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Single Higher Dose of Recombinant Activated Factor VII in the Treatment of Hemorrhages in Patients with Hemophilia Complicated by Inhibitors

Leczenie pojedynczą dużą dawką rFVIIa pacjentów chorych na hemoﬁlię powikłaną inhibitorem

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Abstract

The development of inhibitors is the most severe complication of treating hemophilia patients with Factor VIII or IX, and providing effective hemostasis for inhibitor patients is challenging. Patients with high responding inhibitors (titer > 5 BU/mL) are usually treated with recombinant activated Factor VII (rFVIIa), 90–120 μg/kg every 2–3 hours, or plasma-derived activated prothrombin complex concentrate. The aim of this study was to assess the efficacy and safety of a single dose of 270 μg/kg rFVIIa in inhibitor patients with joint or soft tissue bleeds treated at the Department of Paediatric Hematology and Oncology and the Department of Hematology and Transplantology. 7 inhibitor patients (3 adults aged 23–33 and 4 children aged 3–14) were included in the study. The hemostatic efficacy and tolerability of a single high dose of rFVIIa for home treatment of moderate or severe bleeds was evaluated. Treatment with rFVIIa effectively stopped bleeding in all patients without any adverse events. In most cases a single dose of rFVIIa 270 μg/kg was more effective than 3 or 4 lower doses (90 μg/kg) and less traumatic for pediatric patients. Based on present studies, it can be concluded that a single dose of rFVIIa is effective and well tolerated in the treatment of intra-articular bleeds in patients with hemophilia complicated by the presence of inhibitors (Adv Clin Exp Med 2012, 21, 4, 519–524).

Key words: bypassing agents, hemophilia inhibitors, rFVIIa.

The development of Factor VIII (FVIII) or Factor IX (FIX) alloantibodies (inhibitors) is a serious complication during the treatment of patients with hemophilia with exogenous factor replacement. It mainly affects patients with a severe form of the disease.
The first occurrence of an inhibitor following transfusion of factor VIII (FVIII) in a hemophilia A patient was reported by Lawrence and Johnson in 1941 [1]. The circulating anticoagulant was detected by its ability to prolong the clotting of normal blood. It was only several years later that the nature of this novel type of inhibitor was established. It was first demonstrated that the inhibitor activity was associated with the gamma globulin fraction of serum [2]. In 1947, Craddock and Lawrence [3] finally established that the anticoagulant identified was an antibody, recognizing the protein called at that time "antihaemophilic globulin" and later FVIII. Indeed, they demonstrated that gamma globulin present in the patient’s plasma precipitated a protein in the FVIII concentrate. This phenomenon, called a "precipitin reaction", was then considered the hallmark of the presence of the antibody. Craddock and Lawrence therefore concluded that inhibitor antibodies appeared in response to exposure to the protein lacking in the plasma of hemophilia A patients (3). Reports by several groups further confirmed the presence of anticoagulants, which caused a precipitin reaction with antihemophilic globulin [4].

The incidence of inhibitor development in response to replacement therapy has been reported in various studies as high as 33% in hemophilia A and up to 6.5% in hemophilia B [5]. The treatment of patients with hemophilia complicated by inhibitors is difficult and expensive, and should aim to both treat the bleeds and eliminate the inhibitors. To achieve this, a concentrate of FVIII/FIX should be administered systematically over many months, including the use of immune tolerance induction (ITI) therapy to eliminate the inhibitors when possible. Instead of replacement therapy, preparations that bypass the need for FVIII/FIX in the blood-clotting process can be used to ensure hemostasis. Thus, patients with high responding inhibitors (inhibitor titer > 5 Bethesda Units/mL [BU/mL]) are usually treated with bypassing agents such as recombinant activated Factor VII (rFVIIa) and plasma-derived activated prothrombin complex concentrate (aPCC).

The use of plasma-derived FVIIa was first reported for the treatment of hemophilia complicated by high-titer alloantibodies in 1983 [6].

Recombinant activated factor VII (rFVIIa NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) is a bypassing agent that enhances thrombin formation and promotes hemostasis through direct activation of factor X on the surface of activated platelets, even in the absence of factors VIII or IX. Pharmacological doses enhance thrombin generation and the formation of a stable fibrin plug [7]. Data from clinical trials has demonstrated the safety and efficacy of rFVIIa for bleeding episode management in patients with congenital hemophilia with inhibitors [8–10]. This data represents experience with standard and higher-dose rFVIIa regimens, and primarily reflect in joint and muscle bleeds.

When used to treat intra-articular bleeding, rFVIIa is most frequently administered in a dosage regimen of 90–120 μg/kg every 2–3 hours. According to data from published literature, a single administration of a higher 270-μg/kg dose of rFVIIa is equally efficacious and has a similar safety profile [3–5]. The European Medicines Agency also approved this treatment regimen for mild or moderate bleeds in hemophilia patients with inhibitors [14].

Here the authors report on the hemostatic efficacy and tolerability of a single high dose of rFVIIa for home treatment of moderate or severe bleeds in 3 adult (23–33 years of age) and 4 pediatric (3–14 years of age) inhibitor patients in Poland. The efficacy of rFVIIa was judged by whether there was a need for additional hemostatic treatment and by patient-reported effectiveness. The treatment was described as “effective” when bleeding stopped completely after administration of the factor, and “partially effective” when it was necessary to repeat the dose. The tolerability of a high dose of rFVIIa was assessed by the occurrence of adverse events and bleeding complications.

The demographic details of the 7 patients (6 with hemophilia A and 1 hemophilia B patient) from 2 centers in Poland are provided in Table 1.

The first patient, a 3-year-old boy diagnosed with severe hemophilia A during his first month, was first treated with 25 IU/kg FVIII for gingival bleeds and bleeds from the frenulum of the tongue during his second year. He subsequently received repeated treatment with FVIII for soft tissue and right tarsal joint hemorrhages. The patient was hospitalized for gingival bleeds when he was 2 years of age, despite prophylactic administration of 40 U/kg FVIII every 12 hours. Following admission to the hospital on June 18th, 2007, his activated partial thromboplastin time was found to be 108 seconds after administration of 40 U/kg FVIII. As there was a suspicion that he had developed FVIII inhibitors, the patient was initially given 100 μg/kg rFVIIa. When no improvement in the severe bleeding was observed after 15 minutes, an additional dose of 170 μg/kg rFVIIa was administered, and the bleeding stopped within 3 minutes (cumulative dose: 270 μg/kg rFVIIa). His inhibitor levels were found to be 320 BU/mL.

The second patient, a 12-year-old boy with severe hemophilia A and FVIII inhibitors (14 BU/mL), was first diagnosed at the age of 6 years. He had previously been treated repeatedly with ei-
ther 70–80 IU/kg aPCC (once daily or once every 12 hours) or 90 μg/kg rFVIIa (2–3 doses, usually given at 0, 2, and 5 hours after bleeding onset) for bleeds into his muscles and recurrent hemorrhages into his right knee and right elbow joints. After a hemorrhage into his right elbow joint, he received home treatment with a single dose of 270 μg/kg rFVIIa within 15 minutes of the first symptoms of bleeding. The hemorrhage disappeared within 40 minutes and the patient did not require further hemostatic treatment. His inhibitor level at the time of the hemorrhage was 23 BU/mL.

Case 3, a 14-year-old boy with severe hemophilia B, had been treated with FIX concentrates from the age of 3 years because of bleeds, mainly into his right knee and right elbow joints. After a hemorrhage into his right elbow joint, he received home treatment with a single dose of 270 μg/kg rFVIIa within 15 minutes of the first symptoms of bleeding. The hemorrhage disappeared within 40 minutes and the patient did not require further hemostatic treatment. His inhibitor level at the time of the hemorrhage was 23 BU/mL.

Case 4, a boy diagnosed with severe hemophilia A at 7 months of age, and then with inhibitors 3 months later (12 BU/mL), was treated with aPCC (usually 70–90 IU/kg twice on day 1 post-bleeding; sometimes repeated once on day 2) or rFVIIa (usually 0, 2, and 5 hours after bleeding onset) for recurrent bleeds into elbow and knee joints and soft tissues. ITI therapy was started at 1 year of age, but was not successful. At the age of 3 years, the boy received aPCC prophylaxis (80 IU/kg three times a week) for 1 year, followed by daily doses of 90 μg/kg rFVIIa for 3 months. Intra-articular bleeding occurred frequently despite the prophylaxis. In the 2 years from 2007 (when the patient was aged 10 years), his recurrent hemorrhages were treated (on separate occasions) 14 times with aPCC 70–90 IU/kg twice daily, 18 times with standard doses of rFVIIa (70–90 μg/kg usually given 0, 2, and 5 hours after bleeding onset), and 23 times with a single 270 μg/kg dose of rFVIIa. The efficacy of the therapy was comparable, irrespective of the dose, bypassing agent administered, and hemor-
rhage site. However, on an inquiry form completed by the patient between April and October 2008, the evaluation of pain after a single-dose 270 µg/kg rFVIIa treatment was most frequently recorded as “the same” after 1 hour and “better” after 3 hours. For the evaluation of bleeding control with 270 µg/kgrFVIIa, he commonly selected “partially effective” after 1 hour, and “partially effective” or “effective” after 3 hours. The average time from the occurrence of the hemorrhage to administration of 270 µg/kg rFVIIa was 15–30 minutes.

The fifth patient, a 23-year-old patient with severe hemophilia A, had been diagnosed at 2 years of age, and had since been treated at home with pd-FVIII concentrates (doses of 20–40 U/kg). However, the patient now reported a decrease in the efficacy of his FVIII treatment, despite an increase in the dose of FVIII administered per bleed, and the presence of inhibitors was diagnosed (82 BU/mL). The most frequent bleeds reported were into the elbow and knee joints. A single dose of 270 µg/kg rFVIIa was used with very good effect, as bleeding ceased and pain disappeared in these joints within the first hour after rFVIIa administration, and a second injection of rFVIIa was not required. This treatment regimen was considered to be satisfactory for the patient, and single-dose rFVIIa was also found to be effective for further bleeds.

Case 6, a 33-year-old patient with severe hemophilia A with inhibitors (historical titer of 7000 BU/mL), was treated for many years with either aPCC or rFVIIa. He received aPCC at doses of 50–100 IU/kg once or twice daily (maximum 200 IU/kg) or rFVIIa during bleeding. Initially, the patient self-administered 2–3 doses of 90 µg/kg rFVIIa at home, and bleeding ceased after 2–4 hours. The patient subsequently found that it required 2–3 doses of rFVIIa to maintain hemostasis. During a further intra-articular bleed, treatment with a single dose of 270 µg/kg rFVIIa was recommended. Within 1 hour of administration, bleeding had stopped and pain disappeared. The patient found this therapy to be more convenient, with a smaller number of injections resulting in similar or better efficacy. After 2 years of treatment with rFVIIa alone, his inhibitor titer decreased to 80 BU/mL.

The seventh patient, a 25-year-old patient with severe hemophilia A with inhibitors (30 BU/mL), was initially treated with aPCC, but as the patient showed poor tolerance to this preparation, the use of rFVIIa was recommended. After treating an oral cavity, a maxillary surgeon advised that the patient required 6 teeth to be extracted. Thirty to forty minutes prior to each extraction, the patient self-administered 270 µg/kg of rFVIIa at home. Two teeth were extracted during each procedure without any bleeding complications. During this time, the patient used 1–2 doses of 90 µg/kg rFVIIa every 2–3 hours for small intra-articular bleeds, and when the hemorrhages were more extensive he increased the dose to 270 µg/kg. Bleeds stopped within 1–2 hours after administration of rFVIIa, independent of the dosage regimen used.

Results

The authors presented 7 cases of hemophilia patients with inhibitors who received treatment with single doses of rFVIIa 270 µg/kg. All patients had inhibitor titers > 5 BU/mL at the initial detection of the inhibitor. The rFVIIa was administered for joint bleeds in 5 patients, for bleeding in the oral cavity in 1 patient, and to provide hemostatic cover for planned dental extractions in the final patient reported. In all patients, treatment with rFVIIa was effective and suitable hemostasis was obtained. No adverse events were observed. Moreover, in most cases a single dose of rFVIIa 270 µg/kg was more effective than 3 or 4 lower doses (90µg/kg) of rFVIIa. Present findings are of particular significance for the pediatric patients, as 1 single administration of a higher dose of rFVIIa is much less traumatic for a child.

Discussion

The standard dose of rFVIIa used for treating bleeds in patients with hemophilia complicated by inhibitors is 90–120 µg/kg. In home therapy, the dose is usually repeated 3 to 4 times with intervals of 2–3 hours until bleeding ceases, with efficacy reported to be between 79 and 92% [15, 16]. However, fibrin clots formed in the presence of high amounts of rFVIIa have been reported to be more stable and resistant to proteolysis [17]. Retrospective studies of the use of a single high dose of rFVIIa [18, 19] reported improved efficacy (whilst retaining a good safety profile), providing the impetus for clinical trials on larger patient populations to further investigate the efficacy, safety, and cost-effectiveness of a single-dose therapy. Subsequent research by Santagostino and Kavakli at independent centers on large groups of inhibitor patients showed that a single dose of 270 µg/kg rFVIIa was as effective and safe as 3 doses of 90 µg/kg for home treatment of hemarthroses in these patients [11, 12]. Use of a single dose of rFVIIa controlled 90% of intra-articular bleeds [11]. A further trial reported by Young et al. compared the effectiveness of rFVIIa given as standard dosing (3 × 90 µg/kg)
or as a single dose (270 μg/kg), vs. aPCC (75 U/kg) once daily [13]. This trial showed similar use of rescue medication with either dosage of rFVIIa (8.3% and 9.1% of patients required additional hemostatic therapy within 9 hours of 270 μg/kg and 3 × 90 μg/kg rFVIIa, respectively), with 36.4% of patients requiring rescue medication after aPCC (P = 0.032 and P = 0.069 for aPCC vs. rFVIIa 270 μg/kg and 3 × 90 μg/kg, respectively) [13]. No safety issues were identified with any of the regimens.

Conclusions

Based on the above studies and own observations in the cases reported in this paper, it can be concluded that a single dose of rFVIIa 270 μg/kg is effective and well tolerated in the treatment of intra-articular bleeds in patients with hemophilia complicated by the presence of inhibitors. The application of this dose during home therapy, immediately after the onset of the first symptoms of hemorrhage, results in more rapid bleeding control. Furthermore, single-dose therapy is more convenient and less painful, as only one venous injection is required, resulting in a significant improvement for pediatric patients, as this approach is much less traumatic for a child. Present experiences, described here, of the efficacy and tolerability of a single high dose of rFVIIa in Poland suggest that single-dose therapy could also be used more frequently in other countries.

References

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