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ORIGINAL ARTICLE *Inhibitors*

Single 270 μg kg^{-1}-dose rFVIIa vs. standard 90 μg kg^{-1}-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison

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Summary. Evidence suggests greater doses of recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) than currently administered may result in enhanced haemostasis and convenience for patients with haemophilia A and B with inhibitors. This study evaluated efficacy and safety of rFVIIa and an activated prothrombin complex concentrate (APCC; Factor Eight Inhibitor Bypassing Activity [FEIBA]®, Baxter AG, Vienna, Austria) for controlling joint bleeds in a home-treatment setting. Patients received each of three treatments in one of six possible sequences: 270 μg kg^{-1} rFVIIa at hour 0 + placebo at hours 3 and 6, 90 μg kg^{-1} rFVIIa at hours 0, 3 and 6, and 75 U kg^{-1} APCC at hour 0. Efficacy was assessed by the requirement for additional haemostatics within 9 h and by a novel global response algorithm. The percentage of rFVIIa 270 μg kg^{-1} group patients requiring additional haemostatics within 9 h (8.3%) was significantly lower than that for the APCC group (36.4%, $P = 0.032$). The percentage of rFVIIa 90 × 3 μg kg^{-1} group patients requiring such rescue medication (9.1%) was also lower compared to the APCC group. This result approached, but did not reach statistical significance ($P = 0.069$). Both rFVIIa treatment groups showed similar use of rescue medication (8.3% and 9.1% of episodes for rFVIIa 270 μg kg^{-1} and rFVIIa 90 × 3 μg kg^{-1} groups respectively). No significant differences in treatment response were observed with the global response algorithm ($P = 0.173$). No safety issues were identified. A single dose of rFVIIa 270 μg kg^{-1} is as safe and effective as rFVIIa 90 × 3 μg kg^{-1} dosing, and may be considered a potentially more effective alternative to APCCs for the management of joint bleeding in this population.

Keywords: bleeding disorder, FEIBA, haemophilia, NovoSeven, recombinant FVIIa

Introduction

A thrombin burst on the surface of activated platelets is required to achieve haemostasis. Under normal conditions, coagulation factors VIII and IX play an important role in achieving this thrombin burst. In patients with haemophilia, however, one of these coagulation factors is absent, resulting in the formation of a fragile fibrin clot that is easily dissolved [1]. The frequent re-bleeding pattern seen in patients with haemophilia is characterized by short, intermittent periods of haemostasis due to the formation of these fragile clots.

Glazer *et al.* reported that administration of recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark) at a dose of 90–100 μg kg^{-1} every second hour resulted in effective haemostasis for major bleeding episodes in patients with haemophilia and antibodies against FVIII or FIX [2]. In the home treatment setting, a mean of 2.2 doses 90 μg kg^{-1} of rFVIIa were required to achieve haemostasis. The overall efficacy rate was 92% [3].

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Laboratory and clinical evidence suggest higher doses of rFVIIa than currently administered may result in enhanced haemostasis due to the effect on thrombin generation as well as a more stable haemostatic plug due to a stronger fibrin network [1]. Such dosing may also be more convenient for patients by allowing for a reduction in dosing frequency.

In a cell-based model of haemophilia using rFVIIa concentrations ranging from 25 to 75 nmol L^{-1} (approximating plasma levels following 90 μg kg^{-1} and 270 μg kg^{-1} doses respectively), rate of thrombin generation as well as peak thrombin generation increased as rFVIIa concentration increased [4]. Additionally, the time to peak thrombin generation decreased with increasing rFVIIa concentration [4]. The initiation phase of thrombin generation was also shown to shorten in a concentration-dependent manner in a synthetic blood coagulation model [5].

A retrospective review of the Hemophilia and Thrombosis Research Society (HTRS) Registry (which collects data on treatment and efficacy and safety outcomes for bleeding episodes in haemophilia patients) noted that rFVIIa doses >200 μg kg^{-1} showed a significant increase in efficacy compared with lower dose groups of <100 μg kg^{-1}, 100–150 μg kg^{-1} and 150–200 μg kg^{-1} (97% in the >200 μg kg^{-1} dose group compared to 84% in the lower dose groups combined) [6]. Additionally, rFVIIa appeared well-tolerated at doses up to 346 μg kg^{-1} [6].

Two recently published, prospective, randomized trials have compared the use of standard 90 μg kg^{-1} rFVIIa dosing to a single 270 μg kg^{-1} dose of rFVIIa for the treatment of bleeding in haemophilia patients with inhibitors. In the double-blind Kavakli *et al.* study, a single 270 μg kg^{-1} bolus injection was found to be at least as effective and safe as standard 90 μg $kg^{-1} \times 3$ dosing [7]. In the Santagostino *et al.* open-label study, success rates were again similar for standard- and higher-dose rFVIIa regimens for the home treatment of haemarthroses in these patients [8]. Additionally, 270 μg kg^{-1}-dose rFVIIa was safe, did not require increased total rFVIIa consumption, and resulted in a reduced frequency of rFVIIa infusions. Kenet *et al.* found that the treatment of bleeds with rFVIIa 300 μg kg^{-1} is effective and well tolerated in young inhibitor patients [9]. The clinical data, therefore, suggest that dosing patients with 270 μg kg^{-1} should be safe and may result in enhanced haemostasis via the optimization of thrombin burst production and a strengthened fibrin network. We therefore sought to evaluate the use of a single, 270 μg kg^{-1} dose rFVIIa compared to standard rFVIIa dosing and a standard APCC dosing.

Materials and methods

Trial design

This was a randomized, multicentre, cross-over, double-blind study to evaluate the efficacy and safety of rFVIIa (by two different blinded dose schedules) and an open-label APCC (Factor Eight Inhibitor Bypassing Activity [FEIBA]®, Baxter AG, Vienna, Austria) in producing haemostasis in joint bleeds in a home-treatment setting. Six treatment sequences were generated by the permutation of the following three dosing regimens: 270 μg kg^{-1} rFVIIa at hour 0 followed by placebo at hours 3 and 6, 90 μg kg^{-1} rFVIIa at hours 0, 3 and 6, or 75 U kg^{-1} APCC at hour 0. These sequences were then assigned at random to the 42 trial subjects. Subjects received each of the three treatments (a different treatment for each bleeding episode) and were assessed for 9 h after dosing using both objective and subjective endpoints (described below).

The trial consisted of five clinical visits relating to three bleeding episodes: a screening phase (Visit 1), a randomization phase at ≤14 days postscreening (Visit 2), Visit 3 at ≤7 days after the first bleeding episode, Visit 4 at ≤7 days after the second bleeding episode and an end-of-study visit (Visit 5) at ≤7 days after the third bleeding episode. Joint bleeds were considered qualified for study treatment if subject had no other bleeds within 7 days of onset and had not received any haemostatic treatment for any other bleeds for 5 days prior to the onset of the qualifying joint bleed.

Study population

The study population was composed of patients diagnosed with haemophilia A or B and inhibitors with a history of two or more joint bleeds during the preceding 12 months. Adequate venous access and the demonstrated capacity to administer trial products and assess bleeding episodes (patient or caregiver) were prerequisites for enrolment. Subjects on immune tolerance who developed break-through bleeding could be included. Age and responder type (high vs. low responders) were unrestricted. All joint bleeds were eligible including target joints, as information regarding efficacy in the management of target and non-target joint bleeds was deemed equally important.

Patients were excluded if they had a history of end-stage liver disease, a clinically relevant coagulation

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disorder other than congenital haemophilia A or B, had received treatment for bleeding episodes within 5 days of screening, had experienced joint bleeding within 7 days prior to screening, had a prior hypersensitivity reaction to rFVIIa, APCC or any of their components, or had received any investigational product within the last 30 days prior to the trial.

Drug preparation and administration

Recombinant FVIIa was given as an intravenous bolus injection at doses of either 270 μg kg^{-1} at hour 0, or 90 μg kg^{-1} at hours 0, 3 and 6. Placebo solutions were administered to blind subjects to the rFVIIa dose regimen. The APCC was given as an intravenous injection at a dose of exactly 75 U kg^{-1} at hour 0 and was not blinded due to differences in physical appearance and required volume for injection. The 90 μg kg^{-1} rFVIIa dose is in accordance with Food & Drug Administration (FDA)-approved labelling, while the 270 μg kg^{-1} rFVIIa dose is currently being evaluated by the FDA, and has recently been approved by the European Agency for the Evaluation of Medicinal Products (EMEA). At the time of study initiation, the rationale for 270 μg kg^{-1} rFVIIa dosing was based on data from healthy volunteers pretreated with acenocoumarol [10] and case reports of treating patients with higher doses [11]. The 75 U kg^{-1} APCC dose used in this trial is within the range mentioned in the FDA-approved package insert (50–100 U kg^{-1}) and was selected on the basis of clinical experience with this APCC. This dose is also similar to that used in other trials [12].

Efficacy and safety variables

Efficacy evaluations in this trial included two methods: (i) the percentage of patients achieving haemostasis without requiring use of rescue medication within 9 h of the first administration of trial product; and (ii) a subjective global treatment response algorithm (described below).

Patients with an insufficient treatment response within 6 h of the first treatment administration were evaluated in the clinic or by phone to consider the use of rescue medication. As defined in the protocol, rescue medication refers to additional haemostatic treatment within 9 h post first administration of trial product and included APCC and rFVIIa.

Additionally, as the generally used 3-point scale (effective, partially effective or ineffective) used in most studies assessing response to treatment in haemophilia was thought to be insufficiently discriminatory for this study, a global treatment response based on the self-assessment of pain and joint mobility was developed. The methodology was used for the first time in this and the Kavakli, 2006 [7] trials and has not been formally validated. The algorithm is illustrated in Table 1.

Table 1. Global response efficacy algorithm.

	Pain			Mobility		
	More	No diff.	Less	More	No diff	Less
1 h	F	S	S	S	S	F
3 h	F	S	S	S	S	F
6 h	F	F	S	S	F	F
9 h	F	F	S	S	F	F

F, failure; S, success.
≥6S equals global treatment success.
<6S equals global treatment failure.

Pain and mobility were assessed at 1, 3, 6 and 9 h after the first injection of trial product and were classified based on the following criteria: response to treatment was considered successful at a given time point if pain was assessed as 'less' at any time point, or when assessed as 'no difference' after 1 or 3 h. Pain responses of 'more' at any time point or 'no difference' after 6 or 9 h were considered treatment failures for those time points. Likewise, the response to treatment was considered successful at a given time point if mobility was assessed as 'more' at any time point, or when assessed as 'no difference' after 1 or 3 h. Mobility responses of 'less' at any time point or 'no difference' after 6 or 9 h were considered treatment failures for those time points. This yields 8 scores per patient (1 for pain and 1 for mobility at each of 4 time points tested). The global response to treatment was considered effective if a patient accumulated 6 or more 'success' scores, and ineffective if the patients had fewer than 6 'success' scores. The receipt of additional haemostatic medication to control joint bleeding within 9 h of the first dose of trial product automatically graded a treatment a failure for the global response.

The separate responses for pain and mobility at each time point were also examined individually. Treatment was considered effective if a patient accumulated 3 or more 'success' scores over the 9-h period, and ineffective if the patient accumulated fewer than 3 'success' scores during this period, or if additional haemostatic medication to control joint bleeding was required. The population for efficacy analyses is defined as all patients randomized to treatment for which efficacy data are available.

Safety was assessed by monitoring patients for adverse affects recorded for each bleeding episode from administration of the first dose of trial product until 7 days following the bleed (i.e. treatment-

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emergent adverse events). The population for safety analyses is defined as all subjects randomized to treatment who received at least one dose of study drug.

Statistical methods

The target sample size was $n = 6$ for each of the six treatment sequences. This target size does not reflect a power calculation but was selected based on prior experience with studies of this rare condition and therefore reflects the difficulty in securing trial patients as well as the possibility of withdrawals. Efficacy tests were two-tailed with a 5% significance level. The null hypothesis was defined as no difference in the treatment effects of rFVIIa vs. APCC and was tested using logistic regression stratified by subject with treatment and period as fixed effects. Pair-wise comparisons between treatment groups were made using Fischer's exact test. Intent-to-treat population is presented by assigned treatment.

Ethics and consent

The trial was conducted in accordance with ICH Good Clinical Practice and the Declaration of Helsinki. Consent was obtained in writing prior to any trial-related activities.

The protocol, protocol amendments, consent form, and subject information sheet were reviewed and/or approved by the FDA, according to local regulations, and by each local site's Institutional Review Board prior to trial initiation.

Results

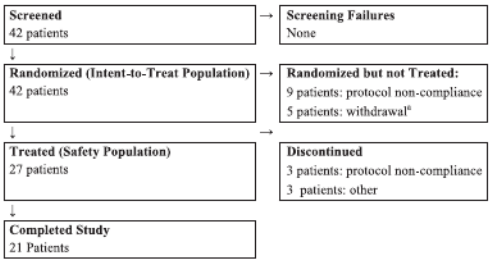
Patient disposition

The overall disposition of patients involved in this clinical study is summarized below in Table 2.

Of 42 total patients randomized for the trial, 27 were treated [24 patients were exposed to a single 270 μg kg^{-1} rFVIIa dose, 22 patients were exposed to the standard dose regimen (3 × 90 μg kg^{-1}) and 22 patients were exposed to a standard dose of APCC (75 U kg^{-1})]. Twenty-one patients completed all three arms of the study and six discontinued (three due to non-compliance, two due to study closure by sponsor and one due to the patient electing to be treated at another haemophilia centre).

Of the 15 patients who were randomized but not treated, nine were due to non-compliance, five were due to withdrawals, and for one patient no further information is available.

Table 2. Patient disposition.



*One additional subject not included here was randomized but not treated. No further information is available for this subject.

There were four completed participants analysed for whom all bleeding episodes occurred in the same joint (right knee = 1 subject, left elbow = 2 subjects, left ankle = 1 subjects). Of these, three participants experienced the three bleeds in a period of 26–54 days and one experienced the three bleeds over a period of nearly 10 months. The three who experienced their bleeds within 54 days all received APCC for the third bleed. There were an additional five completed participants for whom two of the three bleeding episodes occurred in the same joint (left knee = 2 subjects, right knee = 1 subject, right shoulder = 1 subject). Of these, four of five experienced the two bleeds in the same joint within a period of 89 days while in one the period between the two bleeds was more than 7 months. Among the four who experienced the two bleeds within 89 days, three received rFVIIa 270 mcg kg^{-1} for the second bleed and one received APCC for the second bleed.

Patient demographics

Of the 42 patients randomized in the study, all were male; there were 18 Caucasian, 11 African–American, six Hispanic, two Asian and five patients of other ethnic origin. The median age was 19.5 years (range; 1–54 years).

Efficacy

The number of patients requiring additional haemostatic medication to control bleeding within 9 h of first trial product administration is shown in Fig. 1. Additional haemostatic medications included APCCs, recombinant FVIII and rFVIIa.

The percentage of patients requiring additional haemostatic medication was significantly greater for the APCC treatment group than for the rFVIIa 270 μg kg^{-1} group ($P = 0.032$), with 36.4% of

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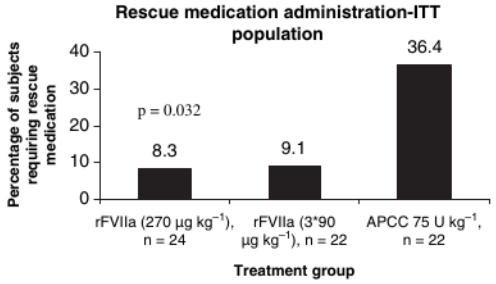

Fig. 1. Additional haemostatic medication administration – intent-to-treat population.

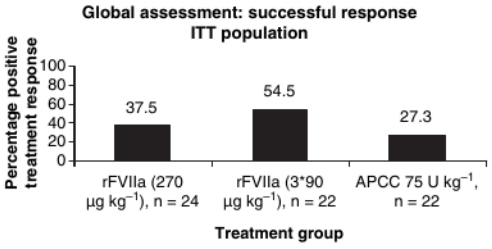

Fig. 2. Global assessment: successful response – intent-to-treat population.

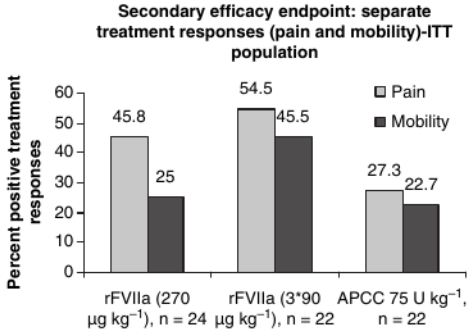

Fig. 3. Separate global assessment for pain and mobility: successful response-intent-to-treat population.

patients in the APCC group requiring such medication. The efficacy difference between the APCC treatment group and the rFVIIa 90 × 3 μg kg^{-1} group approached, but did not reach, statistical significance ($P = 0.069$). Both rFVIIa treatment groups showed similar use of rescue medication (8.3% and 9.1% of episodes requiring rescue medication for the rFVIIa 270 μg kg^{-1} and rFVIIa 90 × 3 μg kg kg^{-1} groups respectively). A total of eight bleeding episodes for APCC, two for rFVIIa 270 μg kg^{-1} and two for rFVIIa 90 × 3 μg kg^{-1} required additional medication.

A successful response to treatment was assessed by 37.5% of patients receiving 270 μg kg^{-1} rFVIIa, 54.5% of patients receiving 90 μg kg^{-1} × 3 rFVIIa and 27.3% of patients receiving APCC. A trend toward better response with rFVIIa was noted, although no significant differences in treatment response for the global response algorithm were observed ($P = 0.173$: an overall value from logistic regression with treatment as a fixed effect) (Fig. 2).

Efficacy analyses included a secondary analysis of the separate responses obtained for pain and mobility. These separate global responses are shown in Fig. 3.

Positive responses to pain were 45.8%, 54.5% and 27.3% for the rFVIIa 270 μg kg^{-1}, rFVIIa 90 × 3 μg kg^{-1}, and APCC treatment groups respectively ($P = 0.219$). Per cent positive treatment responses to mobility were 25.0%, 45.5% and 22.7% for the rFVIIa 270 μg kg^{-1}, rFVIIa 90 × 3 μg kg^{-1}, and APCC treatment groups respectively ($P = 0.903$). A trend toward increased response with rFVIIa was again noted, although there were no statistically significant differences in the separate responses to pain and mobility for any of the treatments.

As the measurement of pain could have been influenced by analgesic use, such use was examined for each dose group. There were no significant differences in the use of analgesics among treatment groups [rFVIIa 270 μg kg^{-1} = 45.8%, rFVIIa 3 × 90 μg kg^{-1} = 54.5% and APCC = 68.2% of bleeding episodes; pairwise *P*-values vs. APCC using Fisher's Exact test = 0.149 (rFVIIa 270 μg kg^{-1}) and 0.537 (rFVIIa 3 × 90 μg kg^{-1})].

All efficacy variables were evaluated at end of study by an independent, external, blinded, physician reviewer given access to complete patient diaries. The assessment of this reviewer coincided with the results given by the Global Response to treatment algorithm.

Safety

No patients withdrew from treatment due to adverse events or serious adverse events, and no thrombotic, fatal, or clinical laboratory adverse events were reported. All adverse events were judged unlikely to be related to study treatment by the investigating physicians.

A total of 32 treatment-emergent adverse events (defined as all adverse events with onset dates on or after the first dose of a given treatment and no later

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than 7 days after the last dose for that treatment) were experienced by 14 subjects: seven events reported by three patients treated with the rFVIIa 270 μg kg^{-1} dose, 11 events reported by five patients treated with the rFVIIa 90 × 3 μg kg^{-1} dose, and 14 events reported by six patients treated with APCC. A relationship to study treatment was considered unlikely for all (as judged by the investigators), and there were no apparent differences in adverse event-type between treatment groups. All patients experiencing adverse events recovered or stabilized.

Eleven treatment-emergent serious adverse events were reported by five patients in this study. These included decreased therapeutic response (i.e. bleeding not controlled) (one event), infection (two events), arthralgia (two events), back pain (one event), pharyngolaryngeal pain (one event), respiratory arrest secondary to a narcotic dose (morphine) for pain (one event) and haemorrhage (non-study joint) (three events). There were no trends evident with respect to age or treatment group. Event durations ranged from 5 to 25 days and all patients recovered from all serious adverse events. A relationship to study drug was considered unlikely for all serious adverse events as judged by the investigators, though the case of a patient reporting that bleeding was not controlled would obviously be due to treatment failure.

Discussion

The optimization of current rFVIIa treatment regimens may provide for enhanced efficacy and/or convenience in the home treatment of joint bleeds in patients with congenital haemophilia A or B and inhibitors. Home treatment itself facilitates early intervention which has been associated with increased efficacy [8,13–15], and laboratory and clinical data suggest that single rFVIIa doses higher than currently indicated may be more effective and are intuitively more convenient than several smaller doses with no negative effects on safety parameters [6,8,9,16,17]. Such single-dose rFVIIa regimens have been recently approved by the EMEA.

There are currently two randomized clinical trials comparing a single high dose of rFVIIa to the standard dose, both utilizing a cumulative dose of 270 μg kg^{-1} [7,8]. Recently, the first study comparing rFVIIa to APCC was published which was designed to demonstrate statistical equivalence of the two treatments but failed to do so [12]. The present study is the first to combine the approaches of the previous studies and to directly compare two rFVIIa dosing regimens with a standard dose of APCC in a randomized, double-blind crossover trial combining home treatment and high-dose rFVIIa treatment. The primary objective was to evaluate the efficacy and safety of rFVIIa (two different blinded dose schedules) and the APCC (open label) in patients with congenital haemophilia A or B and inhibitors being treated for joint bleeds.

The percentage of patients requiring additional haemostatic agents (rescue therapy) within 9 h to achieve haemostasis was used as an objective efficacy parameter in this study. A significantly lower percentage of patients in the rFVIIa 270 μg kg^{-1} treatment group required rescue medication when compared with the APCC treatment group. There was a non-significant trend towards a reduction in rescue medication use in the rFVIIa 90 μg kg^{-1} × 3 arm when compared with the APCC treatment arm. Both rFVIIa treatment groups showed similar use of rescue medication. While this suggests improved efficacy for rFVIIa, this outcome may have been influenced by the fact that patients on either rFVIIa arm will have received three infusions (at hours 0, 3 and 6) and could conceivably have been more reluctant to administer another (rescue medication) within the ensuing 3 h than patients who had received a single infusion of APCC (at hour 0). Conversely, this conjecture may be mitigated by the fact that patients in either rFVIIa arm were aware they may have been receiving placebo. Another potential source of bias stems from the finding that all three patients for whom joint bleeds all occurred in the same joint within approximately 2 months (essentially a target joint) received APCC for the third bleed, when joint responsiveness to treatment might be expected to be the lowest. However, the data suggest that treating a third target joint bleed with APCC did not bias the primary outcome measure in favour of rFVIIa, as none of these three patients received rescue medication.

In addition to the objective measure above, a novel subjective global treatment response scale based on the self-assessment of pain and joint mobility was developed and used in this trial. This unvalidated algorithm was developed to be more discriminatory than the commonly used three-point scale of efficacy, however no statistically significant differences in treatment responses were observed for any treatment group with regard to both global and secondary efficacy assessments (though the study was not powered to detect response differences using this scoring system).

Both the rescue medication requirement data and the global response data suggest that a single, 270 μg kg^{-1} dose of rFVIIa is at least as effective as 90 μg kg^{-1} × 3 for the home treatment of joint

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bleeds in haemophilia patients with inhibitors. This is in agreement with other published prospective randomized trials [7,8] and the added convenience of single-dose therapy may be particularly relevant for patients with difficult venous access.

The present trial is currently the only one to directly compare a single 270 μg kg^{-1} dose of rFVIIa to a standard dose of APCC. In this comparison, our results suggest a significant improvement in treatment response with rFVIIa based on the significantly increased requirement for additional haemostatic agents for the APCC arm, however these data should be interpreted with caution as discussed previously.

In agreement with previous reports addressing 270 μg kg^{-1}-dose rFVIIa safety for the treatment of joint bleeding in patients with haemophilia and inhibitors [7,9,10,18], no safety issues with the use of either dose of rFVIIa were identified, or were any safety issues reported with APCC use. No adverse events were considered related to study medication.

Several limitations to this study should be considered when interpreting the results presented herein. First, due to the difficulty in recruiting patients, sample sizes were smaller than desired, reducing statistical power for efficacy analyses, particularly for the global efficacy scale. In addition, a novel global response scale was used as one of the efficacy outcome measures. While in some respects the scale was designed to reduce subjectivity and improve on the standard three-point subjective efficacy scale often employed in haemophilia trials, it has not been formally validated. That some bleeds were deemed unsuccessfully treated despite not requiring additional haemostatic medication suggests this algorithm may not be as robust as anticipated. Also, although chronic haemophilic arthropathy could affect treatment responsiveness, such information was not collected during this study. Finally, although patients were blinded to rFVIIa dose, they were not blinded to APCC, which could have introduced bias depending on patient product preference, if any.

The global treatment response rates reported here are low in comparison with other studies of standard dosing of rFVIIa and APCC as well as in comparison with studies of single 270 μg kg^{-1}-dose rFVIIa [3,7,8], including the Kavakli study which adopted the same global treatment response efficacy criterion [7]. However, differences in study methodology preclude direct comparison of efficacy results across these studies. In the Kavakli study, for example, participants were required to have had three bleeds within the previous 12 months, vs. two bleeds in 12 months for the current trial. The more severely affected participants in the former trial may have assessed pain and mobility differently than the less severely affected participants of the current trial.

Conclusion

In conclusion, our results corroborate those of the previous studies comparing rFVIIa dosing regimens, suggesting a single 270 μg kg^{-1} dose is as safe and effective as three 90 μg kg^{-1} doses for the management of joint bleeding in patients with haemophilia and inhibitors. Furthermore, the current study demonstrates that a dose of 270 μg kg^{-1} rFVIIa significantly reduces the need for rescue medications compared to APCC suggesting it to be potentially more effective treatment option than APCC. Although not formally tested here, single-dose 270 μg kg^{-1} rFVIIa may also be more convenient in terms of time savings for patients and care givers compared to multiple-dose treatment, and may also be beneficial for patients with difficult venous access. Finally, this trial also highlights the need for standardized efficacy markers for the evaluation of haemophilia patients, as well as the difficulties inherent in studying an infrequent complication of a rare disease.

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Rock, AR); Dr Sally Stabler (University of Colorado Health Sciences Center, Mountain State Regional Hemophilia & Thrombosis Center, Aurora, CO); Dr Cindy Leissinger (Tulane University Health Sciences Center, New Orleans, LA); Dr Claire Philipp (Robert Wood Johnson University Hospital, Division of Hematology, New Brunswick, NJ); Dr Elaine Eyster (Milton S. Hershey Medical Center, Division of Hem./Onc., Hershey, PA); Dr Leonard Valentino (Rush University Medical Center, Chicago, IL); Dr Ralph Gruppo (Children's Hospital Medical Center, Cincinnati, OH); Dr Bradley Lewis (Alta Bates Medical Center, Berkley, CA); Dr Jorge Di Paola (University of Iowa Hospitals and Clinics, Department of Pediatrics, Hem/Onc, Iowa City, IA); Dr Alice Cohen (Newark Beth Israel Medical Center, Division of Hematology/Oncology, Newark, NJ).

Disclosures

The contributing authors to this article have declared the following conflict of interests:

Guy Young has received reimbursement from a symposium and funds for a research. He was also a paid speaker and a paid consultant. Frank Shafer has served as a paid consultant for NovoNordisk Pharmaceuticals. He has also received funds from NovoNordisk for research and for organizing an educational meeting. Patrick B. Rojas was a full-time employee at NovoNordisk Inc. from 12 June 2000 until 26 January 2007. Stephanie Seremetis is a stockholder/shareholder of Novo Nordisk.

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[no notes on this page]