Received: 2 May 2019 | Revised: 27 October 2019 | Accepted: 26 November 2019

DOI: 10.1111/hae.13906

Haemophilia WILEY

LETTER TO THE EDITOR

EHL-FIX in haemophilia B carriers with FIX deficiency

Haemophilia is an inherited bleeding disorder characterized by a deficiency in coagulation factor VIII (FVIII) in haemophilia A (HA) or of factor IX (FIX) in haemophilia B (HB). Women carrying haemophilia typically display a clotting factor level close to 0.5 IU/mL, with only one chromosome affected, resulting in either no or only mild bleeding symptoms.[1] However, there is considerable variability among individuals due to a variable lyonization degree of the unaffected X chromosome.[1,2] Therefore, a proportion of haemophilia carriers exhibit a clotting factor deficiency. They should be referred to as "symptomatic carriers" (HA or HB carrier with a bleeding phenotype and FVIII/FIX > 40%) or "women and girls with mild/moderate/severe haemophilia" depending on their factor levels. In particular, carriers of severe and moderate HB have been shown to exhibit a higher risk of a clotting factor deficiency than carriers of severe and moderate HA.[3]

Haemophilia carriers with a clotting factor deficiency are at an increased risk of bleeding complications that potentially require haemostatic therapy in some situations (DDAVP and/or FVIII concentrate for HA carriers and FIX concentrate for HB carriers).[2,4] With respect to HB carriers with factor levels less than 0.6 IU/mL, recommendations for factor IX replacement with standard half-life FIX concentrates were published, pertaining to those subjects scheduled to undergo surgery or with significant bleeding symptoms.[2,4]

Several extended half-life FIX (EHL-FIX) concentrates have been developed using various technologies (PEGylation, fusion with albumin, or Fc fragment of immunoglobulins) with the aim of decreasing the treatment burden and frequency of infusions in patients with severe HB.[5-8] Although EHL-FIX concentrates have thus far mainly been studied in patients with a severe FIX deficiency treated prophylactically [5,6] and undergoing surgery,[9,10] they could potentially be used in patients with mild or moderate HB presenting with bleeds or requiring invasive procedures, with the advantage of reducing the number of required infusions. In addition, ELH-FIX could be employed in HB carriers with FIX deficiency requiring replacement therapy for invasive procedures or prophylactically, although very few experiences of EHL-FIX concentrates in HB carriers have been reported so far.

Here, we will describe our experiences with the successful use of EHL-FIX in four female patients with mild-to-severe FIX deficiencies before invasive surgery, at time of delivery, or for long-term prophylaxis. These patients were treated with either eftrenonacog alfa (Alprolix®), a recombinant fusion protein comprised of human FIX covalently linked to the constant region (Fc) domain of human IgG1 (rFIXFc),[11] or albutrepenonacog alfa (Idelvion®), a fusion protein between recombinant FIX and recombinant human albumin (rIX-FP).[12]

Case 1: Breast surgery and mastectomy. A 57-year-old HB carrier carrying a missense mutation (p.Ala74Pro—exon 2) of the FIX gene resulting in a mild FIX deficiency (0.3 IU/mL) was diagnosed with a Grade II infiltrating ductal breast carcinoma requiring excision of the superolateral quadrant of the right breast, along with right axillary lymph node dissection (Table 1). Co-morbidities comprised arterial hypertension and severe obesity (weight 105 kg, height 160 cm, BMI 41.02 kg/m^2; ideal body weight 60 kg). She reported a significant bleeding history that included menorrhagia, postpartum haemorrhage and bleeding following dental extractions treated with tranexamic acid. The patient had received fresh frozen plasma on one occasion prior to and following a hysterectomy, without any other blood product or FIX concentrates received in the past.

Breast surgery was covered by a single bolus infusion of rFIXFc at 6000 IU (100 IU/Kg), which was calculated according to the ideal body weight and given 1 hour prior to the procedure, through a peripheral venous catheter. The FIX level, measured by one-stage clotting factor assay (SynthASil APTT and HemosIL® Factor IX deficient plasma, Instrumentation Laboratory Company), increased from 0.27 IU/mL at baseline to 1.42 IU/mL 10 minutes after the bolus (sample taken from the opposite arm to the infusion). FIX assays were repeated 6 and 12 hours later and then once a day for 3 days. The FIX level was maintained above 0.60 IU/mL during this period following a unique preoperative bolus. The patient additionally received tranexamic acid (1 g 3×/day started preoperatively and continued for 5 days) and LMWH thromboprophylaxis (enoxaparin 40 mg/day). She was discharged on Day 4, without overt bleeding complications and a stable haemoglobin level. No delayed bleeding complications were reported.

Due to a disease progression, the patient required a complete mastectomy 7 months later, covered with the same rFIXFc at the same dose in combination with tranexamic acid. The FIX level increased from 0.30 IU/mL at baseline to 0.80 IU/mL 10 minutes after the bolus. The FIX level remained above 0.55 IU/mL until 72 hours after infusion in the absence of repeated bolus infusion. She was discharged 7 days postsurgery without either bleeding complications or any delayed bleeding reported.

Case 2: Plastic surgery. Bilateral otoplasty was scheduled for an 8-year-old girl who was the daughter of a mild-to-moderate haemophilic patient with FIX levels ranging from 0.05 to 0.09 IU/mL (c.1097C > T, p. exon 8 of the F9 gene; Table 1), with no previous history of bleeding. She was confirmed to be a carrier with low factor IX level at 0.29 IU/mL, following which she was treated with a single infusion of 1000 IU (50 IU/Kg) of rFIXFc and received 500 mg of tranexamic acid three times a day. No immediate or delayed

TABLE 1 Patients characteristics and treatment modalities

Age (y)	Indication for replacement	Weight (kg)	Treatment modality (product and dosing)	Total number of bolus to cover procedure	Baseline FIX (IU/mL)	FIX assay postinfusion (IU/mL)[a]
57	Breast surgery	105	rFIXFc 6000 UI	1	0.27	1.42 (postbolus)[b]
	Mastectomy	(ideal 60)	rFIXFc 6000 UI	1	0.30	0.80 (postbolus)[b]
8	Plastic surgery	20	rFIXFc 1000 UI	1	0.29	Not determined
31	Vaginal delivery	82 (before pregnancy)	rIX-FP 6000 UI	2	0.27	1.04 (postbolus)[b]
16	Long-term prophylaxis	65	rIX-FP 3000 UI every 14 d	Not applicable	0.02	0.77 (postbolus)[b] 0.1 (through)

Abbreviation: FIX, factor IX.

[a]Measured by one-stage assay (SynthASil APTT and HemosIL® Factor IX deficient plasma, Instrumentation Laboratory Company).

[b]10-15 min postinfusion.

postoperative bleeding complications were reported. As she was followed up in a hospital with no haemophilia expertise, no postoperative biological FIX monitoring was performed.

Case 3: Delivery. A 31-year-old women with mild HB (substitution c.571C > T in the F9 gene) was referred for delivery management (Table 1). She had a personal bleeding history with menorrhagia since menarche, frequent epistaxis and need of re-intervention for bleeding after a tonsillectomy. Her baseline FIX level before pregnancy was 0.16 IU/mL. During pregnancy, her FIX level remained initially unchanged but rose to 0.27 IU/mL in the third trimester. The delivery by vaginal route was provoked under epidural anaesthesia, following the administration of a bolus of 6000 IU rIX-FP. Her FIX level was 1.04 IU/L postbolus and 0.35 IU/mL on Day 4 following in the absence of repeated bolus of rIX-FP. No additional bolus was needed later on, without any delayed bleeding complications.

Case 4: Prophylaxis. The last patient was a 16-year-old girl with a severe FIX deficiency explained by extreme lyonization (baseline FIX level 0.01 IU/mL, missense p.Cys336Tyr) diagnosed at the age of 1 following hemarthroses in her knees and ankles (Table 1). She was previously treated with recombinant FIX 2000 IU once a week, without any haemorrhagic complaints. To reduce the treatment burden and improve her quality of life, she was switched to rIX-FP 3000 IU (45 IU/Kg) every 2 weeks. Following the first infusion given in hospital, her FIX level raised from 0.09 IU/mL to 0.77 IU/mL. Thirteen days after the infusion, her FIX was still at 0.10 IU/mL. She has now been on this treatment for over a year without any spontaneous or provoked bleeding event; moreover, she has a normal everyday life and is able to practice sports.

Clinical trials have demonstrated that EHL-FIX products are well-tolerated and highly efficacious, reducing the frequency of injections required to treat prophylactically severe male HB patients. As expected, in our HB carrier with severe haemophilia, the prophylactic use of EHL-FIX was proven to be as effective as that reported in male patients.[5,6] The three other cases illustrated that EHL-FIX can also be employed to prevent peri-operative and postoperative haemorrhagic complications in HB carriers with FIX deficiencies requiring major invasive procedures. In peri-operative settings, EHL-FIX use compared to standard rec-FIX showed multiple advantages, such as a reduced frequency of administration, easier venous access (none of the patients needed a central venous access), decreased treatment burden and prolonged haemostatic control with maintenance of haemostatically effective FIX levels during the several days after infusion. Administration was well-tolerated in every patient.

In conclusion, EHL-FIX appear to provide a haemostatically effective and convenient alternative to short-acting FIX concentrates to prevent bleeding complications in HB carriers with FIX deficiencies in different settings. Larger studies investigating the optimal use, dosing regimens and efficacy of EHL-FIX in female patients with FIX deficiencies of varying severity are needed. Such data would be instrumental in providing wider, evidence-based access of HB carriers with FIX deficiencies to innovative treatments like EHL-FIX.

DISCLOSURES

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

Camille Marlière
Laure Maindiaux
Catherine Lambert
Cedric Hermans

Division of Hematology, Hemostasis and Thrombosis Unit, Saint-Luc University Hospital, Université catholique de Louvain, Brussels, Belgium

Correspondence
Cedric Hermans, Division of Adult Hematology, Haemophilia Clinic, St-Luc University Hospital, Université catholique de Louvain, Avenue Hippocrate 10, BE-1200 Brussels, Belgium.
Emails: cedric.hermans@uclouvain.be; hermans.cedric@gmail.com

ORCID

Catherine Lambert https://orcid.org/0000-0003-2222-0357
Cedric Hermans https://orcid.org/0000-0001-5429-8437

REFERENCES

1. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, et al. Bleeding in carriers of hemophilia. *Blood*. 2006;108(1):52-56.
2. Mauser-Brunschoten EP. *Symptomatic Carriers of Haemophilia*. (No. 46). Published by the World Federation of Hemophilia (WFH); 2008. http://www1.wfh.org/publications/files/pdf-1202.pdf
3. Boban A, Lambert C, Lannoy N, Hermans C. Comparative study of the prevalence of clotting factor deficiency in carriers of haemophilia A and haemophilia B. *Haemophilia*. 2017;23(5):e471-e473.
4. Staber J, Croteau SE, Davis J, Grabowski EF, Kouides P, Sidonio RF Jr. The spectrum of bleeding in women and girls with haemophilia B. *Haemophilia*. 2018;24(2):180-185.
5. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. *N Engl J Med*. 2013;369(24):2313-2323.
6. Santagostino E, Martinowitz U, Lissitchkov T, et al. Long-acting recombinant coagulation factor IX albumin fusion protein (rIX-FP) in hemophilia B: results of a phase 3 trial. *Blood*. 2016;127(14):1761-1769.
7. Mancuso ME, Mannucci PM. Fc-fusion technology and recombinant FVIII and FIX in the management of the hemophilias. *Drug Des Devel Ther*. 2014;8:365-371.
8. Nazeef M, Sheehan JP. New developments in the management of moderate-to-severe hemophilia B. *J Blood Med*. 2016;7:27-38.
9. Negrier C, Abdul KF, Lepatan LM, et al. Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia B patients undergoing surgery. *Haemophilia*. 2016;22(4):e259-e266.
10. Powell JS, Apte S, Chambost H, et al. Long-acting recombinant factor IX Fc fusion protein (rFIXFc) for perioperative management of subjects with haemophilia B in the phase 3 B-LONG study. *Br J Haematol*. 2015;168(1):124-134.
11. Hoy SM. Eftrenonacog alfa: a review in haemophilia B. *Drugs*. 2017;77(11):1235-1246.
12. Lyseng-Williamson KA. Coagulation factor IX (recombinant), albumin fusion protein (albutrepenonacog alfa; idelvion): a review of its use in haemophilia B. *Drugs*. 2017, 77(1):97-106.