

“Primary prophylaxis” with rFVIIa in a patient with severe haemophilia A and inhibitor

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The development of antibodies that inhibit or neutralize replacement therapy with factor VIII or factor IX is today the most serious complication of haemophilia and its treatment. Inhibitor patients have more severe joint morbidity than patients without inhibitors, and older adults experience significant orthopaedic disabilities. Because of the serious and disabling consequences of persistent inhibitors, there is considerable clinical and research interest in establishing effective bypassing agent regimens to prevent bleeding in inhibitor patients in much the same way as prophylaxis procedure works in noninhibitor patients. In the majority of these patients, the bypass agent was used as a secondary prophylactic. In this report, the use of recombinant factor VIIa prior to any clinically evident joint bleed in a patient with

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Introduction

The development of antibodies that inhibit or neutralize replacement therapy with factor VIII or factor IX is today the most serious complication of haemophilia. Because of the serious and disabling consequences of persistent inhibitors, there is considerable clinical and research interest in establishing effective bypassing agent regimens to prevent bleeding in inhibitor patients. In this report, the use of recombinant factor VIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) prior to any clinically evident joint bleed in a patient with haemophilia A and high-titre inhibitor is described.

Case report

Our patient is a 4-year-old boy with severe haemophilia A and inhibitor against factor VIII. At the age of 10 months, he was admitted as an acute emergency to the paediatric intensive care unit with a 7-day history of severe upper labial fraenum bleeding. Evaluation of bleeding diathesis showed that factor VIII plasma level was 0 IU/ml. Replacement therapy with recombinant factor VIII was started with cessation of the bleeding. From 1 to 2 years of age, he presented another bleeding from the upper labial fraenum and severe chronic bruises in different parts of the skin due to minor traumas that caused mild anaemia, which needed iron supplementation. A primary prophylaxis schedule with recombinant factor VIII was planned for the patient but the family refused. At 2 years of age, he presented a third traumatic bleeding episode in the upper labial fraenum after a play-related trauma. After a 72 h period of excellent control of haemostasis with recombinant factor VIII (rFVIII) treatment, an

inhibitor against factor VIII with a titre of 440 Bethesda units was detected after 16 exposure days of factor VIII. Treatment with rFVIIa resolved the bleeding. We then planned prophylaxis schedule with rFVIIa during the time when the inhibitor was declining to initiate the immune tolerance therapy (ITT). Thus, 4 months after inhibitor development, a port-a-cath was inserted, and 3 months later the family accepted initiating prophylaxis schedule with rFVIIa at a target dose of 90 µg/kg per day. One month later there was a difficulty in withdrawing blood from the port. The catheter was evaluated with contrast venography. The result of the study was normal. Over the past 15 months, the patient was in prophylaxis programme with rFVIIa with only one episode of haematuria, which was resolved with corticosteroids and antibiotics. During this period severe bruises disappeared and iron supplementation normalized the patient's haemoglobin levels. No episodes of clinical haemarthrosis have been observed before or during the prophylaxis schedule in our patient. No adverse event except for difficulty in withdrawing blood from the catheter has been observed in this child. At the time of writing, the goal of decreasing the inhibitor titre has been achieved, 9.4 Bethesda units, and he is going to undergo ITT without any joint bleeding.

Discussion

Haemophilic patients with inhibitors are a vulnerable population who suffer increased morbidity and risk of mortality compared with the noninhibitor haemophilic population. Bypassing agents have been shown to be effective in controlling bleeding complications. It should,

however, be emphasized that in contrast to factor VIII and factor IX substitution, neither of these agents are able to completely normalize thrombin generation. Consequently, inhibitor patients have progressive joint disease with significant orthopaedic disabilities that are more prevalent in haemophilic patients without inhibitors.

The use of prophylaxis schedule for inhibitor patients has gained much interest in the last decade and some reports have supported the idea that bypassing agents could work in the prevention of chronic haemophilic arthropathy in the same way factor VIII/IX does in haemophilic patients without inhibitors. Nowadays, prophylaxis is a potential strategy for preventing episodes of joint bleeding and protecting joint damage before, during and after failed ITT.

The aim of prophylaxis schedule in our case is to prevent the onset of the first haemarthroses in an inhibitor patient who at two-and-a-half years old had not yet presented any joint bleed. The choice of rFVIIa was made bearing in mind that activated prothrombin complex concentrates aPCC contains residual factor VIII antigen and can therefore provoke an increase in the inhibitor titre.

Nearly 31 patients with haemophilia and inhibitors have been reported to use rFVIIa in prophylaxis procedure, of these, 22 were included in a randomized, double-blind study receiving prophylactic therapy with rFVIIa 90 or 270 µg/kg once daily for 3 months [1,2]. Currently, available data from these studies suggest that a prophylaxis procedure with rFVIIa appears to be efficacious and safe in inhibitor patients.

Our patient differs from previously reported cases who have undergone a prophylaxis procedure using rFVIIa in that this is the first case of a primary prophylaxis defined as starting prior to the appearance of the first joint bleed. After initiating the prophylaxis schedule, severe bruises had disappeared and he only needed to visit our centre for his regular periodical visit, except for one episode of haematuria. Assuming that rFVIIa could work in prophylaxis procedure in patients with inhibitors, the question rises as to why rFVIIa in the prophylaxis schedule would work, given the short biological half-life of rFVIIa in circulation. Very recently it has been hypothesized that rFVIIa may diffuse extravascularly and be available at the site of injury, where it could contribute to the haemostatic plug by increasing thrombin generation on activated platelets [3].

Despite extensive and varied usage of rFVIIa, the incidence of serious adverse events associated with its use is less than 1% [4]. In our case, there are some concerns about safety arising from the difficulty in withdrawing blood from the port, but the normal result in the veno-

graphy study and subsequent extractions from the port without problems suggest that there was probably a mechanical problem with the port rather than a thrombotic complication.

One important limitation arising from our experience, is the fact that our patient had not yet develop any joint bleed prior to the initiation of prophylaxis procedure. It has been reported that age at first joint bleed ranges from 0.2 to 5.8 years with a median of 1.8 years [5]. Our patient was 33 months old when he started the prophylaxis schedule. Perhaps our patient's phenotype means that he would not have had any joint bleeds until later, and perhaps he may have naturally entered a very long bleed-free period. However, since beginning of rFVIIa in prophylaxis schedule, he has had no further bleeds, and this means that his long-term risk of haemarthrosis is decreased. However, this limited experience may offer new opportunities for patients with haemophilia and inhibitor who are condemned to progressive joint disease with significant orthopaedic disabilities, through a schedule of prophylaxis that may prevent or limit the onset of joint bleeding.

In conclusion, our limited experience with the schedule of primary prophylaxis against haemarthrosis with rFVIIa opens a new and interesting field for the investigation of the efficacy and utility of rFVIIa in patients with haemophilia and inhibitors prior to the onset of joint bleeding.

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