The Evidence behind Inhibitor Treatment with Recombinant Factor VIIa

Christopher A. Ludlam

Haemophilia and Thrombosis Centre, Royal Infirmary, Edinburgh, UK

Abstract

Over the past 10 years considerable use has been made of recombinant factor VIIa (rFVIIa) for the treatment of patients with inhibitors to coagulation factors. During this time, its place in the management of acute bleeds and surgery has become better defined. Although pharmacokinetic studies report the half-life of rFVIIa as 2.7 h, there is considerable intersubject variability. Moreover, rFVIIa is cleared more rapidly in children than in adults. Assays for the measurement of rFVIIa plasma levels are not readily available in clinical diagnostic laboratories, although there is evidence that plasma FVII:C levels, measured by a one-stage prothrombin-based assay, reflect the plasma concentration of rFVIIa:C. The level of FVII:C required to achieve haemostasis in different clinical circumstances remains uncertain. In order to overcome the logistic difficulties of repeated frequent bolus injections, and potentially to minimise usage, administration of rFVIIa by continuous infusion has been reported. However, there is some uncertainty as to whether continuous infusion of rFVIIa has similar therapeutic efficacy to an equivalent total dose administered by bolus injections. The extensive clinical experience with rFVIIa in haemophilic patients with inhibitors has been recorded in descriptive accounts of the Compassionate Use Programme and the Emergency Use Study. On the basis of the apparent clinical efficacy and safety reported in these studies, prospective randomised trials of different dose regimens have been undertaken for the treatment of acute bleeds and surgery. These have helped to define the minimum dose needed to achieve haemostasis. There remains considerable uncertainty about the minimal effective dose and appropriate duration of therapy in different clinical circumstances. There is therefore a need for the development of evidence-based guidelines for the use of rFVIIa bolus and continuous infusion regimens in different settings, and for the therapeutic value of measuring plasma concentrations of rFVIIa, to facilitate the optimal use of this product. Furthermore, additional randomised clinical trials will help ensure that rFVIIa is used in the most clinically and cost effective way.

Introduction

Recombinant factor VIIa (rFVIIa) has been available for more than a decade. During this time, a wealth of experience has accumulated in the role of rFVIIa in managing haemophilia patients who have inhibitors to FVIII or IX. Such patients are resistant to conventional factor VIII concentrate therapy. Trials and case reports suggest that rFVIIa is effective in a variety of challenging clinical situations, including emergency treatment of acute bleeds, home treatment, and in acquired haemo-
philia. It is coming under close scrutiny as a potential solution for those inhibitor patients who require surgery, an aspect of haemophilia care that is fraught with difficulties. Research is also focusing on dose regimens and on methods of administration of rFVIIa in an effort to determine the most effective and practical way of using the treatment.

This paper reviews the trial data for rFVIIa and highlights some of the questions that remain regarding the optimum use of this concentrate in the management of haemophilia patients with inhibitors.

Pharmacokinetics

Recombinant FVIIa has a short half life of 2.7 h in adults and only 1.3 h in children [1]. Clinical use of rFVIIa is further complicated by the fact that there is considerable variation in its pharmacokinetic behaviour between individual patients. This has led to suggestions that pharmacokinetic evaluation may be necessary for each patient.

Plasma levels of FVIIa can be measured with a conventional one-stage prothrombin-based, FVII:C assay. The level of FVII:C, hence the dose of rFVIIa, required to achieve haemostasis in different clinical settings is the subject of close investigation.

Early Clinical Studies

During the first 8 years that rFVIIa was available, patients received the agent under the Compassionate Use Programme [2–4]. Of 260 patients internationally who received rFVIIa in this programme between 1988 and 1996, 75% had haemophilia A or B, 14% had acquired haemophilia, and 11% had FVII deficiency. Over 1,000 bleeds were treated with rFVIIa given in bolus doses of 60–90 µg/kg. The efficacy was found to be 80–87% in serious bleeds and 91–94% in surgical bleeds.

The Compassionate Use Program was followed by the 3-year Emergency Treatment Study, completing in 1999 [5, 6]. In this study, 253 acute bleeds in 127 patients were treated with rFVIIa, 90 µg/kg 2-hourly. The efficacy was 93% for haemophilia A or B patients with inhibitors and 71% for acquired haemophilia. In FVII-deficient patients the efficacy was 89% (table 1).

These promising results led to the first prospective randomised trials of various doses of rFVIIa in haemophilia patients with inhibitors.

Dose Finding Study

The first randomised, double-blind trial was an international dose-finding study of acute bleeds in severe haemophilia [7]. The multicentre trial involved 84 patients with 179 joint or muscle bleeds, of which 145 were evaluable. Patients received rFVIIa in a dose of 35 or 70 µg/kg in a parallel group design. Results showed that the two doses achieved similar rates of efficacy, which was graded as excellent or effective in 71% of bleeds. The mean number of doses given to the two groups was similar – 2.7 in the 35 µg/kg group and 3.1 in the 70 µg/kg group. These findings raised questions over optimum dosing for acute bleeds: either 35 µg/kg is adequate, or 70 µg/kg is inadequate.

Home Treatment Studies

Safety and efficacy of rFVIIa as home treatment have been confirmed by four major studies, involving a total of 102 patients and 864 bleeds [8–11]. Similar doses were used in each study, usually 90 µg/kg. Efficacy was approximately 90% in three of the studies and 79% in the fourth. The mean number of injections to obtain haemostasis was 2.2, although in the N American study an additional injection was given after the patients considered that they had stopped bleeding.

Delay to Treatment

In a review of intramuscular bleeds included in the Compassionate Use Study, the Dose-Finding Study and the US Home Treatment Study, it was found that the earlier the rFVIIa treatment is initiated, the better the clinical outcome [8–11] (table 2). During the Compassionate Use
Table 2. Comparison of time of treatment and response for peripheral intramuscular haemorrhages

<table>
<thead>
<tr>
<th></th>
<th>Dosage µg/kg</th>
<th>Time to treatment</th>
<th>Excellent or effective response, %</th>
<th>Mean number of doses of rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compassionate use</td>
<td>60–120</td>
<td>5 days</td>
<td>63.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Dose finding</td>
<td>70</td>
<td>9 h</td>
<td>72</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>9 h</td>
<td>53</td>
<td>3.5</td>
</tr>
<tr>
<td>US home treatment</td>
<td>90</td>
<td>1.2 h</td>
<td>92</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Clinical response to rFVIIa treatment related to time from start of bleed [8–11].

Use Study, in which other treatments were tried first and rFVIIa was not given until day 5, an excellent or effective response was achieved in only 63% of intramuscular haemorrhages. In contrast, in the US Home Treatment Study in which the delay to rFVIIa treatment was only 1 h after the onset of the bleed, the response rate was 92%. There was a corresponding fall in the number of injections needed to achieve haemostasis – a mean of 13.6 injections in the Compassionate Use Study compared with only 2.3 in the US Home Treatment group.

Acquired Haemophilia

The benefit of starting rFVIIa treatment early after the onset of bleeding was shown again in a database analysis of 74 bleeding episodes in 38 patients with acquired haemophilia reported to Novo Nordisk [12]. Patients received rFVIIa as a first-line or salvage treatment for muscle haematoma, urinary/GI bleeds, haemarthroses, or surgery. A dose of 90 µg/kg was used, with a median of 28 doses given over approximately 4 days. For all 14 bleeding episodes where rFVIIa was received as first-line therapy, there was a good haemostatic response, compared with 75% of 60 bleeding episode where FVIIa was used as a salvage therapy.

Surgery

Smith and Hann were the first to describe the successful use of rFVIIa for central intravenous catheter insertion in children with haemophilia [13]. They used a 90 µg/kg dose of rFVIIa administered 2-hourly for 1 day and 4-hourly for a further 2 days, always with tranexamic acid. Their positive results have since been confirmed in a further study [14].

Other studies have attempted to establish the haemostatic dose of rFVIIa to prevent post-operative bleeding in haemophilia patients with inhibitors following surgery. One such study was a prospective double-blind trial comparing 35 µg/kg with 90 µg/kg of rFVIIa [14]. Patients were randomised to receive one of the two doses as a bolus injection, beginning pre-operatively, then 2-hourly for 2 days and 2–6 hourly for a further 3 days. Of the patients, 18 had minor surgery (all central venous catheter insertions) and 11 had major surgery, mostly orthopaedic. At 48 h after wound closure the results showed that for minor surgery, haemostasis was achieved in all 8 of those receiving the 90 µg/kg dose and in 9 of 10 patients receiving 35 µg/kg. Among the patients undergoing major surgery, all 6 patients receiving the higher dose and 3 of 5 receiving the lower dose achieved haemostasis.

For minor surgery, the median total dose of rFVIIa was slightly less for the 35 µg/kg dose group than for the 90 µg/kg dose (45 mg compared with 67 mg) (table 3). However, in patients undergoing major surgery, more rFVIIa was used in the low dose group than in those receiving the high dose (656 vs. 569 mg). Correspondingly, more injections of rFVIIa were needed in the major surgery patients allocated to low dose (median 135 vs. 81 in the high dose group), because of the patients who bled following the low dose. Treatment was given for a median of 15 days with the lower dose compared with 9.5 days for the higher dose. These findings reflect the fact that loss of haemostasis post-surgery can be extremely difficult to control. Therefore, using the lower dose of a coagulation therapy does not necessarily result in less of the drug being used over the course of the treatment period.

The authors concluded that while minor surgery was well controlled with bolus doses of 35 µg/kg of rFVIIa, major surgery needed 90 µg/kg.
Table 3. rVIIa 35 and 90 μg/kg boluses in surgery dosing

<table>
<thead>
<tr>
<th></th>
<th>Minor surgery</th>
<th>Major surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35 μg/kg (n = 10)</td>
<td>90 μg/kg (n = 7)</td>
</tr>
<tr>
<td>Median duration of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing, days</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Range</td>
<td>3–6</td>
<td>3–6</td>
</tr>
<tr>
<td>Median number of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td>29.5</td>
<td>38.0</td>
</tr>
<tr>
<td>Range</td>
<td>24–44</td>
<td>26–67.0</td>
</tr>
<tr>
<td>Median total dose of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFVIIa, mg</td>
<td>45.5</td>
<td>67.0</td>
</tr>
</tbody>
</table>

A prospective double-blind trial comparing 35 μg/kg with 90 μg/kg of rFVIIa in patients undergoing surgery [14].

Table 4. rVIIa by CI at 50 μg/kg/h elective orthopaedic surgery

|                  |               |               |               |               |
| Bolus 90 μg/kg pre-operative |            |               |               |               |
| CI – 50 μg/kg/h | 50 μg/kg/h |            |               |               |
| Duration – at investigators discretion |            |               |               |               |
| Bleeds – bolus 60 μg/kg |            |               |               |               |
| FVII:C – reached 30 IU/ml in 87% |            |               |               |               |

Protocol for continuous infusion of rFVIIa at 50 μg/kg/h for orthopaedic surgery.

Administration

In view of the short half life of rFVIIa, continuous infusion has been investigated as a possible means of overcoming the logistical difficulties of administering frequent bolus injections and possibly to minimise the dose required.

An Italian study investigated the continuous infusion of rFVIIa in doses of 16–20 μg/kg/h in 35 patients with FVIII inhibitors [15]. Of the patients, 11 underwent major surgery, 14 had minor surgery and 10 had spontaneous bleeds. They received an initial bolus dose of approximately 100 μg/kg prior to continuous infusion at a dose determined by the attending physician. Median doses were 20 μg/kg/h for the patients undergoing major surgery, 17 μg/kg/h for those having minor surgery, and 16 mg/kg/h in the spontaneous bleeds group. Treatment was continued for 8 days following major surgery, 3 days after minor surgery, and 5 days for those with spontaneous bleeds.

Haemostasis was effective in 30 of the patients, partially effective in 2 and ineffective in 4 individuals. This study found that plasma FVII level did not appear to be related to the propensity to bleeding.

Continuous Infusion Dose

The relationship between efficacy and plasma levels of FVII was studied more closely by our group in a trial of 8 inhibitor patients undergoing elective surgery [16]. One of the aims of this study was to see whether a continuous infusion dose of 16.5 μg/kg/h would achieve FVII plasma levels of at least 10 IU/ml, believed at the time of the study to be the haemostatic level for FVIIa. Six patients had major surgery (joint replacement) and 2 had minor surgery (1 bladder biopsy, 1 central line insertion). They were given an initial bolus of 90 μg/kg pre-operatively followed immediately by the continuous infusion. If a patient bled, a bolus of 60 μg/kg rFVIIa was given.

The study showed that FVII:C of at least 10 IU/ml was achieved in approximately 90% of assays. However, the clinical outcome was disappointing. Haemostasis was satisfactory in only 3 of the 8 patients: 1 of the 2 patients undergoing minor surgery and 2 of the 6 patients having major surgery.

In the light of these results, we initiated a second study to see whether increasing the dose of continuous infusion of rFVIIa – thereby raising the plasma level of FVII – would lead to less post-operative bleeding. In this study the aim was to achieve a FVII level of 30 IU/ml. Computer modelling predicted that this would be achieved with an infusion of 50 μg/kg/h and this dose was therefore used in the study [17]. Of the 9 patients, 8 had major joint replacements and 1 an amputation. The patients received a 90 μg/kg bolus of rFVIIa pre-operatively prior to continuous infusion, the duration of which was at the investigator’s discretion.

The FVII:C level of at least 30 IU/ml was achieved in almost 90% (table 4). Following surgery bleeding occurred in 6 patients but all except one settled with a single bolus of 60 μg/kg rFVIIa. All patients had a good clinical outcome from the surgery.

Thus the continuous infusion of 50 μg/kg/h results in a FVII:C of 30 IU/ml and this level of FVII is adequate to achieve haemostasis. In this study, patients received the
infusions for a median of 20 days, but for non-trial clinical use it is likely that a shorter duration would suffice. Further investigation is needed to determine whether infusion rates could be reduced over the course of treatment, with corresponding decreasing FVII plasma levels but without losing haemostatic efficacy.

**Adverse Events**

Since registration in various countries until February 2001 it has been estimated that 171,790 doses of rVIIa had been sold. A total of 87 adverse events had been spontaneously reported in association with the use of marketed rVIIa. The list of adverse events includes decreased therapeutic response (16), cardiovascular events (17) which included myocardial infarction (7), cerebrovascular (6), venous thrombosis/thrombophlebitis (6) and disseminated intravascular coagulation (1). Seventeen patients who experienced a serious adverse event died and 8 were causally evaluated by the investigator to be possibly or probably related to the administration of rVIIa [18]. Further work is required to review these adverse events to define their causal relationship to rVIIa.

**Comment**

Evidence gained over the past 13 years demonstrates that rFVIIa has a role in the management of patients with haemophilia and inhibitors to coagulation factors. However, we do not yet know how best to use this agent, and several questions must be answered before it can be used optimally.

**What Is the Minimum Effective Dose?**

Perhaps the most pressing need is to identify the minimum dose of this expensive treatment that is needed to achieve haemostasis. The clinical trials have established that rFVIIa is effective for acute bleeds when given in boluses of 90 μg/kg 2–3-hourly. Major surgery can be accomplished successfully with boluses of 90 μg/kg every 2–4 h. Whether it is feasible to achieve a good response in orthopaedic surgery with smaller doses is yet to be determined. Minor surgery may be safely undertaken with lower doses. Given the importance of maximising the cost effectiveness of rFVIIa, further clinical trials to clarify optimum dose regimens warrant a high priority.

Optimal doses for continuous infusion also remain unclear. The Italian data suggest that rFVIIa is effective at 20 μg/kg/h even for major surgery. In contrast, the studies by our group indicate that, for major surgery, the dose needs to be 50 μg/kg/h.

**Is Continuous Infusion Preferable to Bolus Therapy?**

In determining whether the optimal approach is the 90 μg/kg bolus dose or the 20–50 μg/kg/h continuous infusion, it is important to consider the mechanism of action of rFVIIa. We do not currently know how rFVIIa achieves haemostasis, but there is a view that the key to successful treatment may be the burst of thrombin activity generated particularly by the bolus dose which promotes the formation of a strong fibrin clot at the bleeding site. Furthermore, it has recently been observed that high doses of thrombin are needed to activate TAFI, an inhibitor of thrombolysis [19].

The importance of platelets in the action of rFVIIa is supported by studies of platelet activation and platelet microparticles that are released following stimulation with thrombin. These studies led to the discovery that bolus doses of rFVIIa, particularly in combination with tranexamic acid, are associated with a rapid increase in platelet microparticles in haemophiliac patients [20]. Further research is needed to clarify the mechanism of action of rFVIIa and the role of tranexamic acid.

These questions point to an urgent need for further laboratory studies and clinical trials to optimise the use of rFVIIa.
References


