

Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention

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Summary. To evaluate the feasibility, efficacy and safety of home treatment with recombinant activated factor VII (rFVIIa), 10 inhibitor patients (all haemophiliacs except one acquired post-partum) self-administered up to four doses of 90 µg/kg rFVIIa every 3 ± 1 h. The response was rated by the patient as effective (haemorrhage stopped or decreased substantially), partially effective (reduced) or ineffective (unchanged or worsened). 45 haemarthroses and eight haematomas were treated within a median time of 1.0 h (range 0.3–11.9) from the onset of bleeding, with a median of two rFVIIa doses per course (range 1–4). rFVIIa was effective in 42 episodes (79%), partially effective in six (11%) and failed in five (10%). Compared with

partially effective and ineffective treatments, effective treatments started earlier (median time: 0.6 v 2.7 h, $P=0.02$) and required a smaller number of doses (median: 1.5 v 3, $P=0.007$). The risk of a partially effective or ineffective treatment was smaller for treatments started within 6 h from the onset of bleeding than for those which started later (OR 0.24, 95% CI 0.09–0.63). Mild side-effects were reported only after 3/113 self-infusions (2.6%). Early home treatment with rFVIIa is safe, feasible and effective, inducing and maintaining haemostasis with a small number of doses.

Keywords: rFVIIa, inhibitors, haemophilia, home treatment.

The development of inhibitor alloantibodies to factor VIII (FVIII) is a major complication in the management of haemophilia A, occurring in 25–50% of severely affected patients (Bray *et al*, 1994; Lusher *et al*, 1993; Addiego *et al*, 1993). Even though inhibitors disappear spontaneously in approximately one third of cases, approximately half of the inhibitors reach high titres and persist unless immunotolerance is successfully induced (Bray *et al*, 1994; Lusher *et al*, 1993). Patients without haemophilia may also develop autoantibodies to FVIII. Haemostatic treatments used in patients with high responding inhibitors include porcine FVIII and FVIII bypassing agents, such as a prothrombin complex concentrate (PCC) or activated PCC (APCC), and, more recently, recombinant activated FVII (rFVIIa). Treatment with porcine FVIII requires monitoring of FVIII plasma levels and is sometime associated with thrombocytopenia and allergic reactions (Gringeri *et al*, 1991). Although home therapy with porcine FVIII has been successfully used in selected patients (Hay *et al*, 1996), this approach cannot be a

feasible and safe alternative for the majority of inhibitor patients. PCC and APCC have been widely used as first-line agents in high-responding haemophiliacs, being effective in approximately 50–65% of bleeding episodes (Lusher *et al*, 1980). However, these products are associated with an increased risk of thrombotic complications (Schimpf *et al*, 1982). rFVIIa is a new bypassing agent recently evaluated in compassionate use and investigational studies (Ingerslev *et al*, 1996; Lusher *et al*, 1998a). rFVIIa appears to be effective in 60–90% of treatment courses encompassing different types of haemorrhages and surgical procedures (Ingerslev *et al*, 1996; Lusher *et al*, 1998b). Its mode of action by initiating haemostasis only at the site of tissue injury should minimize systemic activation of coagulation, as demonstrated by a good safety record with respect to thromboembolic events (Hedner & Glazer, 1992). Other advantages of rFVIIa include viral safety, no anamnestic response, small infusion volumes and short infusion times. The main disadvantages of rFVIIa are its short half-life, necessitating repeated infusions at short time intervals, and the current paucity of data on optimal dosage and number of doses required. In this study the efficacy, feasibility and

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safety of a regimen based upon early home treatment with rFVIIa of acute haemorrhages of mild to moderate severity, was evaluated in high-titre inhibitor patients.

METHODS

Study design and patients. This open uncontrolled trial was designed for early self-treatment of patients with high-titre inhibitors using fixed doses of rFVIIa (Novoseven, Novo Nordisk, Denmark) at home. Eligible patients were haemophiliacs with high-responding inhibitors (historic inhibitor peak > 10 BU/ml) or patients with high titre, acquired anti-FVIII antibodies (> 10 BU/ml). To be included in the study, patients had to have already received at least one treatment course with rFVIIa in the hospital without side-effects. Patients were also selected on the basis of adequate venous access, ability in self-infusion, capability of assessing the response to therapy and accuracy in reporting side-effects. Children with inhibitor could enter the study if their carers met the inclusion criteria. Eligible bleeding episodes were mild/moderate haemorrhages, either spontaneous or associated with trauma, whereas patients were encouraged to come to the hospital to treat limb- or life-threatening bleeding episodes. Patients (or carers) were recommended to start rFVIIa treatment as soon as they experienced the early symptoms of bleeding. All information concerning the type and severity of bleeding, the time period between the occurrence of bleeding and initiation of treatment, timing of rFVIIa infusions, efficacy assessment following each infusion and at the end of treatment course and side-effects had to be carefully recorded by patients in a special data collection form. Haemorrhages into target joints, defined as those experiencing frequent bleeds with progressive arthropathy and synovitis, had also to be recorded. No laboratory monitoring was performed.

Home treatment regimen. The time between the onset of bleeding and the first rFVIIa infusion had to be < 12 h. No other haemostatic drug could be used before or during rFVIIa treatment. Analgesic and/or non-steroid anti-inflammatory drugs could be used and were recorded. rFVIIa was injected at the dose of 90 µg/kg b.w. every 3 ± 1 h with up to four infusions per bleeding episode. 3 h after each infusion, patients

were required to assess the response to treatment and to self-administer a further dose if the response was judged ineffective or partially effective. It was recommended to stop treatment if one of the following occurred: achievement of an effective response, or two consecutive infusions rated as ineffective.

Efficacy assessment. The response to rFVIIa was defined on the basis of patients' subjective judgement. The degree of severity of the bleeding episode was reported by the patient on a numeric scale (from 0: very mild, to 4: extremely severe) before starting treatment. The response to treatment was defined as follows: effective if a definite relief of pain, swelling and mobility occurred, suggesting that haemorrhage had stopped or decreased substantially; partially effective if an improvement in pain, swelling and mobility was perceived, suggesting a slowing of bleeding; ineffective if no relief of symptoms occurred and haemorrhage continued or worsened. Patients were asked to rate the response to rFVIIa 3 h after each dose and at the end of each treatment course.

Statistical analysis. For efficacy analysis, ineffective treatment courses and recurrences of bleeding at the same site within 48 h from the first rFVIIa infusion were considered treatment failures. Student's *t*-test and analysis of variance were used to compare different parameters among types of haemorrhages or timing of treatment start. Chi-square and Fisher's exact tests were used to compare the response rates among different types of haemorrhages or different timing of treatment start.

RESULTS

Among 20 patients with high-responding inhibitors regularly followed-up at the Haemophilia and Thrombosis Centre in Milan, 10 were enrolled in the trial because they met the inclusion criteria. All patients had severe haemophilia A, but a woman had post-partum acquired inhibitor. The median age at enrolment was 31 years (range 3–62). The median age at the time of first inhibitor detection was 13 years (range 2–61). Historic inhibitor peaks ranged from 16 to 16 000 BU/ml. The median inhibitor titre at the time of study entry was 18 BU/ml (range 1–870).

From February 1997 to May 1998, overall 59 bleeding episodes were treated at home with a median number of

Table I. Time from the onset of bleeding to the beginning of treatment and number of doses per treatment course in 53 bleeding episodes treated at home with rFVIIa.

Bleeding episode	No.	Hours from the onset of bleeding to the first rFVIIa dose, median (range)	No. of rFVIIa doses, median (range)
Haemarthroses	45 (85%)	0.8 (0.3–11.9)	2 (1–4)
In non-target joints	21 (40%)	0.5 (0.3–11.8)	1 (1–3)
In target joints	24 (45%)	1.25 (0.3–11.9)	2 (1–4)
Haematomas	8 (15%)	5.5 (0.3–11.8)	1 (1–4)
Spontaneous haemorrhage	41 (77%)	0.5 (0.3–11.9)	2 (1–4)
Post-traumatic haemorrhage	12 (23%)	5.5 (0.3–11.8)	3 (1–4)
Total	53 (100%)	1 (0.3–11.9)	2 (1–4)

Table II. Response to home treatment with rFVIIa in 53 bleeding episodes.

Bleeding episode	No.	Response to rFVIIa treatment		
		Effective	Partially effective	Failure
Haemarthroses	45	36 (80%)	4 (9%)	5 (11%)
In non-target joints	21	18 (86%)	2 (9%)	1* (5%)
In target joints	24	18 (75%)	2 (8%)	4† (17%)
Haematomas	8	6 (75%)	2 (25%)	–
Spontaneous haemorrhage	41	34 (83%)	3 (7%)	4 (10%)
Post-traumatic haemorrhage	12	8 (67%)	3 (25%)	1 (8%)
Total	53	42 (79%)	6 (11%)	5 (10%)

* Bleeding recurrency at the same site within 48 h of the first rFVIIa injection.

† Three ineffective treatment courses and one bleeding recurrency at the same site within 48 h of the first dose.

treatment courses per patient of three (range one to 16). Overall 697 mg of rFVIIa (median 48 mg/patient, range 4.8–174) were employed in a total of 113 self-infusions (median eight infusions/patient, range one to 29), and all were considered for safety evaluation. rFVIIa infusions were administered by carers in the only child enrolled in the study. No patient required hospital admission nor experienced technical problems related to factor injections. Mild side-effects occurred after 3/113 infusions (2.6%), all reported by the same patient who complained of a transient increase of pain at the bleeding site after 3/29 rFVIIa injections.

Fifty-three treatment courses (90%) were evaluable for efficacy (Table I). The median amount of rFVIIa administered per treatment course was 12.0 mg (range 4.8–28.8). The median number of rFVIIa doses per treatment course was two and no statistically significant difference was found in the number of doses required to treat the different types of bleeding episodes (Table I). The time spent from the onset of bleeding to the first rFVIIa injection is reported in Table I; haematomas and post-traumatic haemorrhages were treated significantly later than the other episodes, whereas the time to the beginning of treatment was not significantly different between target and non-target joint bleeds. Efficacy data concerning 53 treatment courses are reported in Table II, showing that, on the whole, home treatment with rFVIIa was effective in 42 (79%) bleeding episodes and partially effective in six (11%). Treatment failures occurred in five

episodes (10%). In particular, rFVIIa therapy was judged ineffective in three haemorrhages that occurred into target joints, whereas the remaining two failures were due to recurrent joint haemorrhages within 48 h of the first rFVIIa injection (one of these recurrent haemorrhages was into a target joint). Both bleeding recurrences were treated with APCC. No statistically significant difference was observed in the responses to rFVIIa according to the different types of bleeding episodes. Effective treatment courses started significantly earlier and required a lower number of rFVIIa doses compared to courses with partially effective responses or treatment failures, as shown in Table III. In particular, the risk of having a partially effective outcome or a treatment failure was significantly lower for courses started within 6 h of the onset of bleeding than for those started after 6 h (odds ratio 0.24, 95% confidence interval 0.09–0.63).

DISCUSSION

It is generally agreed that the early treatment of bleeding in haemophilia, as allowed by self-administration at home, results in a high success rate. However, this approach has not been widely adopted in patients with inhibitors, because this complication renders treatment more difficult and that the products available were not safe enough for home infusion. rFVIIa looks promising for home therapy of mild to moderate haemorrhages in inhibitor patients, thanks to its

Table III. Time from the onset of bleeding to the beginning of treatment and number of rFVIIa doses per treatment course in 42 effective treatment courses compared to 11 courses with partially effective outcome or treatment failure.

Treatment outcome	No.	Hours from the onset of bleeding to the first rFVIIa dose, median (range)	No. of rFVIIa doses, median (range)
Effective	42 (79%)	0.6 (0.3–11.8)	1.5 (1–4)
Partially effective or failure	11 (21%)	2.7 (0.3–11.9)	3 (1–4)
<i>P</i> value		0.02	0.007

safety profile and the absence of an anamnestic response. This study, designed to evaluate the efficacy and feasibility of this therapeutic modality, employed a regimen based upon fixed doses of rFVIIa injected at regular time intervals, chosen to simplify patient self-administration at home. The dosage and the time intervals of injections were chosen on the basis of data from pharmacokinetic studies of rFVIIa in humans (Hedner, 1996). Patient reliability and compliance were essential prerequisites for enrolment in this study, because early treatment was strongly recommended and efficacy assessment was based solely on patient judgement. Over 15 months, 59 bleeding episodes, mostly haemarthroses, were managed at home with a small number of rFVIIa infusions by 10 inhibitor patients with no need for hospitalization. The feasibility and safety of home treatment with rFVIIa were excellent. Efficacy was also satisfactory with an effective control of haemorrhage in about 80% of treated episodes. Recurrence at the same bleeding site occurred within 48 h of the first rFVIIa dose in 3.8% of treatment courses. Two rFVIIa infusions were sufficient to achieve a successful outcome in more than half of the bleeding episodes, so that most patients recovered within 6 h of the first dose. Interestingly, the rate of effective responses as well as the number of doses used was similar in treatment courses for target and non-target joint bleeds, although four of the five failures were observed after treatment of target joint bleeds. The size of the study is inadequate to detect differences among different sites of haemarthroses and between haemarthroses and haematomas.

There is little detailed information about the use of rFVIIa as home therapy, because the results of studies currently undergoing in the U.S.A. (Key, 1997), France (Laurian *et al*, 1998) and Denmark (Ingerslev *et al*, 1998) have been only published in abstract form. The preliminary results of the US rFVIIa Home Therapy Study (Key, 1997), which is similar to this study, in terms of treatment regimen and efficacy evaluation criteria, give a rate of effective responses of 92%. Differences in type and severity of treated episodes or the use in the U.S.A. study of a consolidation dose of rFVIIa after successful outcome might account for the slight difference in success rate between the two studies. In the different home therapy studies the number of doses required to stop bleeding was quite low, the median value being <2.0 in the Danish (Ingerslev *et al*, 1998) and our studies, and equal to 2.2 in the U.S.A. study (Key, 1997) and 2.9 in the French report (Laurian *et al*, 1998). A recent report (Key & Laurian, 1998) comparing the U.S.A. and French studies failed to demonstrate any significant reduction in bleeding recurrence using rFVIIa for consolidation of successful outcomes. Our observed recurrence rate at 48 h without consolidation doses (3.8%) was lower than that observed by Key & Laurian (1998) (6.1% using a consolidation dose and 8.2% without) and similar to the recurrence rate at 24 h reported in the U.S.A. study which used a consolidation dose (Key & Laurian, 1998) (4.9%). Therefore the results of our study support the views that additional injections may not be necessary to maintain haemostasis after a successful response in home treatment with rFVIIa.

Recently, many efforts have been made to collect data supporting the hypothesis that early treatment with rFVIIa could produce a better outcome. Lusher (1998) analysed the data of three different studies (Lusher *et al*, 1998a, b; Key, 1997) in which muscle haematomas were treated with rFVIIa enabling a comparison between early versus late intervention. These studies were not strictly comparable in terms of dosages used; however, preliminary results strengthened the views that a greater success rate with fewer doses can be achieved with early intervention. Our study clearly demonstrates the positive correlation existing between effective outcome and early start of rFVIIa therapy. The probability of achieving an effective response was 4 times greater in treatments started within 6 h from the onset of bleeding than in those started later. The mean cost of a single treatment course with rFVIIa in this study was \$8746. Considering that the cost of APCC treatment with two doses per bleeding episode is about \$10,000 in Italy, home treatment of mild/moderate haemorrhages with rFVIIa appears no more expensive than treatment with APCC.

In conclusion, our experience with rFVIIa for home treatment of haemarthroses and haematomas was successful in terms of feasibility, efficacy and safety, confirming that selected inhibitor patients, well-instructed and compliant, may benefit from early self-administration of rFVIIa in the home setting. In these cases rFVIIa may represent a safe first-line treatment requiring a small number of doses and enabling a reduction in the number of days spent in hospital and consequently in the related cost.

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