Rescue factor VIII replacement to secure hemostasis in a patient with hemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement

Emicizumab is a humanized monoclonal bispecific antibody that mimics the co-factorial activity of factor VIII (FVIII) by binding activated factors (F) IX and X.[1] It can be used in patients with hemophilia A with or without inhibitors, because it is not recognized by anti-FVIII antibodies. Its use as prophylactic agent, administered subcutaneously once weekly in patients with hemophilia A and inhibitors aged > 12 years has shown a significant reduction in bleeding frequency compared with previous bypassing therapy.[2,3] Nevertheless breakthrough bleeds may occur during prophylaxis with emicizumab as well as peri-operative bleeding complications,[4,5] and, in those cases, standard bypassing agents (*i.e.* recombinant activated factor VII, rFVIIa and activated prothrombin complex concentrate (aPCC)) are still needed to control bleeding.

Moreover, the lack of routine laboratory tests able to monitor *in vivo* the hemostatic efficacy as well as the prothrombotic potential of bypassing agents renders the clinical management most problematic. The use of the thrombin generation assay (TGA) has been proposed to individually tailor bypassing therapy and/or to monitor the efficacy of such therapy in patients undergoing surgery but with non-univocal results.[6,7] Recently, Dargaud *et al.* proposed the use of TGA as a helpful tool to limit adverse events that may occur when emicizumab is used in association with other hemostatic drugs as in the occasion of treatment of breakthrough bleeds.[4] In fact, in the HAVEN 1 study (NCT02622321), thrombotic microangiopathy and thrombosis were reported in 5 patients who received multiple doses of aPCC >100 IU/kg for more than 24 hours to treat breakthrough bleeds.[2] Thus, during prophylaxis with emicizumab, it is recommended to avoid the association of multiple high doses of aPCC and to use the lowest therapeutic doses of both rFVIIa or aPCC when bypassing therapy is needed.

Because the surgical setting represents a challenge in the management of patients with hemophilia and inhibitors due to the risk of peri-operative bleeding for which intensive by-passing therapy is often required, with unpredictable and sometimes suboptimal efficacy, we present here a major non-elective orthopaedic surgery performed on a patient enrolled in the HAVEN 1 study at our institution, for whom we used TGA to monitor the hemostatic efficacy of rFVIIa in combination with emicizumab.[8] The patient was a 56-year old man with severe hemophilia A and high-responding anti-FVIII inhibitors since childhood (historical peak titer: 126 BU/mL). He was a severe bleeder who used aPCC, plasma-derived porcine FVIII and rFVIIa to treat bleeds during his life. He had previously undergone two major orthopaedic procedures in 2002 and 2012. The first was a femur fracture fixation managed with rFVIIa by continuous infusion (20 µg/kg/h) according to our local practice at that time[9]; the patient was then switched to repeated boluses (130 µg/kg every 2h) to control severe bleeding at the surgical site. The second procedure was a total knee replacement initially managed with high-dose rFVIIa boluses (140-190 µg/kg every 2h) in order to prevent bleeding complications. However, severe blood loss (>1500 mL) and anaemia occurred, so that sequential bypassing therapy (alternate aPCC and rFVIIa every 6-8h) was given on the basis of preliminary evidence available at that time.[10]

The patient required blood transfusions in both occasions (7 and 9 units of red blood cells (RBC) respectively). On the occasion of the second procedure, TGA (see below) was used to measure coagulation activation *ex vivo* after the administration of bypassing agents, both pre-operatively in a non-bleeding state (testing two different doses of rFVIIa and aPCC) and then during the peri-operative period, as previously reported.[7]

In 2017, while on regular prophylaxis with emicizumab 1.5 mg/kg/week in the frame of the HAVEN 1 trial (NCT02622321),[2] the patient required a right hip replacement due to the displacement of the screws used to fix the femoral fracture. Based on our local practice and protocol recommendations,[2] we chose rFVIIa to manage the surgery. This decision was taken considering the strong and persistent anamnestic response previously observed in this patient, in order to save the use of FVIII for potentially life- or limb-threatening bleeds. No thromboprophylaxis was given.

Anti-FVIII inhibitors were measured pre-operatively by a chromogenic assay using bovine substrates (Chromogenix, Coamatic® Factor VIII, IL) and showed 2 BU/mL. The cell blood count, D-dimer, fibrinogen, lactate dehydrogenase (LDH), haptoglobin and blood film were monitored to rule out signs of consumption, disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA). A thrombin generation assay (Thrombinoscope™, Thrombinoscope BV) was performed on platelet-rich (PRP) and platelet-poor plasma (PPP) using 1pM tissue factor and 1µM phospholipids (only in PPP) as previously described.[7]

At the time of surgery (Day 0), a pre-operative rFVIIa bolus of 98 mcg/kg was administered and repeated rFVIIa boluses of 82 mcg/kg were given every 3 hours after-

Table 1. Laboratory parameters and treatment regimen for hip replacement in an inhibitor patient on emicizumab.

	Hb (g/dL)	Platelet count (x10³/mmc)	LDH (IU/mL)	Fibrinogen (mg/dL)	D-dimer (ng/mL)	Haemostatic treatment	RBC
Day 0 (pre-op)	12.7	138	245	256	579	rFVIIa	–
Day 0 (6 h post-op)	7.9	108	na	na	na	rFVIIa	3 Units
Day 1 (morning)	6.6	64	111	155	887	rFVIIa	2 Units
Day 1 (afternoon)	10.3	84	189	251	1055	pdFVIII	–
Days 2-7	8.9-10.6	80-142	na	348	707	pdFVIII	3 Units
Days 8-13	8.7-9.8	182-322	363-391	541-781	1302-2634	rFVIIa+ tranexamic acid*	2 Units

Day 0: day of surgery; pre-op: pre-operatively; post-op: post-operatively; Hb: hemoglobin; na: not available; pdFVIII: plasma derived FVIII; RBC: red blood cells. Normal range is 135-225 IU/mL for LDH, 165-350 mg/dL for fibrinogen and < 230 ng/mL for D-dimer. *10 mg/kg body weight intravenously once daily.

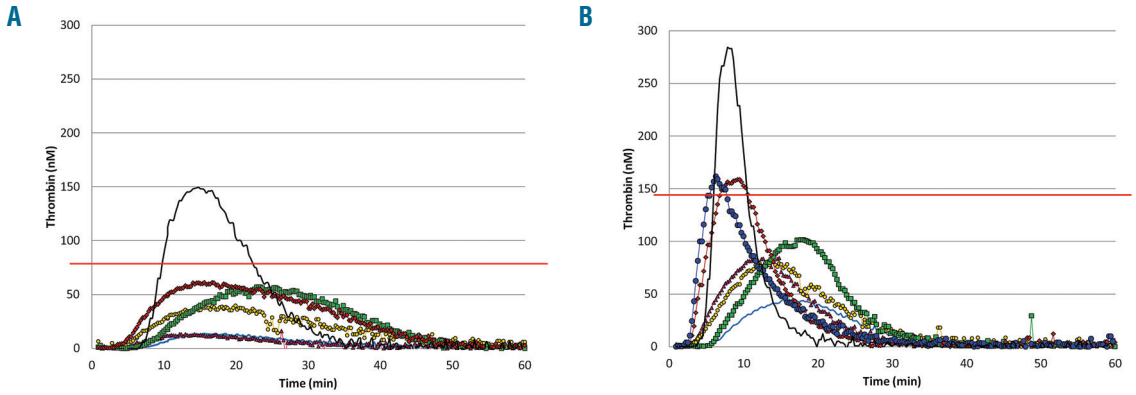

Figure 1. Thrombin generation measured in a patient with hemophilia A and inhibitors treated with rFVIIa before and after emicizumab prophylaxis. Thrombin generation measured *ex vivo* in platelet rich plasma (PRP) (panel A) and platelet poor plasma (PPP) (panel B) in the patient at baseline without any treatment (continuous light blue line), during emicizumab prophylaxis at steady state (green square), 30' post 90 mcg/kg rFVIIa in a non-bleeding state before starting emicizumab prophylaxis (pink triangle), 30' post 190 mcg/kg rFVIIa as pre-operative bolus before starting emicizumab prophylaxis (yellow circle), 30' post 98 mcg/kg rFVIIa as pre-operative bolus during emicizumab prophylaxis (red diamond) and 30' post 80 mcg/kg rFVIIa during emicizumab prophylaxis on post-surgical Day 1 during active bleeding (dark blue circle; measured only in PPP because PRP could not be obtained due to thrombocytopenia). The black continuous line depicts values of a normal control. The horizontal red bars depict the lower limit of the normal range for thrombin peak measured in PRP (78 nM; panel A) and PPP (147 nM; panel B). The higher limits were both out of scale (421 nM in PRP and 435 nM in PPP, respectively).

wards. The procedure lasted 1.5 hours and was uneventful with an intraoperative blood loss of 650 mL as expected for the type of surgery. During Day 0 the hemoglobin (Hb) level and platelet count dropped significantly (Table 1). Schistocytes were never detectable and hemolysis markers were always negative. On Day 1 a right thigh hematoma developed and Hb levels further dropped despite RBC transfusions. Facing this complication, in the presence of a low inhibitor titre, we chose to switch to FVIII as a rescue treatment. Replacement with a plasma-derived (pd) FVIII concentrate was the preferred treatment strategy to control bleeding rather than intensifying the rFVIIa dosing regimen, because we were concerned by the recent report of a thrombotic risk.[2] FVIII treatment was started 36 hours after surgery by bolus injection (115 IU/kg) followed by continuous infusion at 3.3-4 IU/kg/h. FVIII levels were monitored daily by chromogenic assay using bovine substrates (see above) and maintained above 80 IU/dL until Day 7 when FVIII decreased to 24 IU/dL despite increasing the infusion rate up to 6 IU/kg/h due to an antibody anamnestic response (80 BU/mL). At that time, the hematoma was reabsorbed, and the patient switched back to rFVIIa 80 mcg/kg every 4, 6 and 8h de-escalating rFVIIa doses every 72 hours. Antifibrinolytic therapy was associated until the patient's discharge on Day 13. The platelet count progressively improved during the FVIII treatment and was normal by the time the rFVIIa treatment was restored (Table 1).

Thrombin generation (TG) parameters were measured *ex vivo* in this patient during the stand alone emicizumab prophylaxis at a steady state and during the hip replacement while on emicizumab plus rFVIIa. At the previous assessments carried out in 2012 on the occasion of the knee replacement, there was no clear dose-response relationship between the TG parameters and rFVIIa administered in a non-bleeding state, and all the values were well below the normal range.[7] Endogenous thrombin potential (ETP) improved approaching normal values during the rFVIIa treatment on peri-operative Day 0-1, when severe bleeding occurred.[7] During emicizumab prophylaxis at a steady state the ETP reached the lower limit of the normal range (1484 nM*min; range: 1306-3099) but the thrombin peak was low (100 nM; range: 147-435). The ETP and peak values further increased during the rFVIIa treatment on the occasion of the hip surgery (1583 nM*min and 160 nM, respectively). However, despite those increased values, the patient experienced bleeding complications.

Figure 1 shows the TG measured *ex vivo* in this patient in 2012 and in 2017 during the bypassing therapy with and without emicizumab. As recently reported by Dargaud *et al.*,[4] we observed an improvement of the TG values after the addition of the by-passing therapy to emicizumab. However, at variance with the French report, we found no correlation between the TG values and the clinical conditions. Notice that in their case a low-dose aPCC was associated with emicizumab to treat a breakthrough bleed, while we are reporting on rFVIIa treatment in a surgical setting, at a time when factors other than the bypassing treatment influence the hemostatic system and thrombin generation. These complex interactions impact on the global coagulation results provided by the TGA, that cannot selectively measure the hemostatic efficacy of therapeutic agents and their specific effect on a clinical outcome. Indeed, the TGA results in our surgical case treated with rFVIIa in association with emicizumab were unable to predict the occurrence of bleeding complications. The low-dose rFVIIa regimen was used with neither the occurrence of thrombotic microangiopathy nor thrombosis, but it was insufficient to prevent bleeding. Hence, in the presence of an actually low titre inhibitor, FVIII replacement was feasible and was confirmed to be the most effective hemostatic therapy.

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doi:10.3324/haematol.2018.215129

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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