

First report of emicizumab use in a female patient with severe hemophilia A

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Key Points

- This is the first report of successful use of emicizumab in a female patient with severe hemophilia A.

Introduction

Classical treatment of severe hemophilia A (HA; factor VIII [FVIII] <1 IU/dL) consists of regular prophylactic IV self-administration of FVIII concentrates, either derived from plasma or produced by biotechnology.¹ This replacement therapy is burdensome, results in fluctuant and partial correction of FVIII deficiency with peaks and troughs of activity, and is not fully effective in preventing all bleeding episodes, whether spontaneous or provoked.²

Several nonreplacement therapies have recently been developed, and among these, only emicizumab (Hemlibra; Roche) has been approved so far. Emicizumab is a humanized bispecific monoclonal antibody mimicking the cofactor activity of FVIII by bridging activated FIX with FX.³ In contrast to FVIII concentrates, emicizumab is administered subcutaneously once per week to once every 4 weeks and results in a predictable, steady but partial correction of the coagulation defect in patients with HA.⁴ The efficacy of emicizumab in preventing bleeding episodes has been demonstrated in 4 large trials of exclusively male patients with predominantly severe HA with and without inhibitors.⁵⁻⁸

Hemophilia mostly affects males, whereas females are more commonly heterozygous carriers of the disease.⁹ Hemophilia carriers are expected to have an FVIII or FIX plasma concentration corresponding to half that found in healthy individuals, which is generally adequate for normal hemostasis. However, clotting factor levels may vary greatly in carriers, ranging from very low to the upper limit of normal. Rarely, severe FVIII deficiency resulting from homozygous or compound heterozygous defect alleles of the FVIII gene, structural or numerical aberrations of the X chromosome, extreme lyonization, or coinheritance of a variant von Willebrand factor allele has been observed.¹⁰

The prevalence of severe HA in females is very low, with 7 cases reported in 2019 in the nationwide FranceCoag registry (6417 HAs of all severities)¹¹ and 3 cases reported in the UKHCDO (United Kingdom Haemophilia Centre Doctors' Organisation) registry (8410 HAs of all severities).¹² The US My Life, Our Future Initiative collected genetic data from 2401 patients with HA, 81 of whom were females with HA (8 severe).¹³

Case description

Here we report the case of a 47-year-old female obligate carrier of severe HA with an FVIII level $<1\%$, resulting from a compound heterozygosity of type 1 intron 22 inversion inherited from her father and a large FVIII deletion (from 400 to 450 kb) inherited from her mother. Genetic analysis of the patient's mother revealed an int22h-1/int22h-2-mediated Xq28 deletion covering several genes, including exons 1 to 22 of the FVIII gene. These 2 deleterious rearrangements accounted for the undetectable FVIII level in our patient.

Diagnosis of HA in our patient was clinically suspected at 2 years of age after the occurrence of large hematomas. At age 7 years, she was admitted to the hospital after an extensive posttraumatic muscular hematoma and treated with FVIII for several weeks. She reported recurrent episodes of hemarthrosis, mainly in her left ankle, which resulted in spontaneous arthrodesis. Her annual spontaneous joint bleeding rate was estimated at 4 to 5 over the past few years.

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Surprisingly, she had no history of menorrhagia or anemia, but oral contraception was initiated early, and she was prescribed several courses of iron supplementation. She had 1 pregnancy, for which she required blood transfusion after a caesarean section indicated by placenta previa and required FVIII for the delivery and immediate postpartum period. She had no history of inhibitors, and her cumulative number of exposure days to FVIII was estimated at 300. At the time of evaluation, she was not using any contraceptive method, because her husband had undergone vasectomy.

Methods

Despite severe disease with advanced arthropathy and without regular follow-up by a hemophilia treatment center, tertiary prophylaxis with IV FVIII concentrates had never been considered. After the first visit, we concluded that prophylaxis was formally indicated, as it would be in every patient with severe hemophilia, irrespective of age or sex. We believed that compared with FVIII concentrate, emicizumab would be the treatment option of choice in terms of safety, convenience of use, and efficacy.

After obtaining the ethical approval and informed consent required by the pharmaceutical company because of the lack of data in females, treatment with emicizumab was started in August 2019 (3 mg/kg once per week during the first 4 weeks, then 6 mg/kg once every 4 weeks). As seen in other patients receiving emicizumab, activated partial thromboplastin time was shortened to 21 seconds, and FVIII activity determined by the chromogenic method using human reagents was 35%. Circulating emicizumab concentration was not measured.

Results and discussion

At the time of this report, the patient had been receiving this treatment for 8 months, with perfect tolerance and adherence and total absence of bleeding episodes. She reported a positive impact on her quality of life as assessed with the EuroQol 5-dimension questionnaire administered just before and 3 months after she started emicizumab (improvement in daily activities score from 3 of 5 to 1 of 5, pain estimated at 4 of 5 before and 2 of 5 after, anxiety/depression decreased from 3 of 5 to 1 of 5, mobility reduced from 3 of 5 to 2 of 5, autonomy remained stable at 1 of 5; EQ-VAS was at 60% before and 85% after 3 months).

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Because treatment was initiated in the absence of menstruation, the impact of emicizumab on menorrhagia could not be assessed. Additional data would ideally be required to confirm safety in women of child-bearing age not using effective contraceptive methods and during pregnancy. Animal reproduction studies of transplacental transfer of emicizumab have not yet been conducted. As a humanized monoclonal antibody (immunoglobulin G4 [IgG4]), emicizumab should be transferred across the placenta during pregnancy. One should take into account that the potential placental transfer of human IgG is dependent upon maternal levels of total IgG, placental integrity, IgG subclass, and gestational age, generally increasing as pregnancy progresses.^{14,15} For these reasons, fetal exposure to emicizumab would be expected to be very low during the period of organogenesis.¹⁵

This case report describes the use of emicizumab for the first time in a woman with severe HA. Our report does not add new information on the hemostatic efficacy of emicizumab; this would not be expected to be different in females with hemophilia. However, this case should motivate those treating hemophilia to consider use of emicizumab to optimize prophylaxis in females with severe HA. Studies evaluating nonreplacement therapies should ideally enroll female patients with hemophilia. Such data would be instrumental in giving females with hemophilia access to innovative treatments like emicizumab, with the same expected benefits and improvements in quality of care offered to male patients.

Authorship

Contribution: All authors were involved in the clinical management of the reported patient, and contributed to the writing of the manuscript and approved the final version.

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