 6 or 9 hours. Pain received a positive score when assessed as 'less' at any of the time points, or when assessed as 'no difference' after 1 or 3 hours. Mobility was defined as positive when 'more' mobility was observed at any of the time points, or when it was characterised as no different after 1 or 3 hours. Mobility received a negative score when assessed as 'less' at any of the time points, or when assessed as 'no difference' after 6 or 9 hours.

agents; and ii) the use of a novel and robust global treatment-response rating tool.

The primary efficacy endpoint was the global treatment response outcome, based on patient self-assessment of pain and joint mobility. The outcome was determined as effective or ineffective using the scoring system shown in Table 1. Pain and mobility were assessed at 1, 3, 6, and 9 hours after the first injection and were classified as positive or negative based on predefined criteria (Table 1). A total of eight scores were therefore obtained: one score for pain and one score for mobility at each of the 4 timepoints investigated. The global response to treatment was defined as effective if the patient had a total of six or more positive scores for each bleeding episode, and ineffective if the patient had five or less positive scores, or if the patient received additional haemostatic medication to control the joint bleeding episode within 9 hours of the first dose of rFVIIa.

Difference in outcome between the two dose regimens was also investigated for each patient. Treatment "preference" was defined as having effective treatment with one regimen and ineffective treatment with the other. Patients with equally effective or ineffective treatments were scored as having no "preference".

Table 2: Patient baseline characteristics.

	90 × 3/270 μg/kg rFVIIa regimen n=12	270/90 × 3 μg/kg rFVIIa regimen n=10	Total n=22
Age (years)			
Mean (SD)	29.9 (12.7)	24.5 (15.0)	27.5 (13.7)
Range	10 – 60	6 – 59	6 – 60
Ethnic group (N (%))			
White	11 (92)	9 (90)	20 (91)
NA	1 (8)	1 (10)	2 (9)
Weight (kg)			
Mean (SD)	67.5 (13.0)	56.5 (22.1)	61.5 (17.9)
Range	38.9 – 90.0	17.9 – 82.0	17.9 – 90.0
Height (m)			
Mean (SD)	1.7 (0.1)	1.6 (0.2)	1.7 (0.2)
Range	1.5 – 1.8	1.1 – 1.8	1.1 – 1.8
BMI (kg/m^2)			
Mean (SD)	22.7 (3.5)	20.4 (4.8)	21.7 (4.2)
Range	18.2 – 28.5	13.7 – 25.4	13.7 – 28.5

NA: Native American.

Safety was assessed by recording any adverse events that occurred between the first trial injection and up to 7 days after each episode of joint bleeding.

Statistical analyses

The sample size calculation was based on a one-sided exact sign test of equality of paired proportions. With 80% statistical power and a 5% significance level, we calculated that 24 patients would be required to detect a 30% difference between treatment regimens with respect to the proportion of effective treatments. This calculation was based on an assumed proportion of discordant pairs of 33%.

The efficacy analysis was predetermined to be based on only those patients who were randomised and received rFVIIa for two episodes of joint bleeding, thereby enabling intrapatient comparison of the two dose regimens. Safety analyses included all re-randomised patients dosed with rFVIIa.

The aim of the trial was to demonstrate that a single dose of 270 μg/kg rFVIIa is at least as effective and safe as the 90 μg/kg × 3 regimen. The statistical method used to fulfil this aim was to test if the 90 μg/kg × 3 dose regimen is superior to the 270 μg/kg single dose. The null hypothesis of no difference in treatment "preference" between the two dose regimens was tested against the alternative hypothesis: superiority of the 90 μg/kg × 3 regimen over the 270 μg/kg dose. If the hypothesis was rejected, the 270 μg/kg dose regimen was regarded as at least as effective as the 90 μg/kg × 3 dose regimen. This test of superiority, based on "preference" was performed as a one-sided exact sign test, also referenced as an exact version of McNemar's test, with a 5% significance level.

Results

Patient demographics

A total of 24 patients from six countries were screened for eligibility and all were included in the trial and randomised to treatment. Two patients were withdrawn, as they did not experience any haemarthroses within 1 year of randomisation; 22 patients therefore received rFVIIa and comprised the safety analysis population. As one patient had treated an apparent bleeding episode with no concurrent pain, impaired joint mobility, or joint swelling symptoms, this patient was excluded from the efficacy analyses prior to unblinding. A further two patients experienced only one haemarthrosis within the 12-month enrolment period and so did not contribute to the efficacy analysis as they did not complete the cross-over trial.

Baseline characteristics were similar between the treatment groups in terms of age, ethnicity, and body mass index (Table 2). The distribution of haemophilia A and B patients was similar between the two treatment sequences, with only one haemophilia B patient enrolled.

Efficacy

Using the global treatment response tool, 13/20 (65%) patients scored treatment with the single 270 μg/kg dose as effective compared with 14/20 (70%) for the 90 μg/kg × 3 dose regimen (Table 3). An equal "preference" with respect to the global treatment response was noted for the two dose regimens (270 μg/kg:

21%; 90 µg/kg × 3: 21%), and for the majority of patients (58%) there was no "preference". There was no statistically significant difference in the "preference" for the 270 µg/kg versus the 90 µg/kg × 3 dose regimen (p=0.637).

A total of 37/42 (88.1%) bleeding episodes were successfully controlled per protocol (without the need for additional haemostatic agents): 19/21 (90.5%) were successfully treated with the 270 µg/kg dose, and 18/21 (85.7%) with the 90 µg/kg × 3 regimen. Five patients, with one bleeding episode each, received additional haemostatic agents to control or maintain haemostasis within 48 hours of the first rFVIIa dose. Two patients received additional haemostatic medication after treatment with the 270 µg/kg dose, and three patients after the 90 µg/kg × 3 dose regimen (Table 4).

Safety

There were no withdrawals due to adverse events, deaths, serious adverse events, thromboembolic adverse events, or adverse events evaluated by the investigators as possibly or probably related to rFVIIa.

A total of 16 adverse events were reported by nine patients: seven events reported by six patients treated with the 270 µg/kg dose, and nine events reported by six patients receiving the 90 µg/kg × 3 regimen (Table 5). Eleven of the events were mild in severity, four were moderate and one was severe. Three haemorrhagic events, occurring 24 hours to 7 days after the first dose of rFVIIa was administered, were reported as adverse events, but these were not in the joints evaluated in the trial. No rebleeding events were reported. There was no apparent pattern in the distribution of adverse events between the two dose regimens.

Two non-treatment emergent serious adverse events were reported. One patient documented severe cholelithiasis more than 7 days after the first bleeding episode. Another patient reported a moderate respiratory tract infection before the first bleeding episode (pre-treatment). Investigators assessed both events as unlikely to be related to rFVIIa.

There were no clinically relevant changes in safety laboratory parameters when comparing end-of-trial and baseline values; no abnormal laboratory parameters reported after rFVIIa administration were found to be clinically relevant as judged by the investigators. There were no clinically relevant changes in coagulation-related parameters when comparing values at end-of-trial and baseline, and no indication of a systemic activation of coagulation, or consumption of coagulation factors in the rFVIIa treated patients (data not shown).

Table 3: Global treatment response (effective/ineffective) and "preference".

	90 × 3/270 µg/kg rFVIIa regimen n=11	270/90 × 3 µg/kg rFVIIa regimen n=10	Total n=21
90 µg/kg × 3			
n	11	9	20
Effective	7 (64%)	7 (78%)	14 (70%)
Ineffective	4 (36%)	2 (22%)	6 (30%)
270 µg/kg			
n	10	10	20
Effective	6 (60%)	7 (70%)	13 (65%)
Ineffective	4 (40%)	3 (30%)	7 (35%)
Preference			
n	10	9	19[a]
90 µg/kg × 3	2 (20%)	2 (22%)	4 (21%)
No preference	6 (60%)	5 (56%)	11 (58%)
270 µg/kg	2 (20%)	2 (22%)	4 (21%)
			p=0.637[b]

[a]Two patients experienced only one haemarthrosis during the trial; [b]p-value for the exact version of McNemar's test of preference.

Table 4: Additional haemostatic treatment.

Bleeding episode	Joint affected	Additional haemostatic product administered and time from start of trial product to administration of additional haemostatic treatment	Global treatment response
1st (270 µg/kg)	Right ankle	rFVIIa, 46 hours	Effective
2nd (270 µg/kg)	Left knee	FEIBA, ~14 hours	Ineffective
1st (90 µg/kg ´ 3)	Left knee (target joint)	FEIBA, > 3.5 hours[a]	Ineffective
1st (90 µg/kg ´ 3)	Left elbow	FEIBA, ~24 hours	Effective
1st (90 µg/kg ´ 3)	Left wrist	FEIBA, ~25 hours	Ineffective

[a]Start time on FEIBA treatment not available.

Table 5: All treatment emergent adverse events.

	90 µg/kg × 3 rFVIIa n=21		270 µg/kg rFVIIa n=21	
	N	E	N	E
All adverse events	6	9	6	7
Arthralgia	1	1	3	3
Joint crepitation	1	1	0	0
Haemorrhage	2	2	1	1
Nausea	1	1	0	0
Inflammation	0	0	1	1
Pain	1	1	0	0
Bronchitis viral	1	1	0	0
Headache	1	1	0	0
Tongue biting	0	0	1	1
Pruritus	0	0	1	1
Subcutaneous nodule	1	1	0	0

N: Number of patients with adverse event; E: Number of adverse events.

Discussion

Recombinant FVIIa has been used to control bleeding episodes in patients with haemophilia and inhibitors against FVIII or FIX. rFVIIa is thought to enhance thrombin generation on activated platelet surfaces found at the site of injury and the increase in thrombin leads to formation of a stable fibrin clot (19). Using higher than normally administered doses of rFVIIa, greater amounts of thrombin, liberated during the initial phase of clot formation (20), may induce a more stable haemostatic plug that is more resistant to fibrinolysis. Based on this concept, recent case studies have indicated safe and effective treatment of haemophilia patients with inhibitors with a single high dose of rFVIIa, instead of the standard dose regimen of repeated 90 µg/kg injections (12). Using this approach, the reported success rate, when defined as achievement of haemostasis following a single bolus injection, has exceeded 80% with no safety issues or thromboembolic complications (10, 13).

In the double-blind, randomised, cross-over trial described, a single 270 μg/kg bolus injection was as effective at achieving haemostasis, increasing joint mobility, and controlling pain as the 90 μg/kg × 3 rFVIIa dose regimen. 88.1% of bleeding episodes were successfully treated per protocol. Bleeding was controlled in 90.5% of episodes treated with the 270 μg/kg dose, and 85.7% treated with the 90 μg/kg × 3 regimen. This was, however, a small study with only 20 bleeds per treatment arm so further investigations are warranted. Furthermore, it is recognized that some patients may achieve haemostasis with only one or two doses of 90 μg/kg or any dosing up to 270 μg/kg, and this could not be assessed in the current study.

Since our study was designed for home treatment, no laboratory measures were applied in order to assess potential differences of patients' individual thrombin generation. For the purpose of this trial and to identify potential differences between two seemingly efficacious treatment arms, a stringent scoring system was designed and applied, called the global treatment-response rating tool. This system combines subjective pain relief scores and joint mobility measurements and allowed these two endpoints to be evaluated at sequential timepoints. So that a rigorous analysis could be performed, we predefined treatment as globally effective when at least six out of eight scores were positive. The results obtained using the global scoring system show comparable efficacy (65% and 70%) for both treatment regimens.

The global success rate obtained using this unique method of evaluation is lower than previously reported efficacy rates (1, 3, 10). However, other trials defined successful haemostasis according to a patient's subjective response, while we aimed to standardise definitions of effective haemostasis in haemophilia patients by combining subjective pain relief with joint mobility measurements. Joint mobility in haemophilia patients may not improve within the first hours following acute haemarthrosis (21), and pain relief is not always concurrent with improvement in mobility and may also be confounded by the successful use of analgesia, which could mean that an improvement in pain is not possible (22). The combined evaluation of pain and mobility at a given timepoint may, therefore, have led to the slightly reduced efficacy rate observed. In addition, our definition of effective treatment was more stringent than definitions used in other studies. Had effective treatment in our study been defined as more positive than negative responses, the overall rate of efficacy for both treatment regimens would have been increased to the levels reported in the mega-dose studies (10) and the HRS Registry (11). Despite the efficacy rates observed, we found similar efficacy outcomes for both of the treatment regimens tested.

In concordance with previous reports addressing the safety of high-dose rFVIIa treatment for joint bleeding in patients with haemophilia and inhibitors (10, 11, 13), the overall safety profile of rFVIIa was good for both treatment regimens. None of the adverse events occurring after administration of the trial product were serious and the adverse events were equally distributed between the two treatment regimens. Investigators judged all adverse events observed during the trial as unlikely to be related to rFVIIa. No thromboembolic events were reported and no clinical or laboratory signs of disseminated intravascular coagulation were reported.

In summary, administration of rFVIIa as a single 270 μg/kg dose to patients with haemophilia and inhibitors in the home setting for the treatment of haemarthrosis was found to be as least as efficacious and safe compared with administering three single doses of 90 μg/kg at 3-hourly intervals. This could have important implications for patients, their carers and clinicians since therapy consisting of a single dose could facilitate home treatment, which enables early intervention, and be of special benefit to children or other inhibitor patients with restricted venous access. This trial also emphasises the need for a commonly accepted standard efficacy evaluation of haemophilia treatments. Future trials addressing similar issues should use monitoring systems that will serve as biomarkers for treatment efficacy and help evaluate and standardise the efficacy endpoints.

Acknowledgements

The authors would like to thank Novo Nordisk A/S for sponsoring this trial and acknowledge P. B. Schelde (Novo Nordisk A/S) for contribution to the trial design, trial management and interpretation of the results and M. Suntum (Novo Nordisk A/S) for assistance with the data analysis and interpretation. The authors would also like to acknowledge Prof. U. Martinowitz for his input. The diligent cooperation of the trial site staff in the conduct of the trial is also acknowledged, in particular the following investigators: Dr Thierry Lambert (Hôpital de Bicêtre, Centre de traitement des hémophiles, Le Kremlin Bicêtre, France); Drs Chantal Rothschild, Marie-Françoise Torchet and Faézeh Legrand (Hôpital Necker, Centre de traitement des hémophiles JOSSO, Paris, France); Drs László Nemes and Zsuzsanna Szélessy (National Haemophilia Centre, National Medical Centre, Budapest, Hungary); Dr Aharon Lubetsky (Hemophilia Center, Tel-Hashomer, Israel); Dr Ana Cid (Hospital Universitario La Fe, Valencia, Spain); Dr Fernando Hernández (Hospital Universitario La Paz, Madrid, Spain); Dr Mark Winter (Haemophilia Centre, Kent & Canterbury Hospital, UK); Dr Jonathan Wilde (Queen Elizabeth Hospital, Birmingham, UK).

References

1. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. Thromb Haemost 1998; 80: 912–8.

2. Ingerslev J, Thykjaer H, Kudsk-Jensen O, et al. Home treatment with recombinant activated factor VII: results from one centre. Blood Coagul Fibrinolysis 1998; 9 (Suppl 1): S107–10.

3. Laurian Y, Goudemand J, Negrier C, et al. Use of recombinant activated factor VII as first-line therapy for bleeding episodes in haemophiliacs with factor VIII or IX inhibitors (NOSEPAC study). Blood Coagul Fibrinolysis 1998; 9 (Suppl 1): S155–6.

4. Sumner WT, Monroe DM, Hoffman M. Variability in platelet procoagulant activity in healthy volunteers. Thromb Res 1996; 81: 533–43.

5. Erhardtsen E, Nony P, Dechavanne M, et al. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. Blood Coagul Fibrinolysis 1998; 9: 741–8.

6. Schulman S, D'Oiron R, Martinowitz U, et al. Experiences with continuous infusion of recombinant activated factor VII. Blood Coagul Fibrinolysis 1998; 9: S97–101.

7. Schulman S, Bech-Jensen M, Varon D, et al. Feasibility of using recombinant factor VIIa in continuous infusion. Thromb Haemost 1996; 75: 432–6.

8. Shapiro AD, Gilchrist GS, Hoots WK, et al. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. Thromb Haemost 1998; 80: 773–8.

9. Villar A, Aronis S, Morfini M, et al. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) in children vs. adults with haemophilia A. Haemophilia 2004; 10: 352–9.

10. Kenet G, Lubetsky A, Luboshitz J, et al. A new approach to treatment of bleeding episodes in young he-

mophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven). J Thromb Haemost 2003; 1: 450–5.
11. Parameswaran R, Shapiro AD, Gill JC, et al. Dose effect and efficacy of recombinant factor VIIa (rFVIIa) in the treatment of hemophilia patients with inhibitors: analysis from the Hemophilia Research Society (HRS) Registry. Blood 2002; 100: Abstract.
12. Cooper HA, Jones CP, Campion E, et al. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. Haemophilia 2001; 7: 517–22.
13. Abshire TC. Dose optimization of recombinant factor VIIa for control of mild to moderate bleeds in inhibitor patients: Improved efficacy with higher dosing. Semin Hematol 2004; 41 (Suppl 1): 3–7.
14. Kenet G, Lubetsky A, Luboshitz J, et al. High dose recombinant activated factor VII for treatment of patients with hemophilia and inhibitors. Haemophilia 2004; 10 (Suppl 3): 53–66.
15. Lusher JM. Early treatment with recombinant factor VIIa results in greater efficacy with less product. Eur J Haematol 1998; 63 (Suppl): 7–10.
16. Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. Br J Haematol 1999; 104: 22–6.
17. Key NS, Nelsestuen GL. Views on methods for monitoring recombinant factor VIIa in inhibitor patients. Semin Hematol 2004; 41 (Suppl 1): 51–4.
18. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997; 277: 925–6.
19. Gerotziafas GT, Chakroun T, Depasse F, et al. The role of platelets and recombinant factor VIIa on thrombin generation, platelet activation and clot formation. Thromb Haemost 2004; 91: 977–85.
20. Lorand L. Sol Sherry Lecture in Thrombosis: research on clot stabilization provides clues for improving thrombolytic therapies. Arterioscler Thromb Vasc Biol 2000; 20: 2–9.
21. Rodriguez-Merchan EC. Haemophilic arthropathy in haemophilia patients with inhibitors: new perspectives. Haemophilia 2003; 9: 547–8.
22. Lusher JM, Eyster ME, Hilgartner MW, et al. Panel discussion on the treatment of patients with factor-VIII inhibitors. Prog Clin Biol Res 1984; 150: 323–35.