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LETTER TO THE EDITOR

Practical challenges associated with efanesoctocog alfa (ALTUVIIIO) prophylaxis in a 19-month-old male with severe hemophilia A

To the Editor:

Hemophilia A is an inherited coagulation disorder characterized by a deficiency in factor VIII (FVIII), with severity determined by residual FVIII activity: severe (FVIII activity <1%), moderate (FVIII activity 1%–5%), and mild (FVIII activity 6%–40%).[1,2] Individuals with a severe bleeding phenotype are at increased risk for developing spontaneous bleeds, some of which may be life-threatening.[1,2] Since the 1990s, the standard of care has been prophylaxis with plasma-derived or recombinant factor concentrates to prevent bleeding episodes and associated joint damage.[1,2] The majority of FVIII concentrates used according to prophylactic regimens require administration twice or thrice weekly to effectively prevent bleeding events.[1,2] However, efanesoctocog alfa (antihemophilic factor [recombinant], Fc-VWF [Von Willebrand factor]-XTEN fusion protein) [ALTUVIIIO], Sanofi) is a once weekly injection that was FDA approved in February 2023 for prophylactic use in adults and children with hemophilia A.[3] Due to the large hydrodynamic volumes of the two XTEN polypeptide chains and binding to the D'D3 fragment of VWF and Fc, there is reduced clearance and degradation rates, which allow a longer half-life and activity time.[3]

Historically, it has been challenging to administer FVIII concentrate in young children without the presence of a central venous access device (CVAD). Some families choose to forgo CVADs and infuse peripherally due to the known complications of infection, malfunction, and thrombosis risk. We herein describe such a case and unique challenges associated with use of ALTUVIIIO.

A newborn male born via uncomplicated vaginal delivery was diagnosed with severe hemophilia A after being transferred from an outlying hospital for continued bleeding from heel-stick and circumcision sites. Laboratory evaluation revealed an elevated activated partial thromboplastin time (aPTT) of 99.7 seconds (21–32 seconds), hemoglobin concentration of 16.0 g/dL (11.0–14.5 g/dL), and factor VIII activity less than 1%. Genetic testing was obtained due to no family history of hemophilia that showed an F8 gene variant c.5816C>A (p.Ala1939Glu). He was prescribed recombinant factor VIII (rFVIII) concentrate (ADVATE, Takeda; 60 IU/kg) on Day 2 of life, as well as red blood cell transfusion for a decreased hemoglobin concentration of 6.9 g/dL. Bleeding was controlled with further ADVATE (60 IU/kg) every 8 hours for 2 days, then every 12 hours for 2 days without bleeding recurrence.

At 6 months of age, the patient was prescribed once weekly prophylaxis due to requiring eight on-demand doses for four spontaneous and traumatic soft tissue bleeds since diagnosis. Family was provided education regarding emicizumab-kxwh (HEMLIBRA) and PEGylated rFVIII (ADYNOVATE, Takeda), and choose to proceed with ADYNOVATE due to limited infant data with HEMLIBRA at that time. One month later after four soft tissue breakthrough bleeds, the family was given the option to switch to HEMLIBRA or increase ADYNOVATE to twice weekly. The family chose to increase to biweekly ADYNOVATE. Due to his parents' desire to avoid implantation of a CVAD, patients age, family's comfort, and distance from a hemophilia treatment center, all infusions prior to 6 months of age were performed at a local emergency department. After 6 months of age, he was accepted at a local infusion center, and his mother was trained on peripheral venous access and infusion at 8 months of age.

As he became more mobile, his parents noticed an increase in spontaneous ecchymosis requiring 11 on-demand doses despite biweekly prophylaxis, and became concerned for potentially more severe bleeding events. After multiple discussions regarding treatment options including HEMLIBRA and extended half-life factor products, the parents chose to remain on FVIII prophylaxis with ALTUVIIIO (Sanofi Pharma) while avoiding CVAD placement.

At 19 months of age, the patient received his first approximately 50 IU/kg prophylactic dose of ALTUVIIIO (actual 56 IU/kg, three vials of 220-IU vials; 500 IU vials not available at the time). He had attained more than 50 exposure days prior to initiation of ALTUVIIIO. His weight at the time of initial infusion was 11.9 kg. The ALTUVIIIO package insert recommends infusion rate at no faster than 6 minutes per vial if bodyweight is less than 20 kg (Table 1).[4] This is reportedly due to 5% sucrose in the final formulation of ALTUVIIIO, which is in accordance with the maximum infusion rate for intravenous immunoglobulin containing sucrose per the European Medicine Agency guideance.[4] This resulted in a peripheral infusion time of 18 minutes, which was challenging due to patient's age and venous access. The patient's FVIII

TABLE 1 Weight-based vial and injection rate recommendations for Efanesoctocog alfa.[4]

Participant weight (kg)	Minimum injection duration per vial (minutes)
10 to <20	6
20 to <30	3
≥30	2

TABLE 2 FVIII activity levels pre- and post-ALTUVIIIO infusions 1–3.

Infusion number	Factor VIII activity (%)		
	Pre-infusion	30 Minutes post infusion	4 Days post infusion
1	6	85	28
2	14 (7-day trough)	87	
3	21 (7-day trough)		

activity was obtained prior to and 30 minutes post infusion using the same one-stage FVIII activity assay used in the clinical trials (Table 2).[5,6] The patient's parents chose to have subsequent weekly infusions in the clinic setting due to concern over the long infusion time and potential for infusion failure and product wastage with home administration. He tolerated all infusions well with no adverse events.

Our patient's trough FVIII activity was greater than 10% at 7 days, and higher than reported in XTEND-Kids trial.[5] He has experienced zero-breakthrough bleeding episodes to date, which is consistent with XTEND-Kids data that demonstrated 64% of patients with zero bleeding episodes, 82% with zero joint bleeds, and 88% with zero spontaneous bleeds.[5]

The challenge with initiation of ALTUVIIIO prophylaxis in a less than 20-kg child remains the recommended prolonged infusion rate reportedly due to sucrose contained in the final formulation.[4] Per the manufacturer's recommendations, children less than 20 kg require each vial to be infused over 6 minutes compared to 2–3 minutes per vial if ≥20 kg. This presents a unique challenge for prophylactic administration for home use without a CVAD. Our case should encourage production of expanded vial size availability of ALTUVIIIO to allow for a single vial infusion over 6 minutes in less than 20-kg children. Consideration may also be made for the package insert to allow peripheral infusion rate as tolerated by the patient, if this is determined safe through appropriate study.

AUTHOR CONTRIBUTIONS

Jessica N. Mistretta and Jonathan C. Roberts wrote the initial manuscript. All authors critically reviewed, edited, and approved the final version of the manuscript for submission, and were involved in the clinical management of the patient.

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CONFLICT OF INTEREST STATEMENT

Maria G. Español: HEMA biologics: consultancy; Octapharma: consultancy. Michael D. Tarantino: Biomarin: consultancy; Genentech: consultancy; Novartis: consultancy; Octapharma: consultancy; other: clinical trial investigator; Principia: consultancy; Takeda: other: clinical trial investigator, research funding; Spark: other: clinical trial investigator; Amgen: consultancy. Jonathan C. Roberts: Genentech: consultancy; Novo Nordisk: honoraria; Takeda: honoraria; other: consulting; Sanofi: honoraria; other: consulting; HEMA Biologics: other: consulting; Novartis: other: consulting; Pfizer: honoraria; F. Hoffmann-La Roche AG: other: consulting; CSL Behring: consulting. Jessica N. Mistretta, Dane C. Christ, and Maureen D. Jones declare no conflicts of interest.

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