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ORIGINAL ARTICLE *Inhibitors*

On-demand treatment of bleeds in haemophilia patients with inhibitors: strategies for securing and maintaining predictable efficacy with recombinant activated factor VII

B. SØRENSEN,* Y. DARGAUD,† G. KENET,‡ J. LUSHER,§ A. MUMFORD,¶ S. PIPE** and A. TIEDE††

**Haemostasis Research Unit, Centre for Haemostasis & Thrombosis, Guy's & St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK; †Unité d'Hémostase Clinique, Hôpital Edouard Herriot, Lyon, France; ‡National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel; §Department of Hematology/Oncology, Children's Hospital of Michigan, Detroit, MI, USA; ¶Bristol Haemophilia Centre, Bristol Haematology and Oncology Centre, Bristol, UK; **Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA; and ††Hannover Medical School, Department of Haematology, Haemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany*

Summary. On-demand therapy with recombinant activated factor VII (rFVIIa) can provide effective haemostasis for spontaneous bleeds in haemophilia patients with inhibitors. However, treatment approaches vary amongst physicians, positively or negatively affecting outcomes. A panel of physicians proposed recommendations for securing and maintaining predictable efficacy with rFVIIa, comparing these with 'real-life' patient management, using a questionnaire circulated to other expert physicians from haemophilia care centres in Europe and the United States. For rFVIIa treatment of spontaneous bleeds in inhibitor patients, early intervention with the highest appropriate dose is recommended. Home-based therapy can facilitate early intervention. If additional rFVIIa therapy is required after the initial dose, rFVIIa 90 μg kg^{-1} may be administered at 2–3 h intervals. Treatment should be tailored to bleed site/severity, recognizing the advantages of appropriate adjunct therapy. Questionnaire results suggested that many respondents adopted strategies in line with the recommendations. Most (36/46) recommended initial therapy within 1 h of bleed onset. rFVIIa 270 μg kg^{-1} was the most frequently prescribed/recommended initial dose for paediatric (aged ≤15 years; 22/44 respondents) and adult (aged >15 years; 23/44 respondents) patients. However, there may be opportunity for improved bleed management on occasion, with regard, for instance, to dosing and dose interval. To secure and maintain predictable efficacy with rFVIIa, judicious dose selection and treatment timing are important, together with adjunct therapy where necessary. As inhibitor patients present with different bleeding scenarios, a tailored treatment approach should be adopted.

Keywords: haemophilia, inhibitor, recombinant activated factor VII, treatment strategies

Introduction

Recommendations for appropriate treatment of patients with haemophilia A or B who have inhibitors to factors VIII or IX, respectively, have been described in a range of articles [1–8]. Recombinant activated factor VII (rFVIIa, NovoSeven®; Novo Nordisk, Bagsværd, Denmark) is available for the treatment of bleeding in such patients, and data have shown rFVIIa 90 μg kg^{-1} to provide effective haemostasis in over 90% of mild to moderate bleeds after a mean of 2.2 injections [9]. Results from recent clinical trials [10–12] suggest that, for on-demand treatment of haemarthroses in haemophilia patients with inhibitors, rFVIIa 270 μg kg^{-1} administered as one injection is as effective as the repeat standard-dose regimen of 3 × 90 μg kg^{-1}. In 2007, rFVIIa given as a single bolus dose of 270 μg kg^{-1} was approved by the European Medicines Agency for treatment of mild to moderate bleeding episodes in patients with haemophilia A or B and inhibitors.

Although articles reviewing the use of rFVIIa in haemophilia patients with inhibitors are available [13–15],

Correspondence: Benny Sørensen, Haemostasis Research Unit, Centre for Haemostasis & Thrombosis, Guy's & St Thomas' NHS Foundation Trust, 1st Floor North Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, UK.
Tel.: +44 (0) 20 718 82788; fax: +44 (0) 20 740 13125;
e-mail: benny.sorensen@kcl.ac.uk

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practical strategies for securing and maintaining predictable efficacy with rFVIIa remain to be fully described in the literature. The development of improved treatment protocols for haemophilia patients with inhibitors has been described as 'imperative' [16]. Appropriate therapeutic recommendations are important from a clinical point of view, as treatment approaches can vary [17–22], with positive or negative effects on treatment outcome, and from an economic perspective [23], to ensure that maximum benefits are gained from the cost of administering the treatment.

In the light of the fact that treatment approaches can be varied to optimize outcomes [17–22], this article describes strategies for securing and maintaining predictable efficacy with on-demand rFVIIa treatment of haemophilia patients with inhibitors, based on recommendations from an expert group. These recommendations are compared with approaches adopted by other physicians, elucidated from responses to an international cross-sectional survey.

Methods

A panel meeting, held to consider strategies for securing and maintaining predictable efficacy with rFVIIa, was convened on 6th December 2008 in San Francisco (CA, USA). Based on discussions that took place during this meeting, recommendations relating to the role of rFVIIa in the management of spontaneous bleeds in haemophilia patients with inhibitors were proposed.

To obtain further insight into bleed management with rFVIIa in other haemophilia care centres, a questionnaire was devised (Appendix S1). This was sent via e-mail to 115 physicians in Europe and the United States who were known to prescribe rFVIIa to treat patients with haemophilia and inhibitors. Thirty-seven questionnaires were returned by October 2009. In addition, 10 questionnaires were completed at an investigators' meeting that involved physicians from Africa, Australia and Central and South America, as well as from Europe.

Data from the 47 questionnaires were evaluated using Analyse-it® for Excel v2.21 (Analyse-it Software Ltd, Leeds, UK). Summary statistics were produced (numbers of responses and percentages) and, where respondents had been asked to estimate percentages of instances/patients, mean [95% confidence interval (CI)] results were determined (with the normality of the data being assessed using measures of skewness, kurtosis and the Shapiro–Wilk test). The number of respondents and the percentage this represents, based on a denominator, that varied with the total number of correctly completed questionnaires, is provided for each of the particular options. Additional written comments provided by the respondents were collated.

Table 1. Key recommendations for securing and maintaining predictable efficacy with rFVIIa in on-demand treatment of haemophilia patients with inhibitors.

Initial treatment
- Previously treated patients: highest appropriate rFVIIa dose*
- Treatment-naïve children: rFVIIa 270 μg kg^{-1} with dose decrease considered. Treatment-naïve adults: rFVIIa 90 μg kg^{-1} with dose increase considered
- Dose may be tailored according to bleed site (for target joints, muscles and mucocutaneous bleeds), previous response to rFVIIa, any cardiovascular risk factors and/or data from clotting assays assessing *ex vivo* clot formation
- rFVIIa should ideally be administered within 1 h of bleed onset – consider home-based treatment for suitable patients†

Other treatment
- Rest, ice, compression, elevation (as appropriate)
- Consider adjunct therapy
  - Antifibrinolytic treatment (joint, muscle and mucocutaneous bleeds)
  - Steroids (joint and muscle bleeds)
  - Physiotherapy (joint and major muscle bleeds)

Evaluation of bleed cessation
- Reduced pain, less heat, improved mobility as signs of improvement

Further therapy as appropriate
- rFVIIa 90 μg kg^{-1} with a 2–3 h time interval between doses

For difficult-to-treat bleeds
- Ensure the rFVIIa dose and dosing interval is appropriate, considering dose escalation/dose interval reduction, if appropriate, to ensure predictable efficacy
- Enquire about recent diet/homeopathic therapy/use of other drugs that may affect haemostasis
- Consider further evaluations (other coagulation disorders, platelet function etc.)

Possible hospitalization
- For management of severe or abnormal bleeds
- To facilitate treatment and treatment monitoring
- For patients with special problems
  - To facilitate repeat dosing and physiotherapy

Rehabilitation
- To include coordinated/systematic physiotherapy, as appropriate (including for muscle bleeds)

*Literature supporting high dose includes: Kavakli *et al.* [10], Santagostino *et al.* [11], Young *et al.* [12], Salaj *et al.* [20], Abshire *et al.* [21].
†Literature supporting early intervention includes: Lusher [17–19], Salaj *et al.* [20], Santagostino *et al.* [22].

Results

The recommendations of the authors of the manuscript are given below and summarized in Table 1. Therapeutic approaches reported by the questionnaire respondents are also described.

Dose

For treatment-naïve children (and bearing in mind higher drug clearance rates in these younger patients [24]), the recommended option is to initiate therapy at 270 μg kg^{-1}, and then consider subsequent dose decreases. For treatment-naïve adults, it is recommended that therapy is initiated at 90 μg kg^{-1}, with subsequent dose escalation being considered. For initial treatment of individuals at cardiovascular risk, rFVIIa 90 μg kg^{-1} may be prescribed – although the risk of thrombosis is not generally a concern, this might be an issue in patients with predisposing risk factors (e.g. elderly patients with

atherosclerosis, obesity, etc.) if underlying disease is exposed when improving coagulation.

Reassessment of response to rFVIIa after four to five bleeding episodes will provide information to help determine whether the treatment strategy is optimal or requires modification. Continuous critical evaluation of a patient's history of efficacy can help to determine the choice of initial dose of rFVIIa (90 vs. 270 μg kg^{-1}), and efficacy may be optimized by prescribing the highest appropriate initial dose based on previous response history.

If further rFVIIa therapy is required, rFVIIa 90 μg kg^{-1} may be administered at 2–3 h intervals.

Considering the questionnaire responses, an initial dose of rFVIIa 270 μg kg^{-1} was the most frequently prescribed/recommended regimen for paediatric (≤15 years of age) and adult (>15 years of age) patients (Fig. 1). If further treatment was required, for both age groups, rFVIIa 90 μg kg^{-1} was most frequently reported (Fig. 2), with 2- or 3-h time intervals between doses being described most often (Fig. 3). However, more than one-quarter of respondents mentioned using dosing intervals greater than 3 h (Fig. 3).

Timing

An initial dose of rFVIIa should be administered as soon as possible after bleeding starts, ideally within 1 h. It is important that bleeds are recognized, and treated, early; patients should be aware of this.

Most questionnaire respondents recommended that patients receive initial rFVIIa therapy within 1 (36/46; 78.3%) or 2 h (9/46; 19.6%) of bleed onset, with only one respondent recommending treatment initiation within 3 h (1/46; 2.2%). In practice, a mean of 64.6% (95% CI, 56.4–72.8) of bleeds were treated within

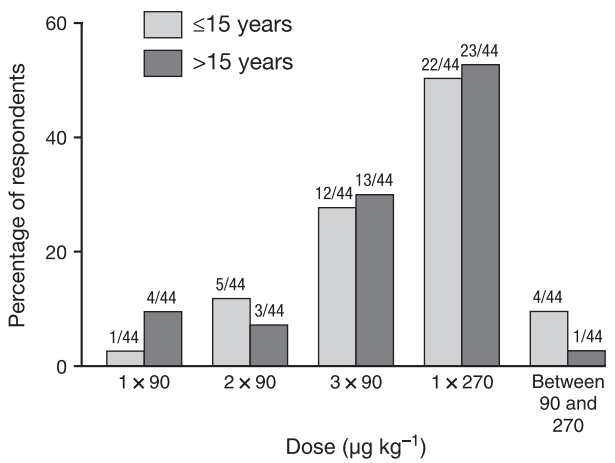

Fig. 1. Questionnaire results: treatment of spontaneous bleeds in paediatric (aged ≤15 years) and adult (aged >15 years) haemophilia patients with inhibitors: rFVIIa doses administered as first-line therapy (the numbers shown above the bars give the number of responses/number of respondents).

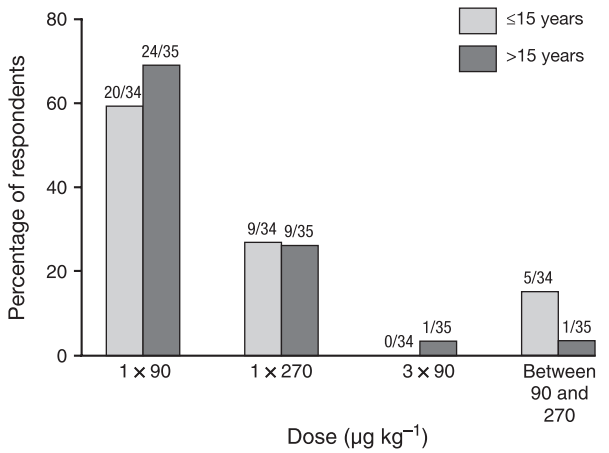

Fig. 2. Questionnaire results: treatment of spontaneous bleeds in paediatric (aged ≤15 years) and adult (aged >15 years) haemophilia patients with inhibitors: rFVIIa doses administered if further therapy is required (the numbers shown above the bars give the number of responses/number of respondents).

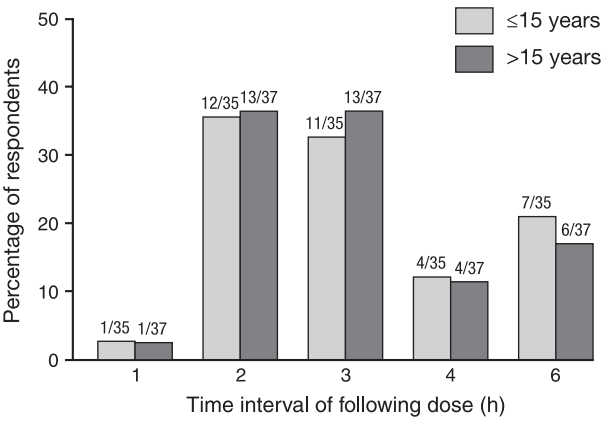

Fig. 3. Questionnaire results: treatment of spontaneous bleeds in paediatric (aged ≤15 years) and adult (aged >15 years) haemophilia patients with inhibitors: time interval between rFVIIa doses if further therapy is required (the numbers shown above the bars give the number of responses/number of respondents).

1–2 h. Recommendations for bleed recognition or information on when and how to treat, were generally considered useful for inhibitor patients, but only around half the respondents (24/47; 51.1%) provided educational material to patients/caregivers.

Type and site of bleed

Although all joint bleeds should be treated comprehensively, with appropriate follow-up and critical evaluation of bleed cessation, treating haemarthroses in target joints can be particularly challenging. In such instances, rFVIIa 270 μg kg^{-1} may be appropriate (although this dose has only been approved for mild to moderate bleeding episodes, based on non-inferiority studies). Adjunct therapy can include antifibrinolytic treatment [25]. Steroids and physiotherapy may also be

considered. No standard evidence-based strategy for managing target joints has been established.

Large intramuscular bleeds should receive aggressive therapy. Adjunct therapy can include antifibrinolytic treatment and steroids. Even in non-haemophilic athletes, repair and rehabilitation following muscle injury may take more than 30 days [26], and thus optimized treatment regimens require optimized measures for assessing ongoing bleeding/achieved haemostasis [27].

For mucocutaneous bleeding, rFVIIa and/or antifibrinolytic therapy may be used. Skin bleeds do not always require factor therapy, and cuts may be treated using local compression. For bleeds in the oral cavity and epistaxis, local measures (e.g. treatment in the oral cavity/nasal passage) may be appropriate.

Both physiotherapy and RICE (rest, ice, compression, elevation) may prove valuable options for bleed management, particularly for muscle bleeds. The nature of any injury, together with its anatomical localization and severity will dictate the type and intensity of physiotherapy, influencing the progression of the rehabilitation programme [26].

In line with the recommendations, the majority of questionnaire respondents altered the therapy they would normally employ when patients experienced haemorrhages affecting target joints (27/47; 57.4%) – when rFVIIa doses were described, the most frequently reported dose was 270 μg kg^{-1} (Table 2). If further rFVIIa treatment was required, a dose interval of 2 or 3 h was mentioned most often (Table 2); adjunct therapy was also widely reported (Table 2). Fewer respondents adjusted therapy for bleeds affecting non-target (19/45; 42.2%) or weight-bearing joints (20/46; 43.5%).

Most respondents altered therapy for muscle bleeds (29/47; 61.7%; Table 2). Around two-thirds (32/47; 68.1%) of respondents adjusted therapy for mucocutaneous bleeds, with adjunct treatment, particularly antifibrinolytic therapy, often playing a role here (Table 2).

The questionnaire respondents recommended physiotherapy in a mean of 63.8% (95% CI, 55.5–72.1) of patients, with the highest percentages recommended for postsurgery patients [mean 86.3% (95% CI, 79.7–92.9)] and for patients with target joints [mean 78.0% (95% CI, 70.8–85.3)]. Overall, RICE was recommended in a mean of 82.0% (95% CI, 73.8–90.1) of patients.

Severe (difficult-to-treat) bleeds

Treatment options for 'difficult-to-treat' bleeds – those with unusual persistence, or worsening of symptoms despite therapy – vary according to circumstance, but include further treatment with standard rFVIIa dosing, dose increase (in patients not receiving rFVIIa 270 μg kg^{-1}), shortening the dose interval, adjunct antifibrinolytic therapy (except for haematuria) and RICE. A recommended course of action may be to initiate early contact with a hospital or treatment centre to facilitate therapy with rFVIIa 270 μg kg^{-1}, followed by rFVIIa 90 μg kg^{-1} at 2-hourly intervals until the bleed has resolved, together with appropriate protective/supportive physiotherapy and additional laboratory monitoring.

Table 2. Treatments for bleeds at different sites and severe (difficult-to-treat) bleeds in haemophilia patients with inhibitors: questionnaire results showing instances in which the majority of questionnaire respondents altered patients' therapy*.

Anatomical localization/ type of bleed	Initial rFVIIa dosage, μg kg^{-1} (%)	Dose interval if further doses are required, h (%)	Adjunct therapy (%)	Antifibrinolytics (%)	Physiotherapy (%)	Steroids (%)
Target joint	270 (58) 120 (16) 90 (26)	1 (6) 2 (56) 3 (25) 6 (13)	93	43	60	40
Muscle bleeds	270 (47) 120–180 (13) 90 (39)	3 (35) 4 (44) 6 (24)	90	75	0	56
Mucocutaneous bleeds	270 × 1 (22) 120–150 × 1–2 (9) 90 × 1 (65)	1 (5) 2 (50) 3 (30) 4 (15)	96	100	0	0
Severe (difficult-to-treat) bleeds	270 × 1 (52) 120–150 (29) 90 (19)	2 (7) 3 (55) 4 (24) 6 (7) 12 (3)	95	78	78	6

*The percentages shown represent the percentages of responses where relevant information was given in relation to questioning: 'Do you generally alter your patient's treatment (in various situations)' and 'If yes, how?'

Patients who do not respond to therapy should be fully assessed, and other causes of bleeding (e.g. other coagulopathies, platelet dysfunction) should be considered. Laboratory/clinical evaluations can prove informative, as might questioning patients about recent use of other drugs, homeopathic therapy and diet. Laboratory screening may include measurement of prothrombin time and quantification of fibrinogen levels. Thromboelastography [28] and thrombin-generation assays [29] are under consideration as potential monitoring methods. Such assessments may help to provide a mechanistic explanation of why responses to rFVIIa may occasionally be attenuated in patients who have previously responded well. In instances of non-response, additional haemostatic intervention, such as platelet transfusion or use of other bypassing or prohaemostatic agents [30] could be considered.

It is recommended that patients receive hospital-based treatment for the management of all severe or abnormal bleeds, including those that continue for more than 24 h or worsen after initial home-based therapy has been administered. Patients with special problems (e.g. children who cannot receive treatment from their parents, individuals with difficult venous access or cases where therapeutic compliance may be suboptimal) should also be treated in hospital. Inpatient admission may also be recommended for bleeds in large joints or in muscles.

The majority of questionnaire respondents (38/46; 82.6%) reported altering treatment in severe or difficult-to-treat bleeds. Over half (27/46; 58.7%) specifically highlighted rFVIIa dosing here, with the most frequently reported dose and dose interval being 270 μg kg^{-1} and 3 h respectively (Table 2). When managing difficult-to-treat bleeds, the rFVIIa dose interval was reported to be reduced in a mean of 39.8% (95% CI, 29.3–50.2) of instances. Adjunct therapy was also described (Table 2). This was most often administered as antifibrinolytic treatment, but other physicians mentioned use of steroids, or antifibrinolytics and steroids.

Most respondents asked patients to contact them or a treatment centre if bleeds did not respond to 2–3 doses of rFVIIa (32/47; 68.1%), as well as if bleeds were severe (29/47; 61.7%) or abnormal (27/47; 57.4%). Hospital admission for acute bleed management was generally recommended in such instances.

When abnormal bleeding occurred, further evaluation to try to ascertain the reason for this was performed in a mean of 60.7% (95% CI, 49.8–71.5) of instances. For patients who experienced unusual persistence or worsening of symptoms, the majority of physicians (38/47; 80.9%) considered it important to enquire about recent diet/homeopathic therapy/use of other drugs. Laboratory evaluations of other coagulation disorders or platelet function in these circumstances were considered important by 30/47 (63.8%) and 24/47 (51.1%) of respondents respectively.

Other points

Efforts should be made to ensure that patients and the healthcare staff who treat them are adequately educated about haemophilia with inhibitors – the term 'prehabituation' was introduced during the meeting, relating to guidance of patients, physicians and other relevant healthcare staff to help secure and maintain predictable efficacy with rFVIIa. The value of a multidisciplinary treatment approach should be recognized.

For many patients (having initially received hospital-based treatment to foster appropriate expectation of therapeutic response and provide guidance on bleed evaluation), initiation of therapy at home should be standard. This can facilitate prompt treatment, but close contact should be maintained between patients and clinics.

When evaluating bleed cessation, patients on home-based treatment should be advised to look for decreased pain, decreased heat and improved mobility. Patients should visit clinics in any instances of doubt, acute lack of response, severe pain, serious/persistent bleeds, or if they suspect a bleed to be severe.

The questionnaire respondents exhibited widespread agreement that having rFVIIa available at home aids more rapid bleed resolution (46/47; 97.9%), and most patients were estimated to have been trained and regularly treated spontaneous bleeds at home [mean of 73.6% (95% CI, 65.1–82.0)]. The majority of respondents considered home treatment to be suitable for patients who have learned when/how to treat themselves, and when to seek further help (34/47; 72.3%), for children whose parents/caregivers have such knowledge (33/47; 70.2%), for compliant patients (28/47; 59.6%), and for patients who live in remote areas (28/47; 59.6%). Most respondents (41/47; 87.2%) recommended that their patients kept diaries so that progress could be monitored and treatment optimized over time. To signal bleed cessation, questionnaire respondents most frequently reported asking patients to look for improved mobility (42/47 responses; 89.4%) and decreased pain (41/47; 87.2%). Decreased swelling was also mentioned by a majority of respondents (36/47; 76.6%), as was the bleeding site being less hot than when bleeding began (24/47; 51.1%).

Discussion

For on-demand treatment of spontaneous bleeding in inhibitor patients, efficacy may be optimized by prescribing the highest appropriate dose of rFVIIa based on a patient's previous history of response (where available). It may be speculated that initial treatment with rFVIIa 270 μg kg^{-1} may be more beneficial than

starting therapy with rFVIIa 90 μg kg^{-1} and subsequently increasing the dose and frequency. Such a recommendation appears to be reflected in physicians' current practice: for both paediatric and adult haemophilia patients with inhibitors, the most frequently prescribed/recommended regimen reported by the questionnaire respondents was an initial dose of rFVIIa 270 μg kg^{-1}. (In some instances, respondents mentioned rFVIIa doses in between the labelled 90 and 270 μg kg^{-1} doses.)

Consideration should be given to the convenience of rFVIIa 270 μg kg^{-1}. Compared with multiple venipuncture, patients might prefer a treatment regimen involving fewer injections. Although some bleeds can be treated with an rFVIIa dose lower than 270 μg kg^{-1}, most bleeds require more than one rFVIIa 90 μg kg^{-1} dose [9], and higher initial doses of rFVIIa do not necessarily increase the amount of product required to treat a bleed [11]. Indeed, it should be noted that recent data have shown initial treatment with higher-dose rFVIIa to be associated with a decline in total rFVIIa consumption [20].

Data generated using *in vitro* models suggest that a higher dose of rFVIIa may result in accelerated clot formation and a stronger, more rapid thrombin burst on the surface of activated platelets [21]. Increased and rapid thrombin formation forms a tight fibrin plug with greater resistance to fibrinolysis [31]. However, it should be emphasized that management of haemophilia involves more than a momentary correction of inadequate haemostasis; multiple bleeds can produce chronic inflammatory reactions that need to be addressed, and adjunct therapy may be important to consider.

Safety data have revealed a remarkably low incidence of thromboembolic adverse events in patients treated with rFVIIa, and no safety issues have been identified relating to treatment of inhibitor patients with rFVIIa 270 μg kg^{-1} [32].

A first dose of rFVIIa should be administered as soon as possible after bleeding starts, ideally within 1 h, and data have shown that early treatment with rFVIIa is associated with even greater efficacy and less product use than later administration [17–20,22]. Although the importance of early treatment was recognized by most questionnaire respondents, responses also indicated that in more than one-third of instances, bleeds may not be treated within 2 h of onset. In relation to this, registry data have shown that when patients are treated more than 2 h after bleeds start, therapy with higher-dose rFVIIa is associated with less re-bleeding [20].

Prompt receipt of a first dose of rFVIIa could be facilitated by patients having the product immediately available, with home-based treatment playing a key role here. According to the questionnaire responses, a mean of over 70% of patients were reported as regularly treating spontaneous bleeds at home. However, when considering a home-based treatment approach, it should be recognized that some patients have limited skills, which could preclude reliable self-administration of rFVIIa, and there may also be issues relating to drug availability for children in school.

We have recommended that patients on home-based treatment should be advised to look for decreased pain, decreased heat and improved mobility when evaluating bleed cessation. The majority of questionnaire respondents reported recommending these criteria. However, around three-quarters also asked their patients to look for decreased swelling – as it may take a considerable period of time for swelling to subside, this may be less useful.

When initial treatment with rFVIIa is followed by further dosing, the time interval is important. Although this was apparent in many of the questionnaire responses, in some cases [including treatment of target joint, muscle and severe (difficult-to-treat) bleeds], doses were administered more than 3 h apart – such treatment seems suboptimal, given the pharmacokinetic and pharmacodynamic properties of rFVIIa [33].

Care in a haemophilia treatment centre is associated with significantly reduced mortality [34]. Staff in these centres can provide expert consultation and suitably close monitoring during periods of haemostatic stress. In addition, such centres may offer intensive patient training, which can ultimately enable home therapy and facilitate early treatment of bleeding episodes.

Some bleeds are difficult to treat; they continue with unusual persistence or symptoms worsen despite treatment. Current knowledge on the mechanism of action of rFVIIa [35,36] may influence treatment strategy here: high dose amplifies non-tissue factor dependent effects and thrombin generation. Although not performed by many of the questionnaire respondents, a full assessment (including consideration of other causes of bleeding) should be encouraged when bleeds prove difficult to treat. Patients should be also asked about their exposure to any factors that may influence haemostasis. For instance, aspirin may affect blood clotting, whereas other non-steroidal anti-inflammatory drugs, prescribed for the treatment of chronic joint pain, can interfere with platelet function, as might herbal compounds such as willow bark or gingko biloba [37]. However, evidence as to the influence that such effects may have on rFVIIa therapy remains to be established.

Comparison of our recommendations with the questionnaire responses suggests that although physicians may already adopt treatment strategies that are generally in line with rational recommendations, there may be an opportunity for improved bleed management on some occasions, with regard to, for instance, dosing and dose interval, and assessing difficult-to-treat cases. However, as inhibitor patients can present with different bleeding scenarios, no single treatment strategy is universally applicable, and clinical judgment will play a key role in effective bleed management.

When considering the recommendations described in this document, it is important to refer to local regulations specific for the country in which rFVIIa is being prescribed. Also, inhibitor patients may receive immune tolerance induction (ITI) therapy [38] and although our recommendations provide general guidelines, ITI can result in issues that are not specifically discussed in this article (e.g. thrombosis may be associated with central venous access devices [39]).

As we used a questionnaire to gain insight into bleed management with rFVIIa in other clinics, it is appropriate to consider the limitations of this instrument. The cross-sectional nature of the questionnaire was intended to facilitate the collection of information in line with each respondent's expertise and available treatment opportunities. However, selection bias in the physicians to whom the questionnaire was sent, or in those who responded, is possible. When respondents reported altering treatment in certain situations, the precise manner in which this was altered was not always apparent. In addition, actions described in the questionnaire may not always have been adopted in clinical practice. Nevertheless, the data collected provide valuable information about bleed management with rFVIIa in clinical practice in a variety of countries.

Conclusion

These recommendations are intended to help physicians secure and maintain predictable efficacy with rFVIIa when treating spontaneous bleeds in haemophilia patients with inhibitors. This can be achieved by judicious treatment timing and dose selection together with, where necessary, adjunct therapy – effective bleed management involves more than a momentary correction of inadequate haemostasis. It may prove particularly beneficial to explore such aspects of therapy in bleeds that have proved difficult to treat. Early intervention (which may be facilitated by home-based therapy) with the highest appropriate dose of rFVIIa is recommended.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Appendix S1. A 'generic' version of the questionnaire is shown. This was amended slightly for distribution to physicians in different countries, to comply with local regulations and drug licensing arrangements.

Appendix S2. Physicians who provided questionnaire data, but did not participate in devising the recommendations made in this manuscript.

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