

LETTER TO THE EDITOR

Management of coronary artery disease in a severe haemophilia patient with high titre inhibitor and anaphylaxis

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Since the early 1970s, there have been great improvements in the availability and quality of treatment for persons with haemophilia [1]. As a result, with the exception of the dramatic consequences of the human immunodeficiency virus (HIV) epidemics in the 1980s, the life span of haemophiliacs has progressively become similar to that of males in the general population, and actually, at least in more developed countries, a considerable number of haemophiliacs reach old age [2]. However, with age, persons with haemophilia develop medical and surgical diseases (e.g. cardiovascular diseases, prostatic hypertrophy, cancers and renal disease) not previously seen in this group [3]. In this case report, we describe the successful management of an acute coronary artery disease in an elderly patient with severe haemophilia A and high-titre inhibitor who also developed anaphylaxis against both plasma-derived and recombinant factor VIII concentrates.

The patient, a 70-year-old male affected by severe haemophilia A (FVIII activity < 1%), had a history of haemophilic arthropathy, chronic hepatitis C, diabetes mellitus and hypertension. He had been treated with cryoprecipitate and plasma-derived [Koate; Sclavo (Siena, Italy), Emoclot; Kedrion [Barga (LU), Italy], Kryobulin and Immunate; Immuno (Vienna, Austria)] FVIII concentrates. From January 1996 to April 2005, he was treated with recombinant (r)FVIII concentrate [Kogenate™; Bayer or Helixate (Leverkusen, Germany); CSL Behring (Marburg, Germany)] for a total of 18 days of exposure (10 days of

treatment was necessary in 1996 for a surgical operation for kidney stones). In April 2005, the patient underwent an operation of left knee arthroplasty and was treated with 59 000 units of rFVIII concentrate (Helixate Nexgen; CSL Behring) during the perioperative period (9000 IU the day of the surgery and 5000 IU day⁻¹ during the following 10 days) plus 3000 IU on alternate days for 2 months as prophylaxis during the physiotherapy rehabilitation. No bleeding complications were recorded. In November 2005, during a laboratory check-up, an high-titre inhibitor against FVIII was detected (7.3 BU, IgG1 subclass) for the first time (previous annual checks for inhibitor resulted negative, also before and after the orthopaedic surgery). A recovery test with rFVIII 50 IU kg⁻¹ was not responsive but was followed by an anamnestic response of the inhibitor (peak of 57.7 BU 13 days after rFVIII infusion with a gradual decrease [9.1 BU] over the next month). Two bleeding episodes (emarthrosis at the left elbow and duodenal ulcer bleeding) occurred in the following months and were successfully treated with recombinant factor VII activated (rFVIIa: NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark). An inhibitor check performed in September 2006 documented a titre of 8.1 BU.

In January 2007 (inhibitor titre 7.1 BU), the patient was admitted to the Intensive Care Unit of our University Hospital for an acute coronary artery episode. During hospitalization, the patient underwent a coronary angiography, which evidenced a severe three-vessel coronary artery disease. This invasive procedure was performed with the concomitant infusion of rFVIIa 90 µg kg⁻¹ i.v. for 2 days (every 3 h during the day of the operation, every 4 h the following day) without haemorrhagic or thrombotic complications. Because of the presence of a coronary artery occlusion and the critical clinical

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conditions (unstable angina), there was a clear indication for an intervention of percutaneous transluminal coronary angioplasty (PTCA) with stent implantation or a coronary artery bypass graft (CABG). However, in consideration of the inhibitor-related high-bleeding risk, these invasive/surgical procedures were not performed and the patient underwent medical treatment without antiplatelet agents. Furthermore, in spite of the advanced age of the patient, the decision to start an immune tolerance (IT) protocol was made with the aim of performing the cardiac intervention with a better haemostatic profile. After the insertion of a central venous catheter (no peripheral veins were accessible) under haemostatic coverage with rFVIIa $90 \mu\text{g kg}^{-1}$ i.v. (every 3 h the day of intervention, every 4 h the second day, every 6 h the third day and every 8 h the fourth day), the patient started IT according to Malmö protocol in March 2007. However, the infusion of the plasma derived FVIII/VWF concentrate (Haemate-P; CSL Behring) was stopped after the first 10 mL because of the onset of an allergic reaction with pruritus, urticaria, headache, bronchospasm and hypotension. The symptoms disappeared after appropriate emergency treatment. A laboratory check performed at that time showed an increase in IgG (2030 mg dL^{-1} ; normal values $700\text{--}1600 \text{ mg dL}^{-1}$) and total IgE (220 mg dL^{-1} ; normal values $0\text{--}200 \text{ mg dL}^{-1}$) serum immunoglobulins and a reduction in the levels of C3 (83%; normal values 90–180%) and total complement activity (20%; normal values 70–140%). The inhibitor titre was 7.2 BU. The following month, the IT was restarted with a rFVIII concentrate (Helixate Nexgen) but the infusion was stopped again after a few millilitres as a result of another urticarial reaction. A similar allergic reaction occurred in December 2007 after the infusion of the bypassing agent FEIBA (Baxter Vienna, Austria), which was administered after the initial clinical scarce response to rFVIIa on occasion of a post-traumatic emarthrosis at the left knee. By contrast, no adverse reactions were recorded to rFVIIa infusion, which was successfully used also in occasion of the CVC removal ($90 \mu\text{g kg}^{-1}$ every 3 h during the day of the intervention). No FVIII-containing concentrates were used since December 2007 and a recent check (November 2008) documented an inhibitor titre of 6.2 BU, and a persisting increase in IgG (1860 mg dL^{-1}) with normalization of total IgE (48 mg dL^{-1}) and total complement activity (90%).

Rare anaphylactic reactions have been reported in patients with haemophilia A with either cryoprecip-

itate, plasma-derived or recombinant FVIII concentrates [4–11]. The mechanism of these severe adverse reactions to FVIII concentrates remains largely unknown. Some authors have described an IgE-mediated hypersensitivity [9], while others have implicated IgG2 or IgG4 as a cause of the anaphylactic response [10,12]. Human antimouse anti-FVIII antibodies or antialbumin antibodies have also been suggested as responsible for allergic reactions in patients treated with immunopurified concentrates or first/second generation recombinant factor VIII products, respectively [11]. Remarkably, the occurrence of the anaphylactic response to factor VIII preparations is not usually coincident with the development of an inhibitor; however, when it does coexist, it greatly complicates the already difficult management of such patients. For instance, Tsuchiya *et al.* [10] described a haemophilia A child with a high titre inhibitor who developed an anaphylactic response (i.e. urticaria and angio-oedema) during immune tolerance induction (ITI) to both plasma-derived and recombinant FVIII products mediated by IgG2 and IgG4 subclass antibodies. Interestingly, the authors observed that although the inhibitor titre significantly decreased at 8 months after the commencement of ITI, circulating IgG2 and IgG4 antibodies against recombinant factor VIII persisted elevated, thus indicating a lack of coagulation inhibitory activity but a persistence of immune anaphylactic response capacity. In our case, the persisting increase of serum IgG levels was probably because of the suspension of IT regimen with inhibitor persistence. By contrast, the progressive decrease in total IgE levels and complement normalization after the avoidance of FVIII products suggest the direct involvement of this antibody in the anaphylactoid reaction. Various therapeutic options have been proposed for the management of anaphylactoid inhibitors in haemophilia A patients, from IT protocols including high doses of steroids and antihistamines to by-passing agents [13]. In this case report, we described the successful use of rFVIIa for the treatment of bleeding episodes in a severe haemophilia A elderly patient with high titre inhibitor and allergic reaction to FVIII, which impeded the infusion of FVIII-containing concentrates. In addition, this agent was found to be useful for the prevention of bleeding associated with coronary artery angiography without thrombotic complications.

Only few case reports are available in the literature describing similar invasive cardiac procedures in severe haemophilia A patients [14–16]. Krolick reported the successful percutaneous coronary intervention in a patient with severe haemophilia

A using bivalirudin as thrombin-specific anticoagulant therapy during the procedure and recombinant FVIII as haemostatic therapy pre- and post-procedure [14]. The largest experience is that reported by MacKinlay *et al.* [16] who described four cases of cardiac catheterization performed in three patients. An intermediate purity FVIII concentrate provided excellent haemostasis in all cases. However, to our knowledge, no previous study has reported the use of rFVIIa in severe haemophilia A patients with inhibitors undergoing coronary artery invasive procedures.

In conclusion, thanks to rFVIIa, we were able to manage the complex clinical situation of this patient caused by the concomitant presence of two rare adverse events, i.e. coronary artery disease and anaphylaxis to FVIII.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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