

Treatment With Efmoroctocog Alfa (Elocta®) in Hemophilia: A Case Series

Case Series

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Abstract

Hemophilia A is a rare X-linked disease that occurs as a result of a defect in the FVIII-encoding gene. The reduction or absence of plasma FVIII compromises the coagulation cascade, resulting in frequent bleeds, especially in joints or soft tissues. Currently, replacement therapy with coagulation factor concentrates is the gold standard for the treatment of FVIII deficiency.

Herein, we report a case series of five hemophilia A patients treated with an extended half-life recombinant human coagulation factor, FVIII-Fc fusion protein (efmoroctocog alfa). The prophylactic regimen for each patient was individualized based on their pharmacokinetic profile. Compared to previous prophylactic treatments, most patients received a reduced weekly dose of concentrate, all underwent a reduced frequency of administration, the annualized bleeding rates (ABR) and hemophilia joint health scores (HJHS) were stable or improved. The half-life of efmoroctocog alfa and the 72-hour trough levels were higher than those observed in the A-LONG Phase III trial.

In conclusion, all patients reported clinical improvements and general subjective wellbeing in the absence of significant safety concerns after switching to efmoroctocog alfa.

Keywords: Hemophilia A; FVIII-Fc; Efmoroctocog alfa; Bleeding; Extended Half-Life; Recombinant Factor VIII

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INTRODUCTION

Hemophilia A is a rare X-linked disease that results from a defect in the *F8* gene, which encodes the coagulation factor VIII (FVIII). FVIII is involved in the coagulation cascade, and its absence or reduction leads to bleeding. The type and severity of hemorrhages depend on the degree of hemophilia. Patients with severe disease can present with spontaneous bleeding, especially in joints, while patients with mild or moderate hemophilia more frequently present with post-traumatic bleeding. International data reported that 70% of spontaneous hemor-

Why Do We Describe This Case

Tailoring treatments to the individual needs of patients is becoming increasingly important in several diseases. It is useful to remind physicians treating hemophilic patients that this is also true in replacement therapy with the coagulation factor concentrates. In our case series, we obtained satisfactory outcomes with regards to patients' perspectives following the use of a recombinant human coagulation factor, FVIII-Fc fusion protein (efmoroctocog alfa)

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rhages affect joints, 15% affect muscles, and 15% represent visceral bleeding [1].

According to the Report on the Annual Global Survey 2017 of the World Federation of Hemophilia (WFH), the global prevalence of hemophilia A was 158,225 patients [2], while in Italy, 4120 patients were estimated to have the disorder. Patients with hemophilia A in Italy are managed by 52 different Hemophilia Treatment Centers (HTCs) distributed throughout the country and coordinated by the Italian Association of Hemophilia Centers (Associazione Italiana Centri Emofilia—AICE) [3] to ensure a homogeneous approach in hemophilia management.

Genetic defects are generally inherited, but in more than 30% of cases they are sporadic due to a *de novo* mutation [4]. More than 900 mutations have been identified [5] and registered in different national and international databases. Each identified mutation was related to a different hemorrhagic phenotype and risk of developing inhibitors against FVIII, which is the most serious event in the treatment of hemophilia. The clinical classification of hemophilia is based on the plasma level of residual FVIII production, which, in turn, determines the severity of the bleeding phenotype:

- <1%, severe;
- between 1% and 5% moderate;
- between 5% and 40%, mild [1].

Joint bleeding is the most frequent hemorrhagic event in hemophilia patients, and different scores have been developed to assess the joint impairment and function; these include clinical features, such as the WFH Physical Examination Score (Gilbert score), Hemophilia Joint Health Score (HJHS), and radiological scores, based on magnetic resonance imaging (MRI), ultrasound, or X-ray (Pettersen score) [6]. These scores must be repeated over time to monitor the effectiveness of the treatment. In hemophilia patients, a single joint may be repeatedly affected by bleeding, and, as reported in the WFH guidelines [6], can turn in a target joint, i.e., a joint in which three or more spontaneous bleeds occur within a consecutive 6-month period.

Replacement therapy with FVIII concentrates is the gold-standard treatment for hemophilia A [7], and, following the WFH guidelines [4], may be administered as follows:

- As a primary prophylaxis (routine prophylaxis started in the absence of documented

joint disease, before the second clinically evident large joint bleed and before 3 years of age);

- As a secondary prophylaxis (routine prophylaxis started after ≥ 2 bleeds in large joints and before the onset of documented joint disease);
- As a tertiary prophylaxis (routine prophylaxis started after the onset of documented joint disease).

Unlike the previous WFH guidelines [6], on demand therapy is no longer considered a long-term treatment option [4].

Additive therapy to standard treatment with coagulation FVIII concentrates includes desmopressin, which is effectively used in patients with mild hemophilia A; tranexamic acid, which may help manage mucosal bleeding [3]; and bypassing agents, such as activated prothrombin complex concentrate (aPCC) and rFVIIa, used in cases with inhibitors. Recently, a novel subcutaneous drug, a monoclonal humanized antibody mimicking the activity of FVIII, emicizumab [8], was developed for the treatment of hemophilia patients with and without inhibitors against coagulation FVIII.

The discovery in 1964 that fresh frozen plasma cryoprecipitate contained high levels of FVIII gave rise to plasma-derived factor replacement therapy [7]. These concentrates have significantly improved the quality of life of hemophilic patients by reducing the number of bleeds and their consequences, such as hemophilic arthropathy. However, in the 70's and 80's, the flawed purification techniques allowed some viruses to remain in the drug, thus contributing to infection of a significant proportion of this patient population. Indeed, over this period, over 90% of hemophilic patients contracted at least one hepatitis virus, while 30% had contracted HIV [3].

Following these events, coagulation factor concentrates of recombinant origin were developed in the 1990's. The first of a long series was marketed in 1992 [7], while the second and third generations of recombinant products were then added to the first generation of rFVIII, with a superior efficacy and safety profile [7].

Once the safety of the concentrates was obtained, improving their efficacy, and consequently their permanence in the blood flow became a primary objective of laboratory and clinical research, as the short half-life of the native FVIII represents a major obstacle to effective prophylaxis. To

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Year of birth	2001	1984	1998	2002	1992
Age at diagnosis	6 months	3 years	9 months	13 years	1 year
Type of hemophilia (% of FVIII)	Severe hemophilia A (FVIII = 0.8%)	Severe hemophilia A (FVIII = 0.8%)	Severe hemophilia A (FVIII < 1%)	Mild hemophilia A (FVIII = 13%)	Severe hemophilia A (FVIII = 1%)
Genetic findings, cDNA (protein)	c.6429+?_6430-?inv (InvInt22)	c.6429+?_6430-?inv (InvInt22)	c.6429+?_6430-?inv (InvInt22)	c.5879G>A (p.Arg1960Gln)	c.4509delC (p.Leu1504Cys fs*63)
Drug**	Before* Octocog 3 times/week 9000 IU 4 (right ankle)	Before* Octocog alfa 3 times/week 6000 IU ND: right ankle reduced range of motion, left knee prosthesis	Before* Moroctocog alfa 3 times/week 9000 IU 11 (elbows and right ankle)	Before* FVIIId on demand On demand On demand	Before* Octocog alfa 3 times/week 9000 IU 12 (elbows and ankles)
Infusion frequency	After Efmoroctocog alfa Every 3 days 7000 IU	After Efmoroctocog alfa 2 times/week 4000 IU	After Efmoroctocog alfa Every 3 days 7000 IU	After Efmoroctocog alfa Every 4 days 3500 IU	After Efmoroctocog alfa Every 3 days 10,000 IU
Drug consumption (week)	3 times/week 9000 IU	3 times/week 6000 IU	3 times/week 9000 IU	On demand On demand	3 times/week 9000 IU
HJHS (target joints)	1 (right ankle)	ND: right ankle reduced range of motion, left knee prosthesis	11 (elbows and right ankle)	0	8
ABR	7-8	3	2-3	8	1
72 h trough level (IU/mL)	0.0015	ND	<0.01	ND	0.006
96 h trough level (IU/mL)	<0.01	ND	<0.01	ND	ND
Half-life (hours)	11	ND	8.50	ND	9
Summary of clinical findings and symptoms	Frequent hemarthrosis with chronic hypertrophic synovitis (right ankle), chemical synovectomy at the age of 16 (right ankle)	Limited right elbow flexion, painful right knee, left knee with arthroplasty, left ankle with reduced joint range, need to reduce the frequency of infusions	Hemarthrosis, relapsing nose and post-traumatic bleeding, synovial hypertrophy (elbows), cartilage alteration (elbows and ankles). Pain in the elbows, and especially in the ankles	HEAD-US: score 0 at knees and ankles, 0-1 at elbows. High incidence of muscle hematoma, and some hemarthroses	Hemarthroses, pain and reduced motility at the ankles. Osteochondral damage at the elbows, synovitis at the ankles = 1

Table 1. Summary of clinical and laboratory findings of the case series

*Before: last drug taken before the switch to efmoroctocog alfa

**In prophylaxis if not otherwise specified

ABR: Annualized bleeding rates; HJHS: Hemophilia joint health score; ND: Not determined

this end, several methods have been used to extend the plasma half-life (EHL) of these concentrates. Among the long-lasting factors that have been developed, the IgG1 Fc fusion molecule [9], rFVIII-Fc (also known as efmoroctocog alfa, Elocta®, Swedish Orphan Biovitrum AB, Stockholm, Sweden), has been shown to effectively lengthen the half-life by 1.5-fold [10, 11], without compromising the effectiveness and binding capacity of the native protein [9, 12]. Efmoroctocog alfa is produced by recombinant DNA technology in the human embryonic kidney (HEK) cell line 293, in which all post-translational modifications are also performed [13].

The production of fusion molecules with Fc was used to successfully create several marketed molecules, such as growth factors, cytokines, and enzymes. This technology takes advantage of Fc binding to the neonatal Fc receptor (FcRn), thus protecting the whole molecule from degradation, and instead favoring recycling [9]. Although the half-life of rFVIII-Fc could be even longer, further extension is limited by the binding with von Willebrand Factor (vWF) [9]. In A-LONG [11] and A-LONG Kids Phase III studies [14] and their extension study (ASPIRE) [15], efmoroctocog alfa was proven to be both safe and effective in the prevention and treatment of bleeding events in patients with severe hemophilia A. Efmoroctocog alfa is indicated in both children and adults with hemophilia A and, thus far, it is the only long-acting FVIII licensed in children [16].

The present case series was born after an online meeting among 7 physicians treating hemophilia in Veneto (Italy) area. The aim was to share expertise about the management of complex clinical cases in 5 different centers. In fact, even though included in the most recent WFH guidelines [4], the use of EHL products, due to the recent marketing authorization and the paucity of data about their use in the real world, is still a matter of concern for some clinicians and patients.

DESCRIPTIONS OF CASES

Herein, we retrospectively describe a series of five clinical cases in five centers located in the Veneto region, Italy (Hematology Unit, AULSS 8 Berica in Vicenza; Veneto Oncology Institute in Castelfranco Veneto [TV]; Hemophilia Center in Padova; Pediatric Oncohematology, AOUI Verona in Verona;

and Hemophilia Center, AOUI Verona in Verona). The main characteristics of the patients and the outcomes before and after the start of prophylaxis with efmoroctocog alfa are reported in Table I.

Case 1

Case 1 was an eighteen-year-old patient affected by severe hemophilia A. He was diagnosed at 6 months of age as a result of left elbow hemarthrosis and started prophylaxis with octocog alfa 40 IU/kg twice a week at 3 years of age. His lifestyle was sedentary and his only physical activity was performed at school. He had consistent physical development and, by age 14, he was 1.83 m in height and 90 kg in weight; at this age, he started to suffer from recurrent hemarthrosis events at the right ankle, as well as the development of hypertrophic chronic synovitis, which was also detectable by joint ultrasound. A chemical synovectomy was attempted at the age of 16 and the weekly dose was raised (30 IU/kg three times a week), but his through levels remained about 1.5 IU/dL, his joint Annualized Bleeding Rate (jABR) was still 7–8/year, and the bleeding was always in the right ankle (target joint). In September 2018, at the age of 17, a switch to efmoroctocog alfa was suggested and pharmacokinetic (PK) testing was performed. The PK profile was very good and the half-life in this patient was 20 hours. The infusion of efmoroctocog alfa 3000 IU every 72 hours (30–35 IU/kg), i.e., a lower weekly dose, allowed this patient to maintain the through levels at 4.2% after 72 hours and the estimated half-life at 20 hours (as predicted using the Web-Accessible Population Pharmacokinetic Service-Hemophilia [WAPPS-Hemo]). Now, he continues to have consistent physical development (2.0 m in height and 93 kg in weight), his ankle remains mobile and painfree, without any pastiness, and his jABR diminished to 1/year. A further joint ultrasound is to be performed.

Case 2

Case 2 was a patient born in 1984; he was diagnosed with severe hemophilia A when he was a toddler, never developed inhibitors, and was never infected by blood-borne viruses. Complete anamnestic data were available from 1996, when 10–15 hemorrhagic events/year were registered, affecting both muscles and joints (knees, ankles, and elbows). Initially, he underwent on-demand

treatment with pdFVIII and subsequently with rFVIII. His joint health worsened, and he underwent arthroplasty to the left knee in 2009. In 2010, he started prophylaxis with octocog alfa 2000 IU three times a week (33 IU/kg), which improved his clinical condition, and joint and muscle hemorrhagic events became less frequent. In 2016, although his general health conditions were self-reported as good, physical examination revealed limited right elbow flexion, pain in the right knee, left knee with arthroplasty, and reduced joint range in the left ankle (he had also undergone infiltration cycles in the knee). He switched to efmoroctocog alfa in 2017 in order to reduce the frequency of administration. PK testing revealed the maintenance of FVIII levels at 3% on the 4th day. He agreed to start a regimen with two infusions (2000 IU each, 33 IU/kg)/week. With this regimen, he presents with only one hemarthrosis/year and two muscle hemorrhages/year, which generally occur just before a new infusion and as a consequence of swimming. He reports a good quality of life, performs moderate physical activity, and does not undergo physiotherapy.

Case 3

Case 3 was a patient born in 1998 who was diagnosed with sporadic severe hemophilia A at the age of 9 months as a result of spontaneous hematomas on the limbs. Initially, he received on-demand moroctocog alfa. He had an active lifestyle and loved to travel. He also suffered from several spontaneous bleeding events, such as hemarthrosis at the elbows and ankles and relapsing epistaxis, and had several Emergency Room (ER) admissions. He started prophylaxis treatment three times a week with increasing doses. Over the course of several years, he had several post-traumatic bleeding events, such as epistaxis after head trauma, internal cheek injury, hand injury, and right wrist hematoma. A joint ultrasound performed in 2015 revealed synovial hypertrophy at the elbows, and cartilage alterations up to 50% in the elbows and ankles. In 2016, MRI detected severe arthropathy in the right ankle. In May 2017, his HJHS score was 11, with elbows and right ankles as target joints. In November 2017, he required ialuronic acid infiltration to the right ankle. His main concern was pain, which he managed with on-demand anti-inflammatory drugs. Joint ultrasound (HEAD-US) performed in January 2019 confirmed hemophilic arthropathy, which

revealed grade 2 synovial hypertrophy and grade 3 osteochondral damage in both the elbows. The right ankle had grade I synovitis at the tibial and subtibial levels and grade I astragalus alteration. Although he felt a higher level of pain in the ankle, ultrasound examination showed that the damage was worse in the elbows. It is worth noting that he worked as a turner.

His last prophylaxis regimen with moroctocog alfa started in July 2017 and involved administration of 3000 IU three times a week. In April 2019, as a result of ultrasound findings and joint pain, PK testing was performed with both moroctocog alfa and a long-acting FVIII (efmoroctocog alfa), even considering that pain worsened 48 hours after the last infusion. He accepted the evaluation of PK for moroctocog alfa, which was consistent with clinical findings and revealed a short half-life that was unable to guarantee at least 1% FVIII between two subsequent infusions, but he did not wish to test efmoroctocog alfa. However, when he changed his mind, in July 2019, PK testing of efmoroctocog alfa was performed and revealed levels above 1% for 100% of time. When the two PK profiles were compared, a 30.6% increase in half-life and a 21.8% yearly reduction in infusions were predicted. It took two further months to make the decision to switch to efmoroctocog alfa 3000 IU every 72 hours. After the switch had been made, he had no bleeding and no pain in the elbows. However, he continues to feel pain at the right ankle, affected by an important arthropathy, although only when he starts moving after extended rest.

Case 4

In contrast to the previously reported cases, case 4 was diagnosed with mild hemophilia at the age of 13, when he was referred to the center in Verona. He had an unknown family history of hemophilia, but the mother affirmed that the boy has always had a lot of hematomas, in addition to having a very active lifestyle. In particular, he had periorbital hematoma at the age of 3, which lasted for 6 months, long-lasting bleeding (several weeks) after a tooth extraction, and he had to stop playing soccer and riding a bicycle due to frequent hematomas and cutaneous bleedings. Following several ER admissions, suspicions of mistreatment were also raised. Even after blood tests, which were performed when he was 10, showed an aPTT ratio of 1.52, the pediatrician did not suspect

hemophilia, but luckily the mother did. He was initially treated with desmopressin, but his response was low. Afterwards, he was treated with on-demand plasma-derived coagulation factor VIII concentrate. Genetic testing was performed, and family analysis revealed that the mother and the grandmother were carriers. In addition, the younger brother, even though he did not experience as much bleeding, was also affected, and had an FVIII of 14%. Due to several episodes of muscle bleeding, including two episodes involving the iliopsoas muscle, as well as the occurrence of hemarthroses (the HEAD-US sonographic scoring system was 0 per knee and ankle and 0–1 at the elbow level), prophylaxis was started in August 2019 after the need for several infusions of pdFVIII. Plasma-derived concentrates were avoided, owing to their high volumes and consequent transport inconvenience. A regimen of 27 IU/kg (2000 IU) efmoroctocog alfa every fourth day was started. The patient never developed inhibitors, and his ultrasound findings did not worsen despite some hemarthroses, although with a reduced incidence. Since the start of prophylaxis with efmoroctocog alfa, he feels much better, has an improved quality of life, and has had just one episode of traumatic bleeding.

Case 5

Case 5 was a patient born in 1992, who was diagnosed with sporadic severe hemophilia A when he was 1 year old. His trough levels were unsatisfactory and he experienced frequent spontaneous and post-traumatic bleeding episodes from 1 year old (melena, hematoma in the right buttock extended to the thigh, frequent bruising, and hematomas), which were treated with on-demand pdFVIII and, later, rFVIII. In particular, he was hospitalized for an important epistaxis, and he experienced frequent traumas due to his active lifestyle. From 10–15 years old, despite the young age, he suffered from reduced mobility and pain due to the ankles, which were target joints. In 2000, he started prophylaxis with octocog alfa, raising the frequency from two to three infusions per week, 2000 IU per infusion, due to frequent hemarthrosis and the fact that his ankles were target joints. Furthermore, in 2003 and 2004, he was also treated with cycles of hyperbaric oxygen therapy. In 2012, the dose of octocog alfa was raised to 3000 IU. Following this increase, he felt generally better and the bleeding was diminished, but

he still had some episodes, most of which were hemarthroses (two in 2016, three in 2017, one in 2018, and one in 2019).

Later, he spoke of a desire to travel, and consequently wished to reduce the frequency of infusions. When octog alfa went out of market, he had to choose a new product. In May 2019, he started prophylaxis with efmoroctocog alfa 4000 IU every 3 days. PK testing was performed with both octocog alfa and efmoroctocog alfa, and the comparison showed high levels of FVIII with the latter. He had no further bleeding after starting prophylaxis with efmoroctocog alfa in May 2019.

Unfortunately, his joints were already damaged. HJHS detected a loss of extension to both the elbows, especially to the left one, while his ankles were less compromised at a functional level; HEAD-US revealed a damage in both the cartilage and bone in elbows and ankle but a synovitis scored 0-1.

DISCUSSION

When comparing the data of these five patients (Table I), the age at diagnosis seems to be related to the severity of the disease, as the patients with severe disease were diagnosed earlier than patients with mild hemophilia. In fact, it is well known that mild hemophilia is generally underdiagnosed, or diagnosed later in life, especially in the absence of known familiarity [17]. Moreover, hemophilia has a wide variety of clinical manifestations, mainly affecting muscles, that, together with the lack of acquisition of self-infusion skills, make this form of hemophilia difficult to manage.

Genetic mutations deserve a special discussion, as they not only determine the amount of functional FVIII, and consequently the severity of the disease, but also play a role in the probability of what is considered the most serious treatment-related adverse event: the development of inhibitors [5]. Therefore, mutation screening should be performed in every patient, even in those with mild hemophilia [17], also crosschecking with available databases for the risk of inhibitor development.

The inversion of intron 22 was responsible for the disease in three of our patients (cases 1, 2, and 3; Table I). An extensive genetic study using an Italian hemophilia A database [5] found that 52% of patients with a severe phenotype had inversion of

intron 22. According to the CHAMP List Mutation Database [18], this significant structural change is reported to be associated with severe phenotypes, as well as with the development of inhibitors. The above-mentioned Italian genetic study found that inhibitors indeed develop in 25% of patients carrying this mutation [5]. Moreover, C5879G>A, which was found in our patient with mild hemophilia (case 4), is a missense mutation that is associated with mild/moderate forms and is not associated with inhibitor development [18]. However, none of the five current patients were found to have inhibitors.

The mutation giving rise to the amino-acidic change p.Leu1504Cysfs*63 (found in case 5) is a frameshift mutation that has not been reported in the CHAMP database [18]. However, another frameshift mutation has been recorded in the same amino-acidic position; this frameshift mutation results in a new termination site in the same position (p.Leu1504Phefs*63) and is associated with more severe forms of disease and no history of inhibitors, as in our case 5.

With regard to clinical manifestations, we found that the genotype-phenotype relationship is not as strict as it may seem; this is clear from the findings that the brother of our case 4 felt much better despite having the same genetics. Lifestyle and other unknown factors may play a role in the different phenotypes of hemophilia.

Case 4, due to the initial diagnosis of mild hemophilia, was the only patient in this case series who was not receiving prophylaxis before the start of efmoctocog alfa infusions. The use of desmopressin has been suggested in patients with mild hemophilia A, as it is able to raise FVIII levels three- to six-fold [17]. In unresponsive patients, as in our case 4, FVIII treatment is suggested, but routine prophylaxis is generally not required. However, case 4 had frequent bleeding, probably due to his very active lifestyle. It is worth noting that, in addition to several other bleeding episodes, he had two episodes of iliopsoas muscle bleeding, which is considered to be one of the most dangerous sites of bleeding, as it is associated with risk of neurovascular compromise, particularly the risk of femoral nerve palsy [4]. As such, it may require hospitalization and strict bed rest may be indicated [4]. In our clinical experience, prophylaxis is sometimes needed even with mild forms of hemophilia; therefore, considering his

clinical manifestations, we decided to start prophylaxis, which subsequently had a positive impact on his quality of life.

Since the other four patients were already receiving prophylaxis with other factors, we had to overcome their resistance to change. In particular, the 21-year-old patient (case 3) was apprehensive about switching. Even though the AICE guidelines [3] advise against frequent product switches in order to ease pharmacovigilance and maintain patient adherence, they support switching for clinical reasons, such as the serious arthropathies found in this patient. As observed, especially in the Padova center, patients feel a strong relationship with their usual drug, which they are frequently reluctant to betray. In this center, PK testing is an essential component of the switching process, in that it often convinces patients to make the necessary switch to another product. In case 3, the insistence of physicians and his girlfriend were essential in changing his mind. In the Verona center, PK testing is generally performed at the first administration because patients like to see the possible changes in order to stay motivated.

It would be ideal to have further objective tools, in addition to PK curves, to evaluate when the switch is appropriate, with a higher degree of certainty and also considering the joint status. Although we already know that joint status should be strictly monitored, particularly in the case of a switch, how to evaluate joint status remains an open question. We hope that increased knowledge on the use of replacement therapy will provide new useful insights in the near future.

As we observed in cases 2 and 5, joint damage unfortunately cannot be reversed. Case 2, who was born in 1984, had limitations of movements that were normal in patients of a similar age. In fact, FVIII prophylaxis has been more freely used in the last 17 years because infections have been a major concern since the marketing of third-generation products [7, 19]. However, there is still hope for younger children who have the opportunity to start early prophylaxis with the new products, thereby preventing joint damage.

With regards to the patients who were previously taking prophylaxis with another FVIII (cases 1, 2, 3, and 5), weekly drug consumption was diminished in 3 of them. In addition, the frequency of administration was reduced in 4/4 patients, because, according to pharmacokinetic (PK) testing, the

half-life was longer and the 72-hour trough levels were higher than those with the previous factor VIII regimen in all three patients with available data (1.33–1.81-fold, similar to that reported in the A-LONG Phase III trial; Table I). Annualized bleeding rates were reduced in 4/5 patients, and remained the same in one patient (case 2; Table I). HJHS was measured in three patients: It was scored 0 before and after the start of prophylaxis with efmoroctocog alfa in the patient with the mild phenotype, while in the other two patients (cases 1 and 5), it was lower with efmoroctocog alfa than with the previous FVIII (Table I).

Therapy individualization is suggested by the WFH guidelines [4] and meeting the individual needs of patients has the potential to raise compliance, as well as clinical outcomes and quality of life. Efmoroctocog alfa further expands the ar-

mamentarium against hemophilia. Data from the A-LONG Phase III study [11] and its extension (ASPIRE) [15] confirm that individualized dose and intervals of administration based on PK curves show better results in terms of ABR compared to fixed-dose regimens.

In this case series, efmoroctocog alfa was able to meet the needs of every patient in terms of pain reduction (cases 1 and 3), greater freedom from infusions (cases 2 and 5), and reducing hematomas (case 4).

In conclusion, the data reported in this case series are consistent with those from previous studies, and demonstrated that the use of efmoroctocog alfa in prophylaxis reduced bleeding, improved joint status, and reduced the frequency infusions. Consequently, efmoroctocog alfa was able to meet the needs of the reported patients, and obtain a wellbeing status.

Key Points

- *The clinical cases reported here confirm the outcomes obtained with efmoroctocog alfa for hemophilia patients in Phase III clinical trials and their extension*
- *Among the described patients, in general, efmoroctocog alfa reduced the number of weekly infusions, the total weekly drug consumption, and the ABR*
- *Efmoroctocog alfa prophylaxis was also useful in one patient with mild hemophilia*
- *Patients treated with efmoroctocog alfa reported clinical improvements and general subjective wellbeing in the absence of significant safety concerns*
- *The convenience of use is also demonstrated by the fact that, so far, efmoroctocog alfa is the only long-acting FVIII that is licensed in children*

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Conflicts of Interests

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Informed consent

All the patients involved gave their informed consent for the publication of this case series.

REFERENCES

1. Orphanet. Emofilia A grave. Available at [https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=IT&data_id=17872&Disease_Disease_Search_diseaseGroup=emofilia&Disease_Disease_Search_diseaseType=Pat&Malattia\(e\)/%20gruppo%20di%20malattie=Emofilia-A-grave&title=Emofilia%20A%20grave&search=Disease_Search_Simple](https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=IT&data_id=17872&Disease_Disease_Search_diseaseGroup=emofilia&Disease_Disease_Search_diseaseType=Pat&Malattia(e)/%20gruppo%20di%20malattie=Emofilia-A-grave&title=Emofilia%20A%20grave&search=Disease_Search_Simple) (last accessed October 2020)
2. World Federation of Hemophilia. Report on the Annual Global Survey 2017. October 2018. Available at <http://www1.wfh.org/publications/files/pdf-1714.pdf> (last accessed October 2020)
3. Rocino A, Coppola A, Franchini M, et al. Principles of treatment and update of recommendations for the management of haemophilia and congenital bleeding disorders in Italy. *Blood Transfus* 2014; 12: 575-98; <https://doi.org/10.2450/2014.0223-14>
4. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia: The Official Journal of the World Federation of Hemophilia* 2020; 26 Suppl 6: 1-158; <https://doi.org/10.1111/hae.14046>
5. Margaglione M, Castaman G, Morfini M, et al. The Italian AICE-Genetics hemophilia A database: results and correlation with clinical phenotype. *Haematologica* 2008; 93: 722-8; <https://doi.org/10.3324/haematol.12427>
6. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013; 19: e1-e47; <https://doi.org/10.1111/j.1365-2516.2012.02909.x>
7. McCue J, Kshirsagar R, Selvitelli K, et al. Manufacturing process used to produce long-acting recombinant factor VIII Fc fusion protein. *Biologicals* 2015; 43: 213-9; <https://doi.org/10.1016/j.biologicals.2015.05.012>
8. Lippi G, Favaloro EJ. Emicizumab (ACE910): Clinical background and laboratory assessment of hemophilia A. *Advances in Clinical Chemistry*. Vol. 88. Elsevier; 2019:151-67.
9. Dumont JA, Liu T, Low SC, et al. Prolonged activity of a recombinant factor VIII-Fc fusion protein in hemophilia A mice and dogs. *Blood* 2012; 119: 3024-30; <https://doi.org/10.1182/blood-2011-08-367813>
10. Powell JS, Josephson NC, Quon D, et al. Safety and prolonged activity of recombinant factor VIII Fc fusion protein in hemophilia A patients. *Blood* 2012; 119: 3031-7; <https://doi.org/10.1182/blood-2011-09-382846>
11. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014; 123: 317-25; <https://doi.org/10.1182/blood-2013-10-529974>
12. Peters RT, Toby G, Lu Q, et al. Biochemical and functional characterization of a recombinant monomeric factor VIII-Fc fusion protein. *J Thromb Haemost* 2013; 11: 132-41; <https://doi.org/10.1111/jth.12076>
13. Mancuso ME, Mannucci PM. Fc-fusion technology and recombinant FVIII and FIX in the management of the hemophilias. *Drug Des Devel Ther* 2014; 8: 365-71; <https://doi.org/10.2147/DDDT.S47312>
14. Young G, Mahlangu J, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Haemost* 2015; 13: 967-77; <https://doi.org/10.1111/jth.12911>
15. Nolan B, Mahlangu J, Pabinger I, et al. Recombinant factor VIII Fc fusion protein for the treatment of severe haemophilia A: Final results from the ASPIRE extension study. *Haemophilia* 2020; 26: 494-502; <https://doi.org/10.1111/hae.13953>
16. European Medicines Agency. Elocta. Available at <https://www.ema.europa.eu/en/medicines/human/EPAR/elocta>. Published September 17, 2018 (last accessed October, 2020)
17. Benson G, Auerswald G, Dolan G, et al. Diagnosis and care of patients with mild haemophilia: practical recommendations for clinical management. *Blood Transfus* 2018; 16: 535-44; <https://doi.org/10.2450/2017.0150-17>
18. CDC. CHAMP | Hemophilia | CDC. Centers for Disease Control and Prevention. Available at <https://www.cdc.gov/ncbddd/hemophilia/champs.html>. Published February 27, 2017 (last accessed October, 2020)
19. Franchini M, Lippi G. Recombinant Factor VIII Concentrates. *Semin Thromb Hemost* 2010; 36: 493-7; <https://doi.org/10.1055/s-0030-1255443>