

Home Treatment of Mild to Moderate Bleeding Episodes Using Recombinant Factor VIIa (Novoseven) in Haemophiliacs with Inhibitors

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Summary

Objective. To assess the safety and efficacy of a fixed dose of recombinant activated factor VII (rFVIIa; NovoSeven™) in the home setting for mild to moderately severe joint, muscle, and mucocutaneous bleeding episodes in patients with haemophilia A or B with inhibitors. Design. Multicentre, open-label, single arm, phase III study of one year duration. Methods. Patients or their caregivers administered up to three doses of rFVIIa (90 μg/kg i.v.) at 3 h intervals within 8 h of the onset of a mild to moderate bleeding episode. Once the subject considered that rFVIIa had been "effective" with regard to haemostasis (after 1-3 injections), one further (maintenance) dose of rFVIIa was administered. Results. Of 60 patients enrolled, 56 experienced at least one bleed, and 46 completed the one year study. 614 of 877 bleeds (70%) were evaluable according to protocol definitions. Haemostasis was rated as "effective" in 92% (566/614) of evaluable bleeds after a mean of 2.2 injections. For successfully treated episodes, the time from onset of bleeding until administration of the first injection was 1.1 ± 2.0 h (mean ± SD). Twenty-four hours after initial successful response, haemostasis was reported as having been maintained in 95% of cases. Efficacy was comparable for muscle, joint and target joint, and mucocutaneous bleeding episodes. In an intent-to-treat analysis of all 877 bleeding events, efficacy outcomes were equivalent to the evaluable bleeds, with an effective response in 88% of treated episodes. Treatment-related adverse events occurred in 32 (3% of all) bleeding episodes and consisted of re-bleeds/new bleeds in more than 50% (18/32) of these events. A single episode of superficial thrombophlebitis was the only thrombotic complication encountered, and there were no patient withdrawals due to adverse events. Development of FVII(a) antibodies could not be detected, and hypersensitivity reactions to rFVIIa were not reported. Conclusion. rFVIIa is effective and well tolerated when used in the home setting to treat mild to moderate bleeding episodes in patients with haemophilia A or B with inhibitors.

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Introduction

The treatment of bleeding episodes in patients with haemophilia A or B with inhibitors remains problematic. Clinicians are frequently faced with a therapeutic choice between a strategy designed to raise FVIII/IX level by infusion of high doses of a coagulation factor concentrate (including porcine FVIII), or to administer a haemostatic agent that bypasses the need for FVIII or FIX (1, 2). Bypassing agents such as (activated) prothrombin complex concentrates that are currently available in the United States fail to produce predictable haemostasis (3) and thereby prevent sequelae in a significant proportion of patients. They may also provoke an undesirable anamnaestic response to FVIII or FIX (4), and, especially when used in large or repeated doses, may be associated with thrombotic complications and disseminated intravascular coagulation (DIC) (1, 2, 5). Recombinant activated factor VIIa (rFVIIa; Novoseven™) is a novel therapeutic agent which probably induces haemostasis by enhancing the activation of factor X, thereby effectively avoiding the need for both factors VIII and IX (6, 7). Its mode of action and early clinical experience have been reviewed elsewhere (8-10). The efficacy of rFVIIa is independent of the inhibitor titer, and it has been used successfully even in patients in whom alternative therapies have failed (11-15). The risk of systemic activation of the coagulation system with rFVIIa appears to be minimal, and it does not provoke an anamnaestic response to factors VIII or IX. Furthermore, in haemophilia A or B patients, surveillance for the formation of antibodies to FVII has so far been consistently negative (16).

All the studies of rFVIIa conducted to date have been undertaken in the hospital setting. In one such randomized, double-blind dose-finding study, the efficacy of two dosage levels of rFVIIa – 35 and 70 μg/kg – administered at an interval of 2.5 h was assessed in the treatment of bleeding episodes of mild to moderate severity in hospitalized patients (17). Both dosage levels demonstrated a comparable efficacy rate (71%) in the treatment of haemarthrosis, while the higher dose regimen was slightly more effective in the treatment of muscle haemorrhage (70% vs. 51%, respectively). Notably however, the median duration from onset of bleeding until the start of treatment was > 8 h, and there appeared to be a trend towards a better outcome for joint bleeds treated within 6 h in both groups. Thus, by prompt administration of rFVIIa

soon after the onset of bleeding, more successful treatment outcomes could theoretically be achieved. Self-administration of factor concentrates in the home setting by patients with haemophilia is now a widely accepted practice which allows early initiation of treatment, minimising pain and morbidity, and improving quality of life (18-21). Furthermore, the potential cost savings of home treatment, both with respect to health care costs and in wider economic terms, are considerable (22). Therefore, the primary objective of this study was to assess the safety and efficacy of a fixed dose (90 μg/kg) of rFVIIa administered in the home to treat joint, muscle, and mucocutaneous bleeding episodes in haemophiliacs with inhibitors. The dose level was selected based on clinical studies with rFVIIa treatment in the hospital setting (data on file, Novo Nordisk). The long-term nature of our study provided an opportunity to assess further the risk of FVII antibody formation in inhibitor patients. We also evaluated patients' acceptance of home treatment with rFVIIa; the result of this analysis will be reported at a later date.

Methods

Study Design

This was an open-label, single arm, unblinded multicenter study of a fixed dose of rFVIIa conducted in the home treatment setting. The planned study duration was one year. The study was conducted at 16 Haemophilia Treatment Centers in the USA according to the Principles of Good Clinical Practice. Written informed consent was obtained from individual patients after the study protocol and consent documents were approved by each Center's Institutional Review Board.

Patients

Patients were recruited for the study by individual Centers. All had severe haemophilia A or B complicated by inhibitors to FVIII or IX (respectively) and a history of two or more mild-to-moderate bleeding episodes suitable for treatment in the home setting in the preceding 12 months (see below for definition of severity of bleeding episodes). Patients and/or their caregiver had to have demonstrated the ability to reconstitute and administer intravenous rFVIIa, and to assess a bleeding episode and response to therapy.

Any patient who had received treatment with an investigational drug other than rFVIIa in the preceding 30 days was excluded from the study. Other exclusion criteria were the presence of any coagulation disorder except haemophilia A or B, any major organ disease (e.g. ischaemic heart disease or hepatic failure), a clinically significant laboratory finding (e.g. five-fold elevated liver function tests), or a diagnosis of AIDS at entry or during the study period. The latter was defined as the occurrence of an opportunistic infection and/or AIDS-related malignancy, and/or a CD4 count of < 200/mm^3. Human immunodeficiency virus (HIV) seropositive patients were eligible in the absence of the above criteria. Finally, patients were excluded if they demonstrated any hypersensitivity or other untoward adverse effects to a test dose of rFVIIa during the screening visit.

Although patients undergoing immune tolerance induction therapy were permitted to enroll in the study, the protocol stipulated that these participants would be withdrawn if their inhibitor was subsequently eliminated by immune tolerance therapy or lost due to another reason, such as HIV disease. Other potential reasons for withdrawal of patients who had been initially enrolled included delayed hypersensitivity to the study drug, development of a clinically significant laboratory finding considered possibly/probably related to the study drug, failure to adhere to protocol requirements, and failure to respond to two eligible treatments (exclusive of non-responsive bleeding events that occurred in target joints).

Table 1 Demographic characteristics and medical history

Characteristic		
Male sex		60 (100%)
Age (years)		4-50 (mean 21.2)
Weight (kg)		15.9-121 (mean 58.5)
Race:	Caucasian	47 (80%)
	Black	4 (7%)
	Other	9 (15%)
Type of haemophilia:	A with inhibitor	55 (92%)
	B with inhibitor	5 (8%)
Secondary diagnoses*:	Hepatitis A	4 (8%)
	Hepatitis B	25 (42%)
	Hepatitis C	49 (82%)
	HIV	6 (10%)

* Each patient may have more than one secondary diagnosis (all defined by serologic testing).

Treatment Protocol and Efficacy Assessment

During the screening visit, patients or their caregivers were instructed on the reconstitution and intravenous administration of a test dose (90 μg/kg) of rFVIIa. Further test doses were administered at the scheduled 6 and 12 month clinic visits. Blood samples were drawn 10 min after each of the three test doses of rFVIIa to measure FVII clotting activity (FVII:C). Plasma FVII:C was assayed at the core laboratory of Novo Nordisk Pharmaceuticals by a one-step prothrombin time-based clotting assay using FVII-deficient plasma as the substrate as previously described (23). Clotting was initiated using a thromboplastin derived from rabbit brain. Patient values were compared to a pooled plasma control obtained from healthy normal patients. FVII:C in normal plasma was assigned an arbitrary potency of 1 U/ml. In addition, serum was drawn at baseline, and at the 6 and 12 month visits for assay of anti-FVII(a) IgG antibodies, using a previously described method (16).

Eligible patients were provided with treatment modules of rFVIIa, with each module consisting of four 90 μg/kg doses (doses were individualized according to patient's body weight). Patients were instructed to initiate self-infusion of rFVIIa within 8 h after the onset of mild-to-moderate joint, muscle or mucocutaneous bleeding episodes. Severe bleeds (that were ineligible for therapy) were defined as those that were associated with significant blood loss, or severe pain, or could not otherwise be managed in the home setting (e.g. CNS bleeding, or internal haemorrhage). Upon developing a haemorrhage, the patient or his caregiver administered rFVIIa (90 μg/kg). Immediately after administering the first dose of rFVIIa, the following details were reported to the Haemophilia Center nurse by telephone: time of onset; location and type of bleeding (joint [target[1], non-target], muscle or mucocutaneous); severity of bleeding, swelling, pain and restriction of motion; and the time and volume of injection. Efficacy was assessed via telephone contact with the clinic 3 h after each dose, and was graded as: "effective" (bleeding ceased or decreased substantially); "partially effective" (bleeding reduced but continued); or "ineffective" (bleeding the same or worse).

Based on the 3 h bleeding assessments, further 90 μg/kg doses were then given as needed at the 3 and 6 h time points. Once the subject rated the haemostatic response as "effective" after 1-3 injections, an additional dose of rFVIIa (90 μg/kg) was given 3 h later to maintain haemostasis. Thus, for effectively treated bleeds, the number of doses varied from a minimum of two (one treatment plus one maintenance) to a maximum of four (three treatment plus one maintenance). Patients could treat bleeding episodes as often as necessary during the study period, with the exception of a new bleed or re-bleed which occurred within 24 h of the last dose of rFVIIa; these events were considered treatment failures, and alternative therapy (at the discretion of each investi-

[1] Target joints were defined as those that experience frequent haemorrhages with deformity, as a result of progressive arthropathy and synovitis.

gator) was initiated. If the patient inadvertently treated a re-bleed occurring within 24 h of treatment with rFVIIa, the outcome of that episode was not included in the efficacy assessment.

Following successful treatment of a bleed, the patient was contacted approximately 24 h later to assess the maintenance of haemostasis, which was then rated simply as "maintained" or "not maintained". Details of concomitant drug therapy and the number of doses needed to produce haemostasis (excluding the maintenance dose) were recorded. In the event that treatment was rated by the subject as "partially effective", or "ineffective" after 3 doses (i.e. at the 9 h time point), no maintenance dose was given and alternative standard care as prescribed by the investigator was initiated.

Concomitant use of (activated) prothrombin complex concentrate ([a]PCC) or another haemostatic agent was not permitted except as alternative therapy for patients in whom three injections of rFVIIa failed to achieve haemostasis, or in whom a new bleed or re-bleed occurred within 24 h of the last dose of rFVIIa. In these cases, alternative treatment was given at the discretion of the investigator, either in the clinic or at home. Antifibrinolytics were permitted only for mucocutaneous bleeding episodes if administered at least three hours after the final dose of rFVIIa.

Safety Assessments

A physical examination and routine clinical chemistry and haematology tests were performed at the pre-arranged 6 and 12 month clinic visits in addition to the screening visit. Patients were questioned about adverse events (AE) following each bleeding episode, and at the 6 and 12 month clinic visits. AE were coded using the NN WHO coding dictionary (version 2.0, dated 1995.05.01), according to body system. Bleeding episodes that were consistent with haemophilia but not treated with rFVIIa were not considered as AE. A serious AE was defined as any experience that suggested a medically significant hazard, including any event that was a) fatal or life-threatening; b) permanently disabling; c) a congenital abnormality; or d) diagnosed as cancer. In addition, any AE that required or prolonged inpatient hospitalization was also classified as serious. Relationship to the study drug was assessed by the investigator as "probable", "possible", "unlikely", or "unknown".

Statistics

The primary endpoints of the study were the percentage of patients achieving an "effective" response to therapy, the number of injections required to achieve this response, and whether the response (haemostasis) was maintained for 24 h following treatment.

For comparison of data requiring an adjustment for the fact that different patients contributed different numbers of bleeding episodes, generalized estimating equations – either with an assumption of no correlation between the successive bleeds or assuming correlation between successive bleeds for each individual patient – was used. A p value < 0.05 was considered significant.

Results

Demographic Characteristics

The demographic and medical characteristics of the enrolled patients are summarised in Table 1. All 60 patients received at least one test dose of rFVIIa, while 56 subsequently received home treatment for bleeding episodes during the study period. Of the 60 patients who entered the trial, 46 completed the 12-month study period, although 2 of these received the test dose only (i.e. they were never treated for bleeding by self-administration of rFVIIa). The reasons for discontinuation of the 14 individuals who failed to complete the trial were noncompliance (n = 4), lack of efficacy (n = 3), intercurrent medical problems (n = 2), successful immune tolerance therapy (n = 1), patient preference (n = 1) and failure to meet entry criteria/change in eligibility (n = 3). Of the latter group, one had a change in diagnosis (to von Willebrand's disease), one was re-classified as a less severe variant of hemophilia A (FVIII level = 4%), and one had significantly elevated liver function tests at screening. There were no withdrawals due to side effects. Five patients were receiving ongoing immune tolerance induction during the study, which was successful in one case (leading to withdrawal of that patient from the trial).

Usage of Other Medications

The nine patients with mucocutaneous bleeding episodes used concomitant tranexamic acid or aminocaproic acid on each occasion (n = 17). Activated prothrombin complex concentrate (aPCC) and PCC were also used by eight and five patients respectively for bleeding episodes during the study period. Recorded indications for the use of (a)PCC included the treatment of bleeding episodes ineffectively controlled by rFVIIa, the treatment of bleeding at a different site, or prior to physical therapy. Other medications used during the study included heparin to flush injection ports, analgesics (75% of patients; mainly

Table 2 Evaluable bleeds: treatment outcome, overall and by bleed severity and type

	Number of episodes	Effective	Partially effective	Ineffective	Missing data	Mean number of injections to achieve haemostasis	Haemostasis maintained for at least 24 h (based on effectively treated bleeding episodes)
Joint - all	490	452 (92%)	24 (5%)	8 (2%)	6 (1%)	2.2	429/452 (95%)
Joint - target	363	331 (91%)	19 (5%)	8 (2%)	5 (1%)	2.3	312/331 (96%)
Joint - non target	127	121 (95%)	5 (4%)	0 (0%)	1 (1%)	2.2	117/121 (97%)
Muscle	116	107 (92%)	6 (5%)	3 (3%)	0 (0%)	2.2	103/107 (96%)
Mucocutaneous	6	5 (83%)	1 (17%)	0 (0%)	0 (0%)	1.6	4/5 (80%)
Unknown site	2	2 (100%)					2/2 (100%)
All Bleeding Episodes	614	566 (92%)	31 (5%)	11 (2%)	6 (1%)	2.2	538/566 (95%)
Mild episodes	239	228 (95%)	7 (3%)	3 (1%)			212/228 (93%)
Moderate episodes	375	338 (90%)	24 (6%)	8 (2%)			326/338 (96%)
Time (h) from start of bleeding to first injection (mean [sd])		1.1 (2.0)	1.9 (1.7)	1.1 (0.8)			

Excluded patients were those with: severe bleeds; other haemostatic agents administered; >8 h from start of bleeding episode to first injection; only one injection of rFVIIa in case not effective.

acetaminophen and morphine), antibiotics (22%), antivirals (7%), anti-inflammatory drugs (12%), anticonvulsants (4%), anxiolytics (4%) and antipsychotic/ antidepressants (7%).

Efficacy

Data are presented initially for evaluable bleeds only (i.e. those meeting protocol definition), and then for all bleeds in an intent-to-treat (ITT) analysis.

a) Evaluable bleeds. Of the 877 total bleeding episodes, 614 (70%) in 52 patients met the protocol criteria for evaluable episodes; the distribution by type and severity of bleed is illustrated in Table 2. Reasons for non-evaluable status of the remaining 263 bleeds included one or more of the following: treatment with another haemostatic within 48 h of treatment with rFVIIa (n = 180), the use of non-permissible combined therapy to treat a bleeding episode (n = 97), elapse of more than 8 h from the onset of bleeding until administration of the first injection (n = 46), the bleed was rated as severe (n = 6) or of unknown severity (n = 1), and treatment was rated as "ineffective" and was erroneously discontinued after only one injection (n = 2).

Haemostasis was achieved in 566 (92%) of evaluable bleeding episodes (Table 2). The mean time to initiation of treatment for successfully treated cases was 1.1 h and a mean of 2.2 injections were administered until successful achievement of haemostasis (i.e. prior to administration of the maintenance dose). Following administration of the additional maintenance dose, haemostasis was maintained in 538/566 (95%) of successfully treated cases and results did not differ materially when bleeding episodes were classified by type or severity (Table 2). Maintenance of haemostasis appeared to be independent of the number of injections required to achieve haemostasis. Specifically, of those episodes in which haemostasis was maintained for at least 24 h, 29% had required 1 injection to achieve initial haemostasis, 24% required 2 injections, and 46% required 3 injections.

b) Intent-to-treat (ITT) analysis. A total of 877 bleeding episodes were recorded in 56 patients, all of which were included in the ITT analysis. The median number of treated bleeding episodes per patient was 8 with a range of 1-120 (Fig. 1). Most patients were treated for 2-10 different bleeding episodes. The distribution by type and severity of bleed is illustrated in Table 3.

rFVIIa was effective in producing haemostasis in 775 (88%) of all bleeding episodes; haemostasis was then maintained for at least 24 h in 720 (93%) of these successfully treated cases. In 23% of all effectively treated episodes haemostasis was achieved with just one injection of rFVIIa, while two injections were effective in a further 26% of episodes and three injections in the remaining 51%. Similar to the analysis of evaluable bleeds, maintenance of haemostasis was independent of the number of injections required to achieve haemostasis. Specifically, of the 720 episodes in which haemostasis was maintained for 24 h, an "effective" response had been achieved with 3 injections in nearly one half of cases (354/720, 49%), while approximately one quarter needed only 1 or 2 injections (172/722, 24%; and 191/720, 27%), respectively.

The mean time from bleeding to treatment onset was 1.6 h for effectively treated bleeding episodes and 2.4 h for episodes in which treatment was partially effective or ineffective. By a mixed model analysis, this time difference was not statistically significant. Of the 91 episodes in which bleeding was not completely controlled (partially effective and ineffective), the full three doses of rFVIIa had not been given on 14 occasions (15%). The majority of bleeding episodes ineffectively treated or maintained by rFVIIa were managed using aPCC (58 episodes in 17 patients) or PCC (29 episodes in 12 patients).

Efficacy, both with respect to achieving and maintaining haemostasis, was similar for all joint, target joint and muscle bleeding episodes (Table 3). Using generalized estimating equations with or without an assumption of correlation between successive bleeds, the apparently lesser response for the mucocutaneous bleeding episodes (12/17, 71%) was not statistically different from the response rate for joint or muscle bleeds. Response to therapy was also independent of the number of previously treated episodes; if anything, there was a trend towards an improved outcome with increasing number of bleeds, as shown in Table 3. Furthermore, the severity of bleeding also did not influence the response to therapy, with comparable outcomes for mild and moderate bleeding episodes (Table 3). As previously noted, although home treatment with rFVIIa should not have been initiated for severe bleeding, six severe bleeding episodes were actually treated. In five cases (83%),

Table 3 Intent-to-treat analysis: treatment outcome, overall and by bleed severity, type, and number

	Number of episodes	Effective	Partially effective	Ineffective	Missing data	Mean number of injections to achieve haemostasis	Haemostasis maintained for at least 24 h (based on effectively treated bleeding episodes)
Joint - all	685	604 (88%)	31 (5%)	43 (6%)	7 (1%)	2.3	562/604 (93%)
Joint - target	518	446 (86%)	26 (5%)	40 (8%)	6 (1%)	2.3	411/446 (92%)
Joint - non target	167	158 (95%)	5 (3%)	3 (2%)	1 (1%)	2.3	151/158 (96%)
Muscle	172	157 (91%)	9 (5%)	5 (3%)	1 (1%)	2.3	148/157 (94%)
Mucocutaneous	17	12 (71%)	3 (18%)	0 (0%)	2 (12%)	1.9	8/12 (67%)
Unknown site	3	2 (67%)			1 (33%)		2/2 (100%)
All Bleeding Episodes	**877**	**775 (88%)**	**43 (5%)**	**48 (5%)**	**11 (1%)**	**2.3**	**720/775 (93%)**
Mild episodes	303	276 (91%)	10 (3%)	13 (4%)	4 (1%)	2.0	248/276 (90%)
Moderate episodes	567	494 (87%)	33 (6%)	35 (6%)	5 (1%)	2.4	467/494 (95%)
Severe episodes	6	5 (83%)	0 (0%)	0 (0%)	1 (17%)	3.0	5/5 (100%)
First bleed	56	49 (88%)	3 (5%)	4 (7%)	0 (0%)	1.8	42/49 (86%)
10^{th} bleed	22	19 (86%)	0 (0%)	2 (9%)	1 (5%)	2.1	18/19 (95%)
Episodes 29-120	221	218 (99%)	1 (0.5%)	2 (1%)	0 (0%)	2.4	212/218 (97%)
Time (h) from start of bleeding to first injection (mean (sd))		1.6 (3.2)	2.4 (2.6)	2.4 (3.9)			

haemostasis was achieved and maintained but these patients required a higher number of injections to achieve an "effective" response (mean: 3) than patients with mild or moderate bleeding episodes.

Safety

Safety data were recorded for 937 infusions, which includes the administered test doses of rFVIIa in addition to the 877 treatment episodes. The investigators reported a total of 32 AE whose association with the study drug was either "probably related", "possibly related", or "of unknown relationship". These AE are presented in Table 4. Because (by definition) serious adverse events included any AE that led to hospitalization, 7 serious AE (incidence 0.7%) were encountered in which patients were admitted for inpatient management of a bleed and/or associated pain. None of the other criteria for serious AE (such as death or permanent disability) were encountered. Of the 7 serious AE, 5 occurred in a single patient. All of these events were haemarthroses (3 in the left shoulder joint, 1 in the right knee, 1 in the right elbow) that were either refractory to rFVIIa or had recurred within 24 h of treatment with rFVIIa (either at the same site or another site). In all cases, the investigator felt that a relationship to rFVIIa was either "possible" or "probable". The remaining two serious events occurred in two other patients (1 haemarthrosis and 1 muscle bleed). In both cases, the patient had not been treated with rFVIIa, and it seems likely that these events represent normal bleeding associated with haemophilia. They are discussed here because causality was assessed as "unknown" by the investigator.

Table 4 Adverse events related to treatment

Type of event	Patients with event (n=60)	Treatment episodes with event (n=937)
Bleeding episodes		
Haemarthrosis	7 (12%)	13 (1.4%)
Muscle haemorrhage	1 (2%)	1 (0.1%)
Haemorrhage (not otherwise specified)	1 (2%)	4 (0.4%)
Other Adverse Events		
Pain (not haemarthrosis)	1 (2%)	5 (0.5%)
Rash	1 (2%)	2 (0.2%)
Arthrosis	1 (2%)	1 (0.1%)
Thrombophlebitis (i.v. site)	1 (2%)	1 (0.1%)
Headache	1 (2%)	1 (0.1%)
Nausea	1 (2%)	1 (0.1%)
Infection	1 (2%)	1 (0.1%)
Fever	1 (2%)	1 (0.1%)
Inflammation at injection site	1 (2%)	1 (0.1%)
Total	13* (21.7%)	32 (3.4%)
Serious	3 (5.0%)	7 (0.7%)
Nonserious	11 (18.3%)	25 (2.7%)

*One patient had both serious and non-serious events

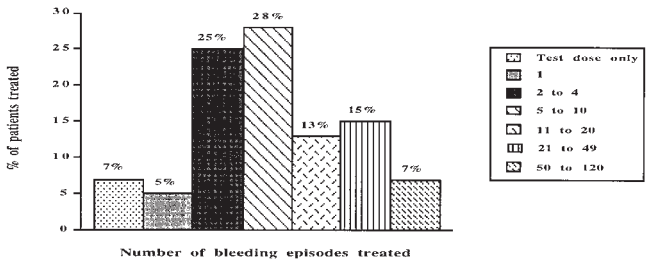

Fig. 1 Number of treated bleeding episodes per patient. Total number of patients = 60

In total, of the 32 related AE, 18 (56%) were bleeding episodes (Table 4), and about two-thirds of these represented re-bleeds after rFVIIa treatment. As discussed above, in view of these patients' underlying haemophilia, adverse events which were bleeds might actually represent treatment failures rather than drug-related adverse events. However, these events are presented as adverse events because, in the opinion of the individual investigators, the existence of a causal relationship with rFVIIa administration could not be excluded. The most frequent AE (serious or non-serious) were haemarthrosis/arthrosis [14 (44%), 6 of which (detailed above) were classified as serious by virtue of the ensuing hospitalization for haemostatic and/or analgesic therapy], muscle haemorrhage or haemorrhage not otherwise specified [5 (16%), 1 of which was serious] and pain not due to haemarthrosis [5 (16%)] (Table 4). Other than defective haemostatic complications, relatively few (14) other AE were encountered. Notably, only one thrombotic event – superficial thrombophlebitis at an intravenous access site (after 3 injections given at the same site) – was reported. No other cause for thrombosis was identified in this patient. This and other miscellaneous events (headache, nausea, infection, rash, fever, injection site inflammation) occurred with individual frequencies of 0.2% or less (Table 4).

There were no clinically significant changes in clinical laboratory parameters, vital signs or other physical examination findings during the 12 month-study period. No evidence for the development of IgG antibodies to rFVIIa was observed in 150 serum samples from 53 patients analysed.

FVII Recovery Studies

At the screening visit, FVII:C plasma levels rose from 0.88 ± 0.42 U/ml at baseline (normal range 0.54-1.23 U/ml) to 36.89 ± 11.71 U/ml at 10 min post-infusion. FVII:C recovery remained unchanged at the 6- and 12-month clinic visits (post infusion levels = 37.3 ± 11.0 and 37.4 ± 13.0 U/ml, respectively). For individual patients across time, there was no difference between the 10-min post-infusion values ($p = 0.22$) at the three visits. In aggregate, these data suggest that neutralizing antibodies to rFVIIa did not develop as a result of therapy.

Discussion

Recombinant FVIIa represents a new therapeutic approach in the management of haemorrhagic episodes in haemophiliacs with inhibitors and also for non-haemophiliac patients who have acquired these inhibitors (8-15, 24-26). In a previous compassionate use programme, rFVIIa was effective in controlling 80% of serious, life-threatening internal bleeding episodes in 60 patients with FVIII or FIX inhibitors refractory to other available products, and was partially effective in a

further 10% of episodes (12). Similar efficacy rates have been reported for central nervous system bleeding episodes including intracranial haemorrhages (13, 14). rFVIIa has also been used successfully to achieve haemostasis in patients undergoing surgery (10, 25).

Analysis of our data suggests that in >90% of cases of mild or moderately severe bleeding episodes in inhibitor patients, early administration of rFVIIa achieves haemostasis after 1 to 3 injections. In more than 90% of responders, haemostasis is maintained for at least 24 h. Furthermore, efficacy is independent of the severity of the bleeding episode (mild or moderate) and the number of previously treated episodes. Efficacy was comparable in joint, target joint and muscle bleeding episodes. Although mucocutaneous events were relatively few, comprising <2% of the number of bleeds, the efficacy of rFVIIa appeared to be comparable.

Comparison of efficacy results in the treatment of bleeding events in this study (of a similar type and severity) to the previous dose-finding study (17) was performed using generalized estimating equations with or without the assumption of correlation between successive bleeds. By this analysis, the difference in the proportion of patients reporting an effective response was significant ($p < 0.001$) in favour of the current study. The improved efficacy probably reflects not only the increase in dose (from 35 or 70 to 90 μg/kg), but also the more rapid initiation of treatment in the home compared with a hospital setting. Specifically, in our study the mean delay to initiation of treatment was 1.6 h compared to 20 h in the dose-finding study.

Safety is of paramount concern for home therapy. The studies of rFVIIa conducted in the hospital environment are reassuring, indicating that rFVIIa is well tolerated over the dose range 35-120 μg/kg, with a very low incidence of serious adverse events (25). We confirmed these findings in the context of home treatment; tolerability was good, even in patients in whom frequent courses were required, and no patient withdrew because of adverse events. A single episode of superficial thrombophlebitis at an intravenous injection site was the only thrombotic event reported in 937 test infusions and treatment episodes. The adverse event profile was also similar to that reported during hospital treatment; "serious adverse events" were infrequent, all were related to bleeding, and therefore most probably should be considered as treatment failures or inadequate treatment. Furthermore, there were no reports of hypersensitivity reactions. Although development of antibodies to FVII(a) could limit the effectiveness of this form of therapy, we were reassured to find no evidence for the development of such antibodies, even in patients who received a large number of treatment courses. These data are in keeping with those reported by Nicolaisen (16) suggesting that rFVIIa therapy in this type of patient is unlikely to be complicated by antibody formation, and are reassuring for both long-term home- and hospital-based treatment.

Home therapy of haemophilia is a treatment option that has been reported for haemophilia patients without inhibitors (18-21), and for those with inhibitors (5, 18, 27-29). Two-thirds of bleeding episodes in a group of 5 inhibitor patients reported by Pabinger and colleagues could be controlled with a single infusion of aPCC (18). Home treatment using porcine factor VIII has been used in inhibitor patients with an absent or modest anamnestic response to FVIII (28). In general, safety issues are infrequent with all forms of home therapy for haemophilia, while patient satisfaction is high (18, 21, 30). As a result, home therapy programmes have expanded over the past two decades. For instance, in the Netherlands during the period 1972-1985, the proportion of haemophilia patients in these programmes increased from 4% to 53% (31). It has been recommended that providing families are motivated, home care can be offered to children over the age of four years, and even earlier if indwelling venous access devices can be used (32). By starting therapy immediately when symptoms appear, the development of full-blown major haemarthrosis is prevented, thereby avoiding the development of synovitis and arthropathy. Minimising blood-induced synovial hyperplasia is likely the basis for the observation that early initiation of prophylactic treatment decreases the severity of chronic arthropathy in haemophilia patients (30, 33).

Similar principles apply to inhibitor patients, in whom acute and chronic morbidity and mortality are increasing in comparison with the general haemophiliac population. Early intervention with rFVIIa in the home setting may lead to more successful treatment outcomes, minimising tissue damage to joints and muscles, and thereby reducing long-term sequelae. Defining the minimum effective dose and frequency of dosing of rFVIIa in the treatment of mild or moderate bleeds was not the object of the current protocol. While the response to rFVIIa was rated as "effective" 3 h after the first dose of rFVIIa in about one quarter of bleeding episodes, it is entirely possible that this is a significant underestimate of the response to a single dose of rFVIIa, which would be better assessed at a later time point – perhaps 6 h or more (29). This can only be resolved by additional studies that specifically address this issue.

In conclusion, rFVIIa is an important addition to our armamentarium for treating inhibitor patients. The results of our study suggest that it is an effective and well tolerated form of therapy when used in the home setting.

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