Susoctocog-alfa (Obizur®) in the treatment of nine elderly patients with acquired haemophilia A: an Italian multicentre real world experience

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Background - In 2016, a new recombinant B-domain deleted porcine FVIII (rpFVIII) was licensed in Italy for the treatment of acquired haemophilia A (AHA), but only a few cases of patients receiving this have been reported in the literature. Here we report the largest registry of the use of rpFVIII for the treatment of AHA. The objective of this retrospective study was to describe the efficacy and the safety of susoctocog-alfa for AHA.

Material and methods - We studied a population of nine patients, recruited in five Italian haemophilia centres presenting AHA, and treated with Obizur® as first- or second-line therapy.

Results - rpFVIII was used as a first-line therapy in one-third of the patients. The median delay between clinical onset and diagnosis was 16 days. Initial bolus of infused susoctocog-alfa was 100 IU/kg, lower than the recommended dose. The treatment was maintained for a median of four days. Only one patient with serious co-morbidities and recurrent infections was treated for 32 days. All patients reached a complete resolution of AHA, and no recurrences were reported. Two patients developed a low-titre inhibitor against rpFVIII, neither experienced any complications.

Discussion - In our real world experience, susoctocog-alfa was proven to be an effective and safe therapeutic option for patients with AHA, also at a lower than recommended dosage. In our report, the appearance of low-titre inhibitors against rpFVIII, was not found to be clinically significant.

Keywords: *acquired haemophilia A, recombinant porcine FVIII, recombinant FVII activated, activated prothrombin complex concentrate.*

INTRODUCTION

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by a spontaneous development of auto-antibodies against the coagulation factor VIII (FVIII) in males and females with a previously normal haemostasis[1]. Morbidity and mortality associated with AHA are high, especially in elderly patients with severe co-morbidities. International guidelines recommend treating bleeding caused by AHA as soon as possible in

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first-line therapy with bypassing agents, such as activated prothrombin complex concentrate (aPCC) or activated recombinant FVII (rFVIIa), or with susoctocog-alfa, a recombinant porcine FVIII (rpFVIII). Moreover, plasma-derived FVIII concentrates can be an option for patients at high thromboembolic risk, especially in the presence of a low-titre inhibitor (<5.0 BU)[1-4]. A safe inhibitor eradication should be quickly obtained with corticosteroids alone or with corticosteroids and cyclophosphamide. Rituximab could be used when cyclophosphamide is contraindicated[5].

In 2016, a new recombinant B-domain deleted porcine FVIII (rpFVIII) was licensed in Italy. The advantage of this concentrate compared with bypassing agents is that it can be easily measured in plasma of treated patients with the one stage assays, like the other FVIII products usually used in the treatment of haemophilia. The efficacy of sustoctocog-alfa has been proven in the Modified Recombinant Factor VIII (OBI-1) Study[6], in which the positive response to treatment was achieved in all 28 patients within 24 hours from the first dose, despite the basal presence of an inhibitor against rpFVIII in ten subjects, four of whom had high-titre inhibitors. In this study, recommended loading dose of susoctocog-alfa was 200 IU/kg, followed by median doses of 100 IU/kg. However, subsequent reports from real practice show that those dosages may not be necessary in all patients. In their clinical experience, Tarantino *et al.*[7] reported that the haemostatic effect was achieved using loading doses of rpFVIII 100 IU/kg (6 of 7 patients) and subsequent doses of rpFVIII between 50-100 IU/kg, i.e. lower than recommended. Similarly, two more groups reported clinical efficacy of rpFVIII in AHA associated to bleeding at much lower doses than those currently recommended[8,9]. Until now, no other studies or reports on the use of Obizur® in clinical practice have been available, other than these four cited manuscripts.

Here, we report our Italian multicentre real-world experience of bleeding treated with susoctocog-alfa in nine elderly patients with AHA.

MATERIAL AND METHODS

Patients

We collected the case reports of nine patients diagnosed with AHA and treated with rpFVIII (Obizur® - Takeda Pharmaceutical Co., Tokyo, Japan) in five Italian haemophilia centres (Padua, Genoa, Turin, Pavia and Rozzano).

METHODS

Retrospective, multicentre real world case series

Bleeding

According to the International Society on Thrombosis and Haemostasis (ISTH) guidelines[10], major bleeding episodes were defined as symptomatic bleeding in an organ or a critical area, that is intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin (Hb) levels of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red blood cells (RBC).

Acute bleeding resolution

Acute bleeding resolution was assessed clinically in terms of bleeding tendency, size of haematoma, stability of Hb / hematocrit (Hct), and resolution of pain caused by the haematoma[11].

Short-term prophylaxis

aPCC was administered at a lower dosage from acute bleeding resolution for at least one week, according to clinical decision, and based on the data from the FAIR Registry (Findable, Accessible, Interoperable and Reusable data registry)[12,13].

Due to the multicentre and retrospective nature of this report, the laboratory and medical parameters were not centralised or standardised, and all data were collected following the clinical decision for each different study subject.

RESULTS

Nine cases of patients diagnosed with AHA and treated with susoctocog-alfa were collected (**Tables I** and **II**).

Case 1

A 77-year old man with multiple valve insufficiency (tricuspid, mitral and aortic) with ejection fraction (EF) 51%, diabetes, previous non-ST elevation myocardial infarction (NSTEMI) and abdominal aortic aneurysm presented at an Emergency Department (ED) with dizziness and upper limb weakness. Angio-computed tomography (CT) scan confirmed an intracranial haemorrhage which required neurosurgery. The intervention was performed

Table I *- Baseline characteristics of acquired haemophilia A (AHA) patients*

	Sex (M/F)	Age (years)	Cause of AHA	Co-morbidities	Previous diseases	Bleeding type/site	First presentation	Time to AHA diagnosis (days)	Surgery during AHA	Other
Case 1	M	77	Idiopathic	Hypertension; diabetes; valve insufficiency	NSTEMI; AA	ICH	ED	17	Haematoma evacuation	Tracheostomy
Case 2	M	68	Oncologic	Hypertension; diabetes; COPD	MI; renal failure; gastritis; hypothyroidism	Face; shoulder; hemitorax	ED	7	None	None
Case 3	M	79	Idiopathic	COPD; diabetes	Ischemic cardiopathy; carothid stenosis; vasculopathy	Ilio-psoas	ED	NA	None	Colonoscopy; Gastroscopy
Case 4	M	72	Idiopathic	COPD	None	Haematuria; leg; knee haemarthrosis	ED	11	None	None
Case 5	M	81	Autoimmune; oncologic	NSTEMI; vasculopathy	Mono-lateral breast cancer (DX)	Upper and lower limbs; soft palate	ED	4	Cholecystectomy	None
Case 6	M	86	Autoimmune; oncologic (suspected)	AF; *ACS; MGUS; renal failure	Pace-maker implantation	Anterior cervical swelling with haematoma	ED	60	None	None
Case 7	M	77	Idiopathic	MGUS; psoriasis	None	Ileo-psoas haematoma	IMD	1	None	None
Case 8	F	84	Autoimmune	Rheumatoid arthritis	Breast cancer; CAD	Lower legs and abdominal rectus muscle haematoma; haematuria	IMD	4	None	None
Case 9	M	84	Autoimmune	Pemphigoid bullous	None	Pectoral muscle haematoma	ED	30	None	None

M: male; F: female; AA: aortic aneurysm; ICH: intracranial haemorrhage; (N)STEMI: (non)ST-elevation myocardial infarction; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; ACS: acute cornary syndrome; MGUS: monoclonal gammopathy of undetermined significance; CAD: coronary artery disease; ED: Emergency Department; IMD: Internal Medicine Department *Patient on anticoagulant treatment.

Table II *- Summary of acquired haemophilia A treatments*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
FVIII at diagnosis (%)	10.7	2.0	0.3	8.0	0.3	1.6	1.1	0	1.0
INH titer (BU/ml)	6.1	55.0	88.0	1.5	110.0	1.8	6.0	292.0	128.0
Hb (g/dl)	9.7	6.3	6.8	5.8	5.7	11.0	8.0	8.0	6.0
Therapy before rpFVIII	aPCC	aPCC	None	rFVIIa; aPCC	None	None	rFVIIa	rFVIIa	rFVIIa
Loading dose rpFVIII (IU/kg)	100	100	200	100	50	100	200	120	200
Peak FVIII (%)	179.6	162.0	190.0	58.0	51.0	161.0	166.0	NA	51.0
Subsequent doses rpFVIII (IU/ kg)	50	50	50	100-50	50-25	28	66	/	100
Infusion doses frequency	12 hours	12 hours	8-12 hours	8-12 hours	8-12 hours	24 hours	24 hours	/	12-24 hours
Duration rpFVIII treatment (days)	7	6	3	5	32	4	4	1	3
Immunesuppressive therapy	CS/Cyp	CS	CS/Cyp	CS/Cyp	CS/Cyp	CS/Cyp	CS/Cyp	CS/Cyp	CS/Cyp
Other treatments	None	Tranexamic Acid	None	Rituximab	aPCC; Rituximab	None	Tranexamic Acid; Rituximab	None	None
Supportive transfusion (n/bags)	None	1	2	6	5	None	3	3	5
Inhibitor rpFVIII (BU/ml)	No	1.0	No	No	1.5	No	No	No	No
Short-term propylaxis	Low dose aPCC	Low dose aPCC	Low dose aPCC	Low dose aPCC	Low dose aPCC	No	No	No	No
Outcome	Resolution	Resolution	Resolution	Resolution	Resolution	Resolution	Resolution	Resolution	Resolution
Adverse Events	None	None	None	None	None	None	None	None	None

CS: corticosteroids; Cyp: cyclophosphamide; rFVIIa: recombinant FVII activated; aPCC: activated prothrombin complex concentrate; NA: not available.

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without any haemostatic treatment because the acquired haemophilia had still not been diagnosed, and the surgeons had considered the intervention at low risk for bleeding. Fourteen days later, the patient was diagnosed with idiopathic AHA on the basis of a prolonged activated partial thromboplastin time (aPTT) (1.98 ratio) and an incomplete resolution of the previous cerebral bleeding. At diagnosis, the plasmatic human FVIII level was 10.7% and human inhibitor titre 6.1 BU/mL. The patient was immediately treated with activated prothrombin complex concentrate (aPCC) 40 IU/kg every eight hours. An immune-suppressive therapy (IST) with corticosteroids 1.0 mg/kg/day (d) and cyclophosphamide 1.5 mg/kg/d was also started. Three days later, the treatment with aPCC was stopped due an incomplete resolution of an intracranial haemorrhage, and a loading dose of 100 IU/kg of susoctocog-alfa was given. The porcine FVIII activity peak after 30 minutes (min) was 180.0%, and subsequent doses of 50 IU/kg of susoctocog-alfa every 12 hours (h) were given for five days (mean porcine FVIII activity 87%). Prophylaxis with low-dose aPCC 25 IU/kg/bid was subsequently initiated to prevent bleeding relapses, and this was stopped one month later. The human inhibitor disappeared twenty days after the AHA onset, when the human FVIII level reached 56.4%. The inhibitor anti-rpFVIII was always negative. During hospitalisation, the patient underwent a tracheostomy under an effective haemostatic coverage with a single bolus of susoctocog-alfa 200 IU/kg. The decision to adopt this dosage was taken because no data regarding surgical treatment were available; therefore, the dosage on the technical product sheet was used.

Case 2

A 68-year old man, a smoker, with arterial hypertension, diabetes, chronic obstructive pulmonary disease (COPD), previous myocardial infarction, chronic renal failure, gastritis and iatrogen hypothyroidism was hospitalised for dyspnoea and lung adenocarcinoma treated only with radiotherapy. Upon discharge, the patient presented Hb 10.7 g/dL and aPTT ratio=1.44. One month later he was once again admitted to ED following a fall, presenting a head and a left shoulder trauma. Laboratory findings showed an aPTT ratio=2.94 and Hb 6.3 g/dL. The patient was discharged after only one supportive RBC transfusion. One week later, the patient was finally diagnosed with AHA after a new admission to ED due to large muscular haematomas in the left shoulder and hemithorax, the right face and periorbital region. Plasmatic human FVIII level was 2% and human inhibitor titre 55.0 BU/mL. The patient was immediately treated with aPCC 80 IU/kg every 12 h, tranexamic acid 10 mg/kg/d, and corticosteroids 1.0 mg/kg/d. Despite the haemostatic treatment, the bleeding had not resolved and the thoracic haematoma had increased in size. The aPCC was then stopped and Obizur® was given at a loading dose of 100 IU/kg followed by subsequent doses of 50 IU/kg every 12 h for six days to maintain a target FVIII level >70%, as reported in the Italian guidelines[2] for AHA management (mean porcine FVIII 81%). The peak of porcine FVIII measured after the first rpFVIII infusion was 162.0%. A low-titre inhibitor anti-rpFVIII (1.0 BU/mL) was found before the onset of treatment with susoctocog-alfa and confirmed when the treatment was stopped, without any impact on the porcine FVIII levels. A short-term prophylaxis with low-dose aPCC 50 IU/kg twice a week for 14 days was then started to prevent bleeding recurrences, until human inhibitor eradication.

Case 3

A 79-year old man, presenting COPD, diabetes and previously ischaemic cardiopathy, bilateral carotid stenosis, and vasculopathy was hospitalised for dyspnoea, followed by a syncope, and pain on the right side. CT-scan performed at admission revealed the presence of a large ilio-psoas haematoma (10x10 cm). An AHA was then suspected and confirmed by a prolonged aPTT (65 sec); plasmatic human FVIII level was 0.3% and human inhibitor titre 88.0 BU/mL. The patient was immediately treated with a loading dose of rpFVIII 200 IU/kg (porcine FVIII peak 190.0%), and subsequent doses of rpFVIII 50 IU/kg every 8-12 h for a further two days. Prophylaxis with low-dose aPCC 50 IU/kg twice a week for one month was then prescribed to prevent bleeding recurrence. The haematoma was progressively reduced until complete resolution, as reported at the CT-scan examination performed at follow up three months later. Immunosuppressive therapy (IST) with corticosteroids 1.0 mg/kg/d and cyclophosphamide 1.5 mg/kg/d was started after AHA diagnosis; the inhibitors had completely disappeared 35 days later. During hospitalisation, the patient was tested for cancer and autoimmune diseases,

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usually considered risk factors for AHA. A colon cancer was suspected due to a mild elevation of carcino-embryonic antigen (CEA) and the presence of occult blood in the stools. A colonoscopy was then planned for when the plasmatic human FVIII level reached 5.0%, under haemostatic coverage with Obizur® 100 IU/kg infused one hour before the examination, followed by a gastroscopy five days later under treatment with rpFVIII 50 IU/kg. No bleeds occurred during these analyses. The colonoscopy revealed only the presence of a diverticulosis at the ascending and sigma colon, and two small polyps on the transverse colon, while the gastroscopy did not reveal any abnormality.

Case 4

A 72-year old man with COPD was hospitalised for haematuria and spontaneous haematoma in the right leg. Coagulation analyses showed: a prolonged aPTT of 75 second (s), human FVIII level 1.5%, human FVIII inhibitor titre 8.0 BU/mL, and Hb 5.8 g/dL. The patient was diagnosed with AHA, and immediately treated with six red blood cell (RBC) units, corticosteroids 1.5 mg/kg/d, cyclophosphamide 2.5 mg/kg/d, and recombinant FVII activated (rFVIIa) 90 µg/kg every three hours. Despite these treatments, the patient required other supportive transfusions. rFVIIa was then stopped two days later and replaced with aPCC 100 IU/kg every 12 h. However, in this case, the patient still continued to need transfusion support due to persistent haematuria and to the appearance of haemarthrosis in the left knee. aPCC treatment was stopped two days later and rpFVIII 100 IU/kg every 12-24 hours was started, when aPTT was 72.9 sec and FVIII level 3%. The porcine FVIII peak of 58.0% reached immediately after the first infusion of Obizur®. Haematuria was quickly resolved and no other supportive transfusions were required. A prophylaxis with aPCC 100 IU/kg day was then prescribed to reduce the risk of relapses, which was subsequently reduced to 100 IU/kg every other day, and stopped ten days from onset. The IST with corticosteroids-cyclophosphamide was replaced with rituximab 375 mg/sqm/weekly (three doses). Inhibitors disappeared one month after the AHA diagnosis. No inhibitors against rpFVIII were found after Obizur® treatment.

Case 5

An 81-year old man, with history of rheumatoid arthritis, breast cancer and carotid vasculopathy was hospitalised for an acute NSTEMI, severe anaemia (5.7 g/dL) initially treated with supportive transfusions, and suspected AHA. Coagulation analyses performed upon admission showed a prolonged aPTT, plasmatic human FVIII 0.3%, and human FVIII inhibitor titre 110 BU/mL. Within a few days, large subcutaneous haematomas had also appeared in the lower and upper limbs, and in the soft palate. A confirmed diagnosis of AHA was then performed. An initial treatment with rpFVIII 50.0 IU/kg/tid was then started to resolve this severe and life-threatening bleeding (porcine FVIII peak after infusion 51.0%), while an IST with corticosteroids 1.0 mg/kg/d and cyclophosphamide 1.5 mg/kg/d was immediately prescribed to eradicate the inhibitors. The recommended initial dose of concentrate is 200 IU/kg; however, in this case, we decided to treat the patient with a lower dosage due to a concomitant presence of an acute coronary syndrome. This ensured a plasmatic FVIII level (>50%), while preventing it from reaching too high a peak which could be potentially dangerous. Ten days later, the haemostatic treatment with rpFVIII was reduced to 25.0 IU/ kg/tid a day. Twenty-five days from AHA diagnosis, a first infection by *Morganella morganii* complicated the clinical condition of our patient, and the inhibitor titre reached 212 BU/mL. Cyclophosphamide was stopped, and an antibiotic therapy was immediately started. At the same time, the patient had pain in the right hypocondrium. An ultrasound image revealed the presence of an extended gallbladder that was treated surgically. The cholecystectomy intervention was performed under rpFVIII coverage. A single bolus of 87.5 IU/kg was administered 30 min before surgery, followed by 62.5 IU/kg/tid for two days, and by 37.5 IU/kg/tid for another week. The peak of porcine FVIII reached during surgery was 111%, while in the seven days after surgery, the FVIII activity was steadily maintained at >50%. After discharge from the surgical division, the treatment with rpFVIII was reduced to 25.0 IU/kg/three times a day. A second infection due to *Enterococcus faecalis*, immediately treated with a combined antibiotic therapy, worsened the patient's clinical condition. The treatment with rpFVIII was reduced to 25.0 IU/kg/d only to maintain the haemostasis. A subsequent microbiological analysis showed a concomitant *Candida albicans* infection, requiring treatment with fluconazole. During this period, the patient did not present bleeding, but a check of the coagulation parameters revealed human FVIII 4.3%,

human inhibitor titre 144.0 BU/mL, and the appearance of a low titre (1.5 BU/mL) inhibitor against rpFVIII. The treatment with Obizur® was stopped on the clinician's decision, even though the treatment had been effective up to that point, and replaced with aPCC 40.0 IU/kg/d, needed to maintain a minimal haemostasis during the concomitant infection treatment with fluconazole and to reduce the risk of bleeding relapses. Despite these treatments, the human FVIII level remained very low (3.2%), and the human inhibitors very high (139.0 BU/mL). A new treatment with rituximab 375 mg/sqm/weekly (four doses) was then started ten days later. The follow-up control performed two months after the last infusion of rituximab showed the complete disappearance of the inhibitors.

Case 6

An 86-old man with a history of renal failure, acute coronary syndrome (ACS), atrial fibrillation, monoclonal gammopathy of undefined significance (MGUS), rheumatic polymyalgia, and suspected lung cancer, on treatment with apixaban, was hospitalised for the first time in an otorhinolaryngology (ORL) department due to mouth bleeding; aPTT prolongation was identified, but not considered. In the days prior to admission to ORL, the patient developed a haematoma in the left superior limb; the general practitioner (GP), considered it to be caused by the apixaban and replaced it with enoxaparin. Two months later, there was a second hospitalisation due to oral cavity haematoma without acute bleeding. Laboratory analyses confirmed the previous prolongation in the aPTT; acquired haemophilia A was then suspected and subsequently confirmed by a plasmatic human FVIII of 1.6% and human FVIII inhibitor of 1.8 BU/mL. An IST with corticosteroids 1.0 mg/kg/d and cyclophosphamide 1.5 mg/kg/d was prescribed to eradicate the inhibitors, while a bolus of 100 IU/kg of rpFVIII was immediately infused, reaching a FVIII peak of 161.0%. Another three doses of Obizur®, 28 IU/kg each, were needed to solve subcutaneous bruising, and maintain a mean porcine FVIII level of 34% after infusion. The patient was then discharged a few days later without any other treatment or any complications.

Case 7

A 77-old man presenting psoriatic arthritis, MGUS and anxiety syndrome was admitted to an ED due to epistaxis lasting some months, and a large ileo-psoas haematoma. The patient was also treated for a few days with non-steroidal anti-inflammatory drugs (NSAIDs) to treat a chest and lumbar pain, and with cephalosporins to treat bronchitis. Due to the suspecion of AHA, he was quickly transferred to an Internal Medicine Department, and an initial treatment with corticosteroids 1.0 mg/kg/d and rFVIIa 90 µg/kg every 6 h, later increasing to every 4 h, was started. Four days later, the bleeding continued despite the ongoing therapy requiring RBC transfusions. rFVIIa was then stopped and replaced by a bolus of Obizur® 200 IU/kg associated with cyclophosphamide 1.5 mg/kg/d. The treatment with rpFVIII continued for another three days at a dose of 66 IU/kg/d to maintain FVIII activity >70%[2]. A short treatment (six days) with tranexamic acid was also started. Despite IST, the human inhibitor did not disappear and human FVIII remained low. A new treatment with rituximab 375 mg/sqm/weekly (four doses) was then started. The follow-up check-up performed two months after the last infusion of rituximab showed a complete remission of the AHA.

Case 8

An 84-year old female presenting prior bilateral mastectomy due to breast cancer (in 1989), rheumatoid arthritis under treatment with corticosteroids and hydroxychloroquine, and coronary artery disease was admitted to an ED for a right lower limb muscle haematoma and was transfused with three blood units. A little later, the hematoma also expanded to the left lower limb, and a diagnosis of AHA was made (human FVIII <1%; human FVIII inhibitor 292.0 BU/mL). Immediate treatment with rFVIIa 90 µg/kg every 4 h was started and subsequently increased to every 3 h for the appearance of new haematomas. Prednisone 1.0 mg/kg/d was also immediately started, and cyclophosphamide 1.5 mg/kg/d was added a week later. Four days later, the rFVIIa was stopped for the sudden appearance of haematuria, and replaced with rpFVIII 120 IU/kg. One infusion of Obizur® was sufficient to solve the acute bleeding, while the other four infusions of rpFVIII (66 IU/kg every 12 h) also helped to reduce the haematomas. At discharge, plasmatic human FVIII was 33%, and human inhibitors against FVIII 67 BU/mL. Two months later, the plasmatic human FVIII level reached 73%, and the human inhibitors disappeared; cyclophosphamide was stopped, while a tapering therapy with corticosteroids was maintained.

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Case 9

An 84-old man, a former smoker presenting bullous pemphigoid, was admitted to an ED for a large haematoma in the left upper limb. He was treated only with paracetamol and discharged without other treatments, despite a prolonged aPTT ratio of 2.25 (normal range 0.80-1.20). At home, the patient had widespread pain that was treated by his GP with ibuprofen. Two months after the first admission, the patient was hospitalised again due to the appearance of large haematomas in the lower limbs, thorax and face. A diagnosis of AHA was then made (human FVIII 1.0%; human FVIII inhibitor 128.0 BU/mL), corticosteroids 1.0 mg/kg/d and rFVIIa 90 µg/kg every 6 h, subsequently increased to every 4 h, was immediately started. The patient was also transfused with five blood units. However, despite all these treatments, the CT-scan performed to rule out the possible presence of a cancer revealed an increase in the thoracic haematoma and an initial bleeding in the thoracic cavities. rFVIIa was then stopped and replaced with a first bolus of Obizur® 200 IU/kg (porcine FVIII peak 51%) followed by other three infusions of rpFVIII 100 IU/kg; five days later, cyclophosphamide 1.5 mg/kg/d was added. No other treatments were needed to solve the bleeding. Despite the low peak reached, no inhibitors against porcine FVIII were found.

DISCUSSION

We present here the largest case series of AHA patients treated with rpFVIII to control bleeding, of whom 66.7% were treated following an unsatisfactory response to aPCC and/or rFVIIa. Haemostatic efficacy was observed in all cases and no adverse events related to rpFVIII were observed. In three cases, the loading dose was that recommended and tested in the registration study[6], while in the other cases, the dose was lower, as previously described[7-9]. Although the basal presence of anti-rpFVIII reaches high percentages, as indicated in the OBI-1 Study[6] and other reports[15], and their detection is, therefore, recommended before starting the treatment with Obizur®, in our case, these data were not applicable due to the need to treat the patients promptly in response to active bleeding or because previous treatments had failed. The clinicians used the "recovery" after the administration of Obizur® to evaluate the efficacy of the drug because it appeared to be quicker. However, the low recovery of FVIII activity observed after the first dose of rpFVIII in cases 4 and 9 raised suspicion of the pre-existing antibodies against porcine FVIII, data not confirmed by controls performed after treatment. Nevertheless, in both patients, the low dose of rpFVIII led to the same effective haemostasis observed in the remaining patients.

Low-titre inhibitors against the susoctocog-alfa was found in two patients after the treatment with Obizur®, but this was without clinical significance.

In our report, almost all patients were males, similar to the reports by Tarantino and Stemberger[7,9]. However, in great contrast to the other data reported in the large studies in which the subjects were almost equally divided between males and females[12,15,16], the fact that in our study almost all patients were male is very likely to be due to the small number of subjects included in the case series reports. All our patients were elderly, with a mean age of 78.6 years, and presented some co-morbidities, as reported in the largest registries[12,15-19] on AHA.

In four cases (44.5%), AHA was idiopathic, while in the other cases it was equally caused by an underlying autoimmune and/or oncological disease, similar to reports in the other registries and studies[7,12,15-19].

The majority of bleeds were spontaneous, and mainly involved muscle or skin. Intracranial haemorrhage and haemarthrosis both occurred in only one patient. The average delay in diagnosis was 16 days (range 1-60 days), but this did not affect patient outcomes, unlike the cases observed by Tarantino *et al.*[7].

rpFVIII was used as first-line therapy in one-third of patients. In the remaining patients, bypassing agents were the first-line treatment, but in the majority of cases, these were used at a lower dosage than that reported in the guidelines. This could be due to the fact that patients had cardiovascular comorbidities that put them at thromboembolic risk. However, a reduction in the initial dosage of aPCC and rFVIIa proved ineffective. On the other hand, there are no thromboembolic risks with the use of rpFVIII in these patients, so it can be safely used at the recommended dosage or at a dosage of 100 IU/kg, as already used by many clinicians[7-9]. In our study, the median initial bolus was 100 IU/kg (range 50-200 IU/kg); this is lower than the dose used in the registration trial[6], but similar to what was reported by Tarantino, Martin and Stemberger[7-9]. This dosage allowed us to obtain a porcine

FVIII peak of between 50.0% and 180.0%, and therefore to obtain a valid haemostasis in our patients, allowing bleeding resolution. Subsequent doses were infused at a median dosage of 50 IU/ kg (range 25-100 IU/ kg), guided by FVIII activity assay.

The treatment with Obizur® was maintained for a mean of 4 days (range 1-7 days), while only one patient was treated for 32 days at a low dosage to maintain an efficient haemostasis during the different concomitant diseases and recurrent infections. As suggested by international guidelines[2,5], all patients received IST with corticosteroids, where cyclophosphamide was added in 89% of cases. Despite the fact that antifibrinolytics were proven to be safe also in patients with cardiovascular disease, treated with a bypassing agent[20], in this registry, only two patients underwent this combination of therapy; neither experienced any complications. No thromboembolic events were reported during treatment or follow up. AHA recurrence occurred in over 20% of patients with a first bleeding episode, and at the moment there are no guidelines as to how to prevent it. However, a short-term prophylaxis with aPCC was proven to be effective in preventing these events, as reported in the FAIR Registry[12,13]. Cases 1-5 (55.6%) of our patients received a low-dose aPCC as prophylactic treatment. Dosage, timing of infusions and treatment duration differed, based on the individual clinical decision; therefore, no statistical evaluation can be made due to small numbers of treated subjects. No recurrences were reported in this retrospective study during a mean one year period follow up.

CONCLUSIONS

In our real world experience, susoctocog-alfa was proven to be an effective and safe option for patients presenting severe bleeding in AHA, also in those with concomitant cardiovascular diseases, even if used at a lower dosage than recommended. In fact, a safe haemostasis and a rapid bleeding resolution were observed in all our cases.

We confirm that in those hospitals where FVIII activity level can be measured in real time, such as specialised haemophilia centres, a personalised approach could be adopted to give rpFVIII at much lower doses than recommended, thus avoiding the supraphysiological FVIII levels that may put the patient at risk for thrombosis; such an approach would also result in consistent savings in resources. Only two patients developed low-titre inhibitors against rpFVIII, but neither experienced any clinical complications. We also highlight the increasingly widespread use of a short-term prophylaxis with a low-dose of aPCC to prevent bleeding relapses. More experience and larger studies are needed to confirm the efficacy and safety of low-dose rpFVIII, and to identify those patients who could benefit from such a regimen.

AUTHORSHIP CONTRIBUTION

Thanks to all authors for their contribution to this case series. All authors collected the anonymous patient data for their cases, reviewed and revised the drafts of the manuscript. All of the authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published

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