haematologica

Journal of The Ferrata Storti Foundation

# Rescue FVIII replacement to secure haemostasis in a patient with haemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement

by Elena Santagostino, Maria Elisa Mancuso, Cristina Novembrino, Luigi Piero Solimeno, Armando Tripodi, and Flora Peyvandi

Haematologica 2019 [Epub ahead of print]

*Citation: Elena Santagostino, Maria Elisa Mancuso, Cristina Novembrino, Luigi Piero Solimeno, Armando Tripodi, and Flora Peyvandi. Rescue FVIII replacement to secure haemostasis in a patient with haemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement. Haematologica. 2019; 104:xxx*
*doi:10.3324/haematol.2018.215129*

**Rescue FVIII replacement to secure haemostasis in a patient with haemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement**

Elena Santagostino[1], Maria Elisa Mancuso[1], Cristina Novembrino[1], Luigi Piero Solimeno[2], Armando Tripodi[1], Flora Peyvandi[1].

[1]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, and [2]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Traumatology and Orthopaedic Unit, Milan, Italy.

*ES and MEM contributed equally to this work*

**Word count of the text**: 1343

**Tables**: 1

**Figures**: 1

**References**: 10

**Running title**: Surgery in an inhibitor patient on emicizumab

**Corresponding author**:

Maria Elisa Mancuso, MD, PhD

Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center

Via Pace 9 – 20122 – Milan, Italy

Tel: +390255034072

Fax: +390255034439

e-mail: mariaelisa.mancuso@policlinico.mi.it; elisamancuso@gmail.com

**Case report**

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 haemophilia 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 haemophilia A and inhibitors aged > 12 years showed a significant reduction in bleeding frequency as 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 haemostatic efficacy as well as the prothrombotic potential of bypassing agents renders the clinical management utmost problematic. The use of 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 haemostatic drugs as in the occasion of treatment of breakthrough bleeds.[4] In fact, in 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 haemophilia 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 in a patient enrolled in the HAVEN 1 study at our Institution, for whom we used TGA to monitor the haemostatic efficacy of rFVIIa in combination with emicizumab.[8]

The patient was a 56-year old man with severe haemophilia 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 already underwent 2 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 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 evidences 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 2 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 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 surgery. This decision was taken considering the strong and persistent anamnestic response previously observed in this patient, so that we wanted 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 chromogenic assay using bovine substrates (Chromogenix, Coamatic® Factor VIII, IL) and resulted 2 BU/mL. Cell blood count, D-dimer, fibrinogen, LDH, haptoglobin and blood film were monitored to rule out signs of consumption (Disseminated Intravascular Coagulation, DIC) or Thrombotic MicroAngiopathy (TMA). 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 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 afterwards. The procedure lasted 1.5 hours, was uneventful with an intraoperative blood loss of 650 mL as expected for the type of surgery. During Day 0 Hb level and platelet count dropped significantly (Table 1). Schistocytes were never detectable and haemolysis 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 titer, we chose to switch to FVIII as rescue treatment. Replacement with a plasma-derived (pd) FVIII concentrate was the preferred treatment strategy to control bleeding rather than intensifying rFVIIa dosing regimen, because we were concerned about 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 antibody anamnestic response (80 BU/mL). At that time, the hematoma was solved, 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 discharge on Day 13. Platelet count progressively improved during FVIII treatment and was normal when rFVIIa treatment had been restored (Table 1).

Thrombin generation (TG) parameters were measured ex-vivo in this patient during standalone emicizumab prophylaxis at steady state and during hip replacement while on emicizumab plus rFVIIa. At the previous assessments done in 2012 on the occasion of the knee replacement, there was no clear dose-response relationship between TG parameters and rFVIIa administered in a non-bleeding state, and all values were well below the normal range.[7] Endogenous thrombin potential (ETP) improved approaching normal values during rFVIIa treatment on peri-operative Day 0-1, when severe bleeding occurred.[7] During emicizumab

prophylaxis at steady state 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). ETP and peak values further increased during rFVIIa treatment on the occasion of hip surgery (1583 nM*min and 160 nM, respectively). However, despite those increased values, the patient experienced a bleeding complication.

Figure 1 shows TG measured ex-vivo in this patient in 2012 and in 2017 during bypassing therapy with and without emicizumab. As recently reported by Dargaud et al[4], we observed an improvement of TG values after the addition of by-passing therapy to emicizumab. However, at variance with the French report, we found no correlation between TG values and clinical conditions. Notice that in their case low-dose aPCC was associated with emicizumab to treat a breakthrough bleed, while we are reporting on rFVIIa treatment in the surgical setting, at a time when factors other than bypassing treatment influence the haemostatic system and thrombin generation. These complex interactions impact on global coagulation results provided by TGA, that cannot selectively measure the haemostatic efficacy of therapeutic agents and their specific effect on clinical outcome. Indeed, TGA results in our surgical case treated with rFVIIa in association with emicizumab were not able to predict the occurrence of bleeding complication. The low-dose rFVIIa regimen was used with no the occurrence of thrombotic microangiopathy nor of thrombosis, but it was not sufficient to prevent bleeding. Hence, in the presence of an actually low titer inhibitor, FVIII replacement was feasible and was confirmed to be the most effective haemostatic therapy.

**References**


1. Uchida N, Sambe T, Yoneyama K, et al. A first in human phase 1 study of ACE 910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. Blood. 2016;127(13):1633-1641.
2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809-818.
3. Mancuso ME, Callaghan MU, Kruse-Jarres R, et al. Emicizumab prophylaxis in adolescent/adult patients with hemophilia A previously receiving episodic or prophylactic bypassing agent treatment: updated analyses from the HAVEN 1 study. Blood. 2017;130(Suppl 1):1071.
4. Dargaud Y, Lienhart A, Janbain M, et al. Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab. Haematologica. 2018;103(4):e181-e183.
5. Kruse-Jarres R, Callaghan MU, Croteau SE, et al. Surgical experience in two multicenter, open-label phase 3 studies of emicizumab in persons with hemophilia A with inhibitors (HAVEN 1 and HAVEN 2). Blood. 2017;130(Suppl 1):89.
6. Dargaud Y, Lienhart A, Negrier C. Prospective assessment of thrombin generation test for dose monitoring of bypassing therapy in hemophilia patients with inhibitors undergoing elective surgery. Blood. 2010;116(25):5734-5737.

7. Mancuso ME, Chantarangkul V, Clerici M, et al. Low thrombin generation during major orthopaedic surgery fails to predict the bleeding risk in inhibitor patients treated with bypassing agents. Haemophilia. 2016;22(4):e292-e300.
8. Santagostino E, Mancuso ME, Novembrino C, Anzoletti Boscolo M, Clerici M, Pasta G, Solimeno LP, Peyvandi F. Management of joint replacement in hemophilia A with inhibitors during emicizumab prophylaxis. Blood. 2017;130(Suppl 1):2360.
9. Santagostino E, Morfini M, Rocino A, Baudo F, Scaraggi FA, Gringeri A. Relationship between factor VII activity and clinical efficacy of recombinant factor VIIa given by continuous infusion to patients with factor VIII inhibitors. Throm Haemost. 2001;86(4):954-958.
10. Schneiderman J, Nugent DJ, Young G. Sequential therapy with activated prothrombin complex concentrate and recombinant factor VIIa in patients with severe haemophilia and inhibitors. Haemophilia. 2004;10(4):347-351.

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

| | **Hb (g/dL)** | **Platelet count ($x10^3$/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: haemoglobin; na: not available; pdFVIII: plasmaderived FVIII; RBC: red blood cells

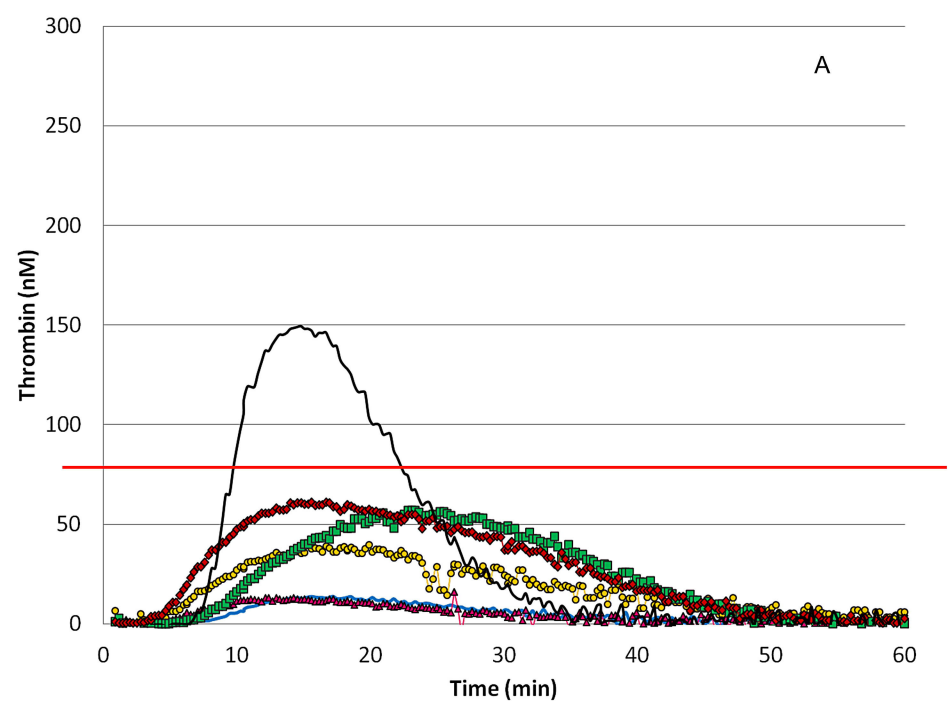
Normal range is 135-225 IU/mL for LDH, 165-350 mg/dL for fibrinogen and < 230 ng/mL for D-dimer

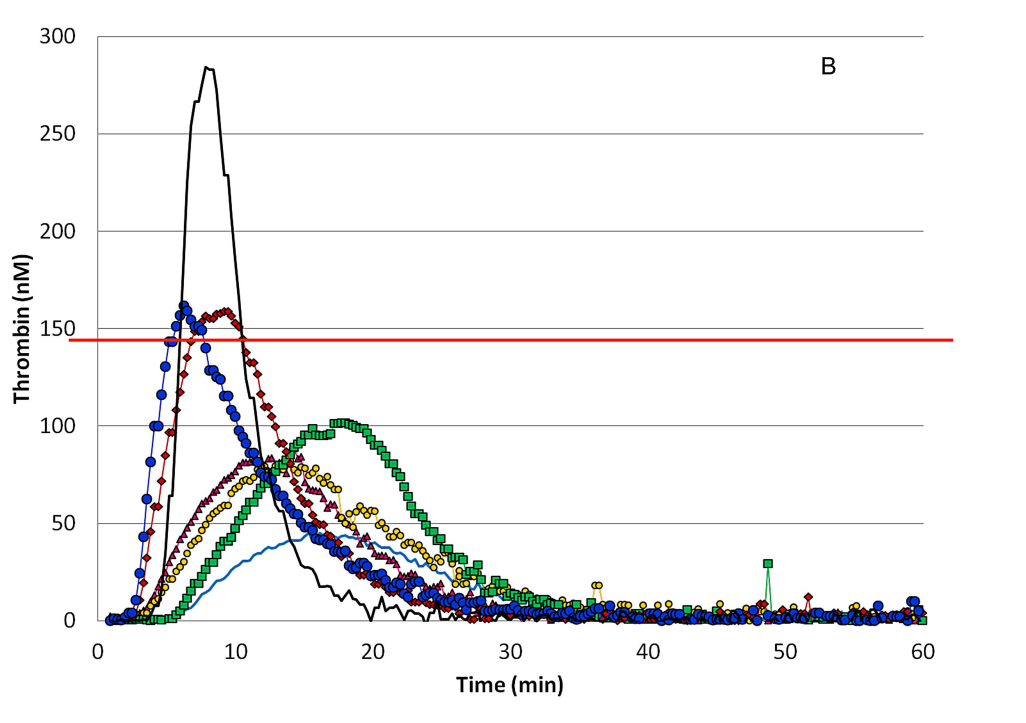
*10 mg/kg body weight intravenously once daily

**Figure 1. Thrombin generation measured in a patient with haemophilia A and inhibitors treated with rFVIIa before and after emicizumab prophylaxis.**

Thrombin generation measured ex-vivo in platelet-rich (panel A) and platelet-poor (B) plasma 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).


A
Thrombin (nM)
Time (min)
300
250
200
150
100
50
0
0
10
20
30
40
50
60


B
Thrombin (nM)
Time (min)
300
250
200
150
100
50
0
0
10
20
30
40
50
60