An overview in acquired hemophilia A

An overview on acquired hemophilia A:

a rare but complicated disease

Samantha Pasca

An overview on acquired hemophilia A: a rare but complicated disease

Thesis Maastricht University

Cover: "*Home*"– Dolomiti Friulane, UNESCO heritage (Forni di Sopra - Udine, Italy)

An overview on acquired hemophilia A:

a rare but complicated disease

DISSERTATION

To obtain the degree of Doctor of Philosophy at the Maastricht University,

on the authority of the Rector Magnificus,

Prof. Dr. Pamela Habibovic

in accordance with the decision Board of Deans,

to be defended in public on

Monday 09th of October 2023, at 16:00 hours

by

Samantha Pasca

Supervisors

Prof. dr. Hugo Ten Cate

Prof. dr. Pier Mannuccio Mannucci (University of Milan)

Co-Supervisor

Dr. E. Zanon (Padua University Hospital)

The Assessment Committee

Prof. Dr. E.A.M. Beckers(chair)

Prof. Dr. R. De Cristofaro (Catholic University School of Medicine, Rome)

Dr. M. Morfini (University of Florence)

Prof. Dr. Y.M.C Henskens

Dr. H.M.H. Spronk

Contents

Chapter 1

General introduction pag. 9

Chapter 2

Can the plasmaderived FVIII still play a role in the treatment of acquired haemophilia A at the time of new drugs? pag. 17

Chapter 3

Activated prothrombin concentrate (FEIBA®) in acquired hemophilia A: a large multicenter Italian study - the FAIR Registry pag. 37

Chapter 4

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

pag. 45

Chapter 5

Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not

related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry

pag. 67

Chapter 6

pdFVIII/VWF may be an alternative treatment for old medical patient with acquired haemophilia A and systemic vascular disease?

pag. 81

Chapter 7

Acquired haemophilia A, concomitant acute myocardial infarction and urgent major surgery: how to successfully treat a critical patient with rpFVIII (Obizur®) pag. 93

Chapter 8

Low dose of aPCC after the initial treatment in acquired hemophilia A is useful to reduce bleeding relapses: data from the FAIR Registry

pag. 105

Chapter 9

Emicizumab in acquired hemophilia A: pros and cons of a new approach to the prevention and treatment of bleeding pag. 117

Chapter 10

Summary and general discussion pag. 139

Impact Paragraph pag. 155

Curriculum Vitae pag. 161

List of publications pag. 163

CHAPTER 1

General introduction

General introduction

Acquired hemophilia A (AHA) is a very rare bleeding disorder that equally affects males and females; its incidence is estimated between 1 to 6 cases per million persons/year, but these numbers could be higher because not all AHA cases are promptly recorded, hence the AHA diagnosis may be underestimated[1].

This disease is caused by a loss of tolerance of autologous factor VIII (FVIII) and a concomitant development of autoantibodies against FVIII. The mechanism that triggers this disorder is not yet fully understood but appears to involve anergy or loss of antigenic specific T and B lymphocytes and the elimination of autoreactive T lymphocytes during the maturation of the immune system[2].

The age at which cases of acquired hemophilia are more frequently observed follows a biphasic trend, with a first peak in young women during pregnancy or the puerperium and a second peak in the elderly population. The different published registries showed an average age of AHA onset of 69.9 years in the FAIR registry[3], which is younger than in the FEIBHAC registry (83 years)[4] and EACH2 registry (75.4 years)[5], but older than in the American study (57.5 years)[6], and comparable with the French study (72 years)[7].

The life expectancy of the general population has much increased in the last decades from 51.1 years in the 50's, to 65.4 years in the 90's, finally reaching 73.5 years today[8]. An increase in the elderly population will therefore likely imply an increase in AHA cases and it

is therefore even more important that clinicians are trained to recognize the symptoms and signs of this disease immediately. In fact, it often happens that the diagnosis of AHA is not or too late diagnosed, with potentially fatal consequences, when it is masked by the clinical condition of the patient. A typical example of this is the patient being treated with anticoagulants in which the hematomas, typical of acquired hemophilia, are attributed to the pharmacological treatment as well as the elevation of some coagulation parameters, primarily the activated partial thromboplastin time (aPTT)[9,10].

AHA is in half the cases idiopathic, the remainder is usually associated with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or Sjogren's syndrome, dermatologic diseases such as pemphigus or psoriasis, infectious diseases, postpartum or pregnancy, drugs, or hematological or solid cancer[11].

Skin bleedings are the typical manifestation of AHA, followed by muscle, gastrointestinal, genitourinary, and retroperitoneal bleeds. Unlike inherited hemophilia, hemarthroses and intracranial hemorrhage are very rare, and only few case reports are available[12,13].

International guidelines recommend treating bleeding caused by AHA as soon as possible with bypassing agents, such as activated prothrombin complex concentrate (aPCC), activated recombinant FVII (rFVIIa), or recombinant porcine FVIII (rpFVIII). In patients with AHA the risk of bleeding does not strictly depend on the level of FVIII present or on the antibody titer, and in fact remains high even when the plasma

level of FVIII is around 50% and the inhibitors are absent. When the bypassing products are not available, or the auto-antibodies titer is low (<5 BU/ml), AHA can be treated with recombinant or plasma-derived FVIII. Normal hemostasis must be immediately ensured, and the inhibitor eradication should be quickly instituted with corticosteroids alone, or with corticosteroids and cyclophosphamide. If these recommended treatments fail or are contraindicated, patients should be treated with rituximab, a monoclonal antibody effective against B cells[14,15].

Nowadays, emicizumab is added to the aforementioned drugs in the treatment of acquired hemophilia. This is a recombinant, humanized, bispecific monoclonal antibody that mimics the FVIII activity, recently authorized for the prophylaxis of congenital hemophilia A patients with or without inhibitors[16,17]. Its use in AHA is still off-label, but more and more cases are being disclosed to clinicians and a phase III study, the AGEHA study[18], is currently ongoing.

In this thesis I like to focus attention on a disease, which, although rare, is still today a cause of high mortality because it is not fully known by many clinicians, and its incidence will probably increase over the years due to the increase in the average age of the general population. In addition, in this thesis I want to take a special look at available and investigational treatments that will help clinicians better treat patients with AHA.

Chapters 2-5 report different acute therapies for AHA. In chapter 2 I discuss the treatment with an immune

tolerance induction (ITI), or a continuous infusion of plasmaderived FVIII (pdFVIII) in terms of efficacy, concentrate consumption, and therapy duration also in patients with high-titer inhibitors. The Chapter 3 deals with the efficacy and safety of aPCC in a retrospective-prospective multicenter Italian study. The use of rpFVIII is described in nine different cases in Chapter 4, while a concomitant use of by-passing agents and antifibrinolytics also in patients with cardiovascular co-morbidities is discussed in Chapter 5. Two different case reports dealing with patients presenting severe diseases at high thromboembolic risk treated with pdFVIII and rpFVIII have been described in Chapter 6 and in Chapter 7, respectively. Long-term prophylaxis with low dose aPCC to prevent AHA relapses is discussed in Chapter 8, while the future of AHA therapies, now represented by emicizumab, is illustrated by the review in Chapter 9.

References

1. Mingot-Castellano ME, Rodríguez-Martorell FJ, Nuñez-Vázquez RJ, Marco P. Acquired Haemophilia A: A Review of What We Know. J Blood Med 2022 Nov 23; 13: 691-710
2. Reding MT, Wu H, Krampf M, et al. CD4+ T response to factor VIII in haemophilia A, acquired haemophilia and Healthy subjects. Thromb Haemost. 1999; 82: 509–515
3. Zanon E, Pasca S, Santoro C, et al; Activated Prothrombin Complex Concentrate (FEIBA®) in Acquired Hemophilia A: a large multicentre Italian study - the FAIR Registry; Br J Haematol. 2019 Mar; 184 (5): 853-8
4. Borg JY, Négrier C, Durieu I et al.; FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans

l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia. 2015 May; 21(3):330-7
5. Knoebl P, Marco P, Baudo F et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J ThrombHaemost 2012; 10: 622–31
6. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor bypassing activity. Haemophilia 2004; 10: 169–73
7. Goudemand J. Treatment of bleeding episodes occuring in patients with acquired haemophilia with FEIBA: the French experience. Haemophilia 2004; 10 (Suppl 3): 70
8. GBD 2019 Demographics Collaborators. Global age-sex-specific fertility, mortality, healthy life expectancy (HALE), and population estimates in 204 countries and territories, 1950-2019: a comprehensive demographic analysis for the Global Burden of Disease Study 2019. Lancet 2020 Oct 17; 396 (10258):1160-203
9. Gutierrez N, Park J, Leighton T. "Accessory After the Factors": A Rare Case of an Acquired Factor VIII Inhibitor in a 75-Year-Old Man on Rivaroxaban. Cureus 2021 Oct 8; 13 (10): e18597
10. Vadikolia CM, Riddell A, Brooks S, et al. Acquired haemophilia masked by warfarin therapy. Int J Lab Hematol 2007 Feb; 29 (1): 64-8
11. Mingot-Castellano ME, Núñez R, Rodríguez-Martorell FJ. Acquired haemophilia: epidemiology, clinical presentation, diagnosis and treatment. Med Clin. 2017;148(7):314–22
12. Wei F. Successful treatment of acquired hemophilia A associated with immune thrombocytopenia and joint hemarthrosis: A case report and literature review. Medicine (Baltimore) 2018 Sep; 97 (38): e12044
13. Akamatsu Y, Hayashi T, Yamamoto J, et al. Newly Diagnosed Acquired Hemophilia A Manifesting as Massive Intracranial Hemorrhage Following a Neurosurgical Procedure. World Neurosurg 2018 Mar; 111: 175-80
14. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017 Jul; 92 (7): 695-705

15. Pishko AM, Doshi BS. Acquired Hemophilia A: Current Guidance and Experience from Clinical Practice. J Blood Med 2022 May 11; 13: 255-65
16. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 2017 Aug 31; 377 (9): 809-18
17. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med 2018 Aug 30; 379 (9): 811-22
18. Shima M, Amano K, Ogawa Y, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in patients with acquired hemophilia A: primary analysis results from a phase III study (AGEHA). Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2022: London, UK; OC 40.2

CHAPTER 2

Can the plasmaderived FVIII still play a role in the treatment of acquired haemophilia A at the time of new drugs?

Samantha Pasca, Vincenzo De Angelis, Marta Milan, Ezio Zanon

Blood Coagul Fibrinolysis2018 Jul;29(5):417-422
doi:10.1097/MBC.0000000000000734PMID:29608457

Abstract

Background: By-passing agents are the first-line therapy in the treatment of acquired hemophilia A (AHA), but not the only one. Other options as recombinant porcine factor VIII or plasmaderived concentrates (pdFVIII) are available to clinicians.

Aim: To evaluate whether the pdFVIII can still play a role in the treatment of AHA, and which patients could benefit from this therapy.

Methods: All patients with AHA, presenting severe cardiovascular co-morbidities, and treated with pdFVIII with or without von Willebrand factor (vWF), referred to two different Hospital were initially considered.

Results: Eight patients were studied and divided into two groups: 1-patients treated with daily infusion of pdFVIII; 2-patients treated with pdFVIII continuous infusion. After six months of follow-up all patients reached complete response. Mean consumption of clotting factor (219,000 IU vs 142,000 IU), mean duration of therapy (61.5 days vs 10.5), and meantime necessary to disappearance of the inhibitors (64 days vs 9) were higher in group-1, and the differences between the two groups were statistically significant ($p<0.05$). Patients in group-1also had a mean inhibitor titer of 20.4 BU, higher than that of group-2 patients (8.4 BU), with a lower detectable FVIII level.

Conclusions: Our study showed that pdFVIII can be an effective option for patients at high thromboembolic risk, even for those with high-titre inhibitors, especially if combined with vWF. The immunomodulatory role of

vWF should, however, better investigated in wider trials. The days of treatment with pdFVIII continuous infusion was proven to be similar to those reported with other drugs.

Background

Acquired Hemophilia A (AHA) is a rare bleeding disorder that affects equally males and females. This disease is characterized by a development of auto-antibodies against the factor VIII (FVIII), often its etiology is unknown, but in almost 50% of cases it is secondary to cancer, autoimmune diseases or infections. AHA is more frequent in elderly people, while a peak of events was found in young females secondary to pregnancy[1].

Cutaneous bleeding is the most frequent manifestation of AHA, followed by gastrointestinal, muscle, genitourinary and retroperitoneal bleeding. The severity of hemorrhage can be very different and, in some cases, can be life threatening[2,3].

The management of AHA consists in controlling bleeding, in preventing recurrences, in eradicating inhibitors, and, if possible, in treating the concomitant disease that caused AHA[4].

Haemostatic treatment must be started as soon as possible. Recombinant Factor VII activated (rFVIIa) and activated Prothrombin Complex Concentrate (aPCC) are usually considered the first-line of therapy for AHA. In the EACH2 Registry the efficacy of these by-passing agents to control bleeding exceeded 90%, but because of their potential thromboembolic risk, their use should be limited in case of patient presenting cardiovascular diseases. Replacement therapy with plasmaderived factor VIII (pdFVIII) can be an alternative to by-passing agents, but the published

guidelines recommend this treatment only in case of a low-titer inhibitors (<5.0 BU)[5,6]. In the last years a new recombinant porcine factor VIII (rpFVIII) was approved for the treatment of bleeding in AHA, its advantage is that it can be easily monitored with one stage monitoring assay, and its efficacy was proven in a prospective study on patients with AHA and severe bleeding[7]. As in case of pdFVIII, even in case of rpFVIII, thromboembolic risk is very low. rpFVIII should therefore be considered as first-line therapy of AHA[4].

A treatment with corticosteroids alone or corticosteroids with cyclophosphamide is recommended to eradicate inhibitors, while the use of rituximab is suggested only in cases of a contraindication to immunosuppressive therapy[3,4,8].

In case of AHA immune tolerance induction (ITI) with FVIII concentrates is rarely reported but can be also an available approach[9].

The options to treat AHA is often different, as the patients are different, the best therapy should be performed considering the efficacy and safety of single drugs needed to control bleeding and eradicate inhibitors and considering the risk factors for venous or arterial thromboembolism for each patient. The aim of our study is to assess the role still played by the plasmaderived products in the treatment of AHA compared with the old and new drugs.

Aim

The primary end point of this study is to evaluate the efficacy plasmaderived FVIII (pdFVIII), with or without von Willebrand Factor (vWF) in the treatment of AHA.

The secondary end point is to evaluate which population of AHA patients could benefit from therapy with pdFVIII and to assess the difference between the treatment with an immune tolerance induction (ITI) and continuous infusion of pdFVIII in terms of concentrate consumption, therapy duration and clinical response.

Methods

This is a retrospective study were enrolled all patients with diagnosis of AHA and treated with pdFVIII at the Hemophilia Center (University Hospital of Padua) and at the Transfusion Medicine Department (University Hospital of Udine).
Major bleeding as defined according to the ISTH guidelines[10].
According to AICE (Italian Association of Hemophilia Centers) guidelines[11], complete response to AHA treatment was defined as "*a persistent undetectable inhibitor (<0.6 UB/mL) with normal plasma levels of FVIII (>70%) is the criterion for the definition of complete response to eradication therapy (Grade 2B recommendation)"*.
Plasmaderived concentrates administered were: 1) Emoclot®, Kedrion, Italy; 2) Fanhdi®, Grifols,

Barcelona, Spain; 3) Haemoctin®, Biotest, Dreieich, Germany

Emoclot® and Haemoctin®: since the vWF factor is present in minimal non-standardized quantity, these products have been considered as constituted exclusively by pdFVIII

Scheduled visits for the laboratory controls followed the protocols established at the two different hospitals involved in this study, but all patients underwent two planned visits of follow-up at 6 and 12 months.

Comparative statistics between two different groups were performed with the Mann-Whitney Test ($p<0.05$).

Results

Nine patients were initially enrolled, but subsequently one patient was excluded from the study due to a lack of data regarding inhibitor titer and disappearance. Baseline characteristics of patients and significant cardiovascular co-morbidities are shown in the table 1.

ID patient	Age (years)	Sex	Site of bleeding	Comorbidities
01	70	M	Ileopsoas hematoma	Pulmonary infection, hypertension
02	71	M	Mucocutaneous syndrome	AMI, endarterectomy, CABG
03	64	M	Upper limbs and pharynx hematoma	DM2, hypertension
04	79	F	Mucocutaneous syndrome	Atrial fibrillation
06	69	M	Rectus femur hematoma	AMI
07	65	M	Upper limbs hematoma	Bilateral endarterectomy, pancreatitis
08	75	M	Calf hematoma	Carotid artery stenting, CHD
09	78	M	Retroperitoneal hematoma	AMI, endarterectomy

Table 1*. Baseline characteristics of patients and co-morbidities. AMI. Acute myocardial infarction; CABG: coronary artery by-pass graft; DM2: diabetes mellitus type 2; CHD: coronary heart disease*

Eight patients were studied, divided into two groups: 1) patients with confirmed AHA, treated with daily administrations of pdFVIII (immune tolerance induction); 2) patients with confirmed AHA, treated with continuous infusion of pdFVIII.

An immunosuppressive therapy (IST) was prescribed to all patients. 100% of them were treated with corticosteroids for a mean of 75 days (tapering dose); 7/8 patients received cyclophosphamide for a mean of 30 days (tapering dose). Only one patient with concomitant pulmonary infection (patient 01) received only prednisone, while one patient (patient 05) even received a high-dose of intravenous immunoglobulin 30 g/day for 5 days. All data regarding laboratory findings for each patient have been reported in table 2.

- *Group-1 (immune tolerance induction)*

Four patients with confirmed AHA, mean age 71 years (range 64-79 years) were included in this first group. 75% were males; three patients were treated with pdFVIII alone, while one, a 71-year-old-man, was treated with a concentrate of pdFVIII/vWF. All these patients had an inhibitor titer > 5BU (see table 2).

Patient 01: A 70-year-old-man, with previous atrial fibrillation, aneurysm to middle cerebral artery, renal failure, chronic obstructive pulmonary disease (COPD) was admitted to hospital with ileo-psoas hematoma revealed by CT-scan and initially attributed to oral anticoagulants. The anticoagulation was interrupted, but the haemorrhagic state was not solved and a diagnosis of AHA was carried out. The patient was initially

treated with pdFVIII 2000 IU/bid for 12 days, followed by an infusion of pdFVIII 3000 IU/day for 21 days. Subsequently the concentrate was reduced to 3000 IU/3 times week (3 weeks), followed by pdFVIII 2000 IU/ 3 times week (2 weeks), by pdFVIII 2000 IU/2 times week (1 week) and finally by pdFVIII 2000 IU/ day for 15 days. Three months later the inhibitor disappeared.

Patient 02: A 71-year-old-man admitted to hospital with anemia (Hb 10.3 g/dl) and a serious hemorrhagic muco-cutaneous syndrome with extensive hematomas on the face, left arm and suprapubic region. A diagnosis of suspected AHA was initially formulated due to these symptoms, and to negative result of a family and personal history of coagulation diseases negative, and subsequently confirmed by the laboratory results. This patient presented also some previous severe vascular and cardiology co-morbidities as thromboendoarterectomy to the left carotid artery, aorto-iliac by-pass, acute myocardial infarction (AMI) with consequent coronary artery by-pass graft (CABG). A treatment with pdFVIII/vWF was then started with an initial infusion of 4000 IU/bid for 6 days, followed by 3000 IU/bid for 7 days, and finally by 4000 IU/day for 3 days. The inhibitors disappeared on day 43.

Patient 03: A 64-year-old-man, with concomitant diabetes mellitus type II and hypertension, was admitted to hospital with upper limbs hematoma followed by a severe pharynx hematoma, suspected for AHA. The patient did not present inherited coagulation disorders, and the laboratory findings confirmed the suspicion.The patient was initially treated with pdFVIII 2000 IU/bid for 3 days in association with rFVIIa 8 mg/day,

followed by an infusion of pdFVIII 3000 IU/bid for 30 days (first three days associated with rFVIIa 8 mg/day), by pdFVIII 2000 IU/bid for 8 days, by pdFVIII 4000 IU/day for 3 days, and finally by pdFVIII 3000 IU/3 times a week (3 weeks). The inhibitors disappeared on day 48.

Patient 04: A 79-year-old-woman with concomitant atrial fibrillation and hypertension was admitted to hospital due to a mild anemia (Hb 10.7 g/dl) and a severe hemorrhagic muco-cutaneous syndrome with large hematomas in the thorax, abdomen, and upper limbs. A suspicion of AHA was formulated due to elderly age, to presenting symptoms and family and personal history excluded coagulation diseases, and subsequently confirmed by the laboratory data. A treatment with plasmaderived concentrate was then started with pdFVIII 2000 IU/bid for 27 days, followed by 3000 IU/day for 23 days, by pdFVIII 3000 IU/3 times a week (3 weeks) and finally by pdFVIII 3000 IU/2 times a week (2 weeks). The inhibitors disappeared after two and half months.

- *Group-2 (continuous infusion)*

Four patients with confirmed AHA, mean age 72 years (range 65-78 years) were included in this second group. All males, three were treated with plasmaderived FVIII/vWF, while one only with pdFVIII. All patients had concomitant severe cardiovascular diseases. One patient included in this group had a high titer inhibitor at the onset of the treatment (see table 2).

Patient 05: A 69-year-old man admitted to hospital with severe anemia (Hb 7.9 g/dl) solved with red blood transfusion, femur muscle hematoma revealed by CT-scan, bruising secondary to slight trauma, and hematomas at the lower limbs. Family and personal history excluded hemorrhagic diseases; laboratory analysis confirmed a diagnosis of AHA. The patient also presented a history of acute myocardial infarction (AMI) treated with percutaneous transluminal coronary angioplasty (PTCA) and stenting followed by a double antiplatelet therapy. The patient was initially treated with a bolus of pdFVIII/vWF 263 IU/kg, followed by a continuous infusion of pdFVIII/vWF 10 IU/kg/h for 13 days, adjusted to achieve a FVIII level of 60–80%. The inhibitors disappeared on day 6.

Patient 06: A 65-year-old man, admitted to hospital with a very severe anemia (Hb 4.6 g/dl) due to large bilateral hematoma located on his upper limbs and treated with red blood transfusion. The patient presented a previous history of hypertension, carotid artery disease (CAD) treated with bilateral endarterectomy, and pancreatic jejunal anastomosis for chronic pancreatitis. No family or personal of coagulation disease were reported, laboratory analysis confirmed diagnosis of AHA. A treatment with a continuous infusion of pdFVIII/vWF 4 IU/kg/h for 14 days was administered. The inhibitors disappeared on day 14.

Patient 07: A 75-year-old man admitted to hospital with a hematoma located on right wrist and left calf. The patient presented a previous carotid artery stenting, and a severe coronary heart disease treated with aspirin. No family or personal history of coagulation disorders were

reported, laboratory data confirmed AHA. The treatment was performed with an initial bolus of pdFVIII/vWF 120 IU/kg, followed by a continuous infusion of pdFVIII/vWF 3.3 IU/kg/h for nine days. FVIII inhibitor disappeared on day 7.

Patient 08: A 78-year-old man admitted to hospital with spontaneous hematomas at the upper limbs, without a family or personal history of hemorrhagic disorders, followed by a left retroperitoneal hematoma revealed by a CT-scan. The patient presented also a previous significant cardiovascular history: AMI, ventricular tachycardia, and right carotid endarterectomy, currently in treatment with aspirin, and a chronic renal failure. Laboratory findings showed a mild anemia solved with red blood transfusion and confirmed a diagnosis of AHA. The hemostatic treatment was performed with an initial bolus of pdFVIII 300 IU/Kg followed by a continuous infusion of pdFVIII 15IU/kg/ h on day 1. The dosage was then adjusted in the subsequent days to achieve a correct FVIII level resulting in a total of a 7-day therapy. The inhibitors disappeared on day 8.

- *Comparison between two groups and clinical outcomes*

A synthesis of the laboratory data, the total consumption of plasmaderived concentrates, the duration of treatment and the time to inhibitor disappearance was shown in table 2.

ID patient	FVIII at diagnosis (%)	INH titer (BU/ml)	FVIII (IU total dose)	FVIII/vWF (IU total dose)	Duration (days)	Time to INH disappearance
01	0.4	32.3	231 000		90	90
02	2.5	28.0		178 000	16	43
03	3.5	15.2	271 000		55	48
04	15.0	6.0	198 000		85	74
05*	0.3	4.36		164 000	13	6
06*	10.4	1.0		84 000	14	14
07*	15.3	3.48		159 000	8	7
08*	2.4	10.5	162 000		7	8

Table 2 *Synthesis of laboratory data, plasmaderived consumption, duration of treatment and time to inhibitor disappearance. *Treatment with continuous infusion; INH: inhibitors*

The consumption of plasmaderived concentrates to reach FVIII >70% was lower in the group-2 (continuous infusion treatment), with a mean of 142,000 IU vs 219,000 IU. In the group-1, patients treated with daily infusions of concentrate (ITI), the duration of therapy was higher than in the other group (mean 61.5 days vs 10.5), such as the time necessary to the inhibitor disappearance (mean 64 days vs 9 days). For all these three topics the difference between the two groups were statistically significant ($p<0.05$).

In the case of the only patient included in group-1and treated with pdFVIII/vWF (patient 02), the duration of treatment and the consumption of concentrate resulted similar to patients treated with continuous infusion and was included in the group-2, but the time needed to the inhibitor disappearance was comparable with the other group-1 patients.

Conversely in the case of the latter patient in the group-2 treated with pdFVIII alone the consumption of concentrate, the treatment duration, and the time needed to inhibitor disappearance are comparable with the other ones included in the same group.

The younger patient (patient 03) without thromboembolic risk factors and concomitant cardiovascular diseases was even treated with rFVIIa for six days in association to pdFVIII, but the concentrate consumption, the treatment duration, and the time to inhibitor disappearance remained similar to other patients of the group-1, never treated with by-passing agents.

At the beginning of the pdFVIII treatment, the mean of inhibitor titer in the group-1 was 20.4 BU/ml, and 8.4 BU/ml in the group-2, the difference between two groups was statistically significant ($p=0.036$). At the same time, the mean of FVIII level in the group-1 was 5.35%, while in the group-2 it was 7.1%, even in this case no differences statistically significant were found ($p=0.84$).

At six months of follow-up all patients had reached complete and permanent response (FVIII > 70%).

No patient had recurrences of AHA or was hospitalized for any hemorrhagic episode. No thromboembolic events were reported during treatment or during 6 and 12-months of follow-up. Only one patient died eight months after discharge (patient 06), but the death was related to a cancer progression.

Discussion

By-passing agents, rFVIIa and aPCC, are the first-line therapy for the treatment of AHA, but in the last years a new product has been licensed, a recombinant porcine FVIII (rpFVIII). In the past a porcine plasmaderived

FVIII was successfully used in patients with AHA, but are no longer available; this new concentrate, proved to be effective in the control of bleeding events at the initial dose of 200 IU/kg, can be easily used and monitored with the one stage laboratory method[7]. Similar to plasmaderived products, rpFVIII provides another treatment option for the clinicians, and reduces the thromboembolic risk also in elderly patients with severe co-morbidities.
In the EACH2 Registry[12], thromboembolic events occurred in the 3.6% of patients treated with by-passing agents, but in our case all patients had severe and concomitant cardiovascular diseases that contraindicated the use of these drugs.

With this background, and due to lack of the rpFVIII at the time of study, all our patients were even treated with plasmaderived products.

As reported in different trials[1,13], acquired hemophilia A is usually considered a bleeding disorder that affects equally males and females, but in our little experience 87.5% were males. Only one of our patients suffered from cancer, in the other cases the AHA were all considered idiopathic.

International guidelines recommend use of plasmaderived products only in case of low-titer inhibitors[5,6], but our study has clearly shown that also in case of patients with high-titer inhibitors on the onset of AHA, the use of pdFVIII was very effective. Continuous infusion was used after an initial bolus of concentrate to quickly reach a high level of FVIII

needed to achieve a hemostatic response[14]and an inhibitor eradication with combined use of IST, while immune tolerance induction in AHA[9]patients is not usually adopted, the duration of treatment, and the need of daily infusions lead to a low compliance by these setting of patients. In our case the duration of therapy resulted longer when the patients were treated with an ITI regimen if compared to continuous infusion, where the days of exposure to pdFVII were similar to those reported in the large trials with by-passing agents[12,13] or with rpFVIII[7]. Based on our experience and published data[9,15,16], a clear explanation of this result is not available.

In our study, a difference was found among the patients treated with pdFVIII alone and the patients treated with pdFVIII/vWF. In the second case fewer days of exposure, and a reduction of clotting factor consumption were reported. The role of products containing vWF was assessed in case of immune tolerance induction (ITI) in patients with congenital hemophilia A and inhibitors. Different case reports and a recent international study have proven the efficacy of these concentrates to eradicate alloantibodies, but the pathophysiological mechanism with which it occurs is still unclear[17-20]. An immunomodulatory role of vWF has been hypothesized, but not completely confirmed. In a recent "in vitro" study, Chen et al.[21]have shown the role of VWF in attenuating FVIII memory immune responses in hemophilia A mice, but a confirm in the human subjects is needed.

Plasmaderived concentrates are often used in the ITI rescues in patients with inherited haemophilia A and inhibitors[22,23], but their use in patients with AHA is very rare, and only few cases are published in literature[15,16]. As AHA often occurs with severe bleeding in the presence of high-titer inhibitors and very low level of FVIII, pdFVIII are not considered the first-line therapy, but also the severe co-morbidities for each patient could be considered when an AHA occurs, especially in case of elderly people.

Conclusion

The reply to question: "Can the plasmaderived FVIII still play a role in the treatment of acquired hemophilia A at the time of new drugs?" is yes, it can play.

Our study showed that plasmaderived concentrates can be an option for patients at high thromboembolic risk, and when rpFVIII is not available. pdFVIII was proven to be effective even in patients with AHA and high-titer inhibitors, especially if combined with the von Willebrand factor, that seems to be actively involved in reaching a complete response. The immunomodulatory role of vWF should, however, better investigated in wider trials. The continuous infusion was proven to reduce the days of treatment and the clotting factor consumption, if compared with the daily infusions, but also in this case, more studies are needed to assess the efficacy and safety of this mode of replacement therapy in patients with AHA.

Limitation

The major limitation is due to retrospective nature of this study. All the data were collected "a posteriori" based on what was reported in the patient records kept at the two different hospitals involved in the study. Another limitation is due to small sample size. AHA is a rare disease, few cases are usually observed in our hospitals, and among these only a small number of patients is treated with plasmaderived FVIII. A larger study would be needed to confirm our data.

References

1. Knoebl P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost. 2012; 10:622–31
2. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol. 2003; 121:21–35
3. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007; 109:1870–7
4. Kruse-Jarres R, Kempton CL, Baudo F. et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol 2017; 92: 695–705.
5. Huth-Kühne A, Baudo F, Collins P et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009 Apr; 94 (4):566-75
6. Franchini M, Castaman G, Coppola A, et al;and the AICE Working Group. Acquired inhibitors of clotting

factors: AICE recommendations for diagnosis and management. Blood Transfus.2015 Jul;13(3):498-513
7. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety ofOBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia 2015; 21:162–70
8. Collins PW, Baudo F, Knoebl P, et al; EACH2 registry collaborators. Immunosuppression for acquired hemophiliaA: results of the European Acquired Haemophilia (EACH) registry. Blood 2012; 120: 47-55
9. Zeikler H, Ulrich-Merzenich G, Hess L, et al. Treatment of acquired hemophilia by the Bonn-Malmo¨ Protocol: documentation of an in vivo immunomodulating concept. Blood 15 March 2005; 105 (6): 2287-93
10. S. Schulman, C. Kearon, Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J Thromb. Haemost, 2005; 3: 692–4
11. Franchini M, Castaman G, Coppola A, et al.; AICE Working Group. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. Blood Transfus 2015 Jul; 13 (3): 498-513
12. Baudo F, Collins P, Huth-Kühne A, et al.; EACH2 Registry Contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012; 120: 39–46
13. Borg JY, Négrier C, Durieu I et al.; FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia. 2015 May; 21(3):330-7
14. Kasper CK. Treatment of factor VIII Inhibitors. Prog Hemost Thromb. 1989; 9: 57-86
15. Zanon E, Milan M, Brandolin B, et al. High dose of human plasma-derived FVIII-VWF as first-line therapy in patients affected by acquired haemophilia A and concomitant

cardiovascular disease: four case reports and a literature review.Haemophilia, 2013 Jan;19(1): e50-3
16. Barillari G, Pasca S. pdFVIII/VWF may be an alternative treatment for old medical patient with acquired haemophiliaA and systemic vascular disease?Transfus Apher Sci. 2013 Feb; 48 (1): 59-62
17. Batorova A, Holme P, Gringeri A, et al. Continuous infusion in haemophilia: current practice in Europe.Haemophilia, 2012 Sep; 18 (5): 753-9
18. Castaman G, Linari S. Human von Willebrand factor/factor VIII concentrates in the management of pediatric patients with von Willebrand disease/hemophiliaA.Ther Clin Risk Manag 2016 Jun 30; 12: 1029-37
19. Sholzberg M, Floros G, Teitel J. Successful immune tolerance induction with von Willebrand factor containing concentrate in an adult with haemophilia A and chronic inhibitor - a case study.Haemophilia2016 Mar;22(2):e104-6
20. Kreuz W, Escuriola Ettingshausen C, Vdovin V, et al.; ObsITI study group; ObsITI committee. First prospective report on immune tolerance in poor risk haemophilia A inhibitor patients with a single factor VIII/von Willebrand factor concentrate in an observational immune tolerance induction study. Haemophilia 2016 Jan;22(1):87-95
21. Chen J, Schroeder JA, Luo X, Shi Q. The impact of von Willebrand factor on factor VIII memory immune responses.Blood Adv2017 Aug 22;1(19):1565-74
22. Santagostino E. More than a decade of international experience with a pdFVIII/VWF concentrate in immune tolerance. Haemophilia 2013 Jan;19 Suppl 1:8-11
23. Jiménez-Yuste V, Oldenburg J, Rangarajan S, et al. Long-term outcome of haemophilia A patients after successful immune tolerance induction therapy using a single plasma-derived FVIII/VWF product: the long-term ITI study.Haemophilia2016 Nov; 22 (6): 859-65

CHAPTER 3

Activated prothrombin concentrate (FEIBA®) in acquired hemophilia A: a large multicenter Italian study – the FAIR Registry

EzioZanon, Samantha Pasca, Marta Milan, Cristina Santoro, Gabriella Gamba, Chiara Ambaglio, Sergio Siragusa, Marisanta Napolitano, Angiola Rocino, Isabella Cantori, Augusto B. Federici, Lucia Mameli, Gaetano Giuffrida, Anna Falanga, Corrado Lodigiani, Rita Santoro, Maria Grazia Mazzucconi

Br J Haematol 2019 Mar;184 (5):853-855
doi: 10.1111/bjh.15175 PMID:29528100

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by a spontaneous development of auto-antibodies against coagulation Factor VIII (FVIII) in males and females with previously normal haemostasis[1].

The purpose of our study was to assess dosage, duration of treatment, as well as effectiveness and safety of aPCC in patients with AHA. Secondary objectives were the evaluation of the role of the concomitant use of antifibrinolytic agents, anamnestic response, and the number of relapses, along with effectiveness of a short-term prophylactic treatment with aPCC starting after the first bleeding episode.

The FAIR study is a retrospective-prospective registry that included patients with AHA treated with aPCC (FEIBA®) at 12 Italian Haemophilia Centres. The study collected data from January 2003 to December 2012 for the retrospective group, and from January 2013 to December 2015 for the prospective one. Fifty-six patients were included in the registry, seven of whom had been included in a previous study[2].

All the events occurring in the four weeks following resolution of the qualifying bleeding episode were recorded. Major bleeds and the resolution of acute bleeding were defined according to the ISTH guidelines[3]. A "bleeding relapse" was defined as any bleeding event occurred into the previous site or a different site within a month after the resolution of the first episode. Short-term prophylaxis was defined as aPCC administered at a lower dosage, after resolution of an acute bleeding episode, for at least one week. Short-

term prophylaxis was administered based on the clinical evaluation and bleeding severity of each patient and performed by local physicians. Antifibrinolytics were administered exclusively based on clinical evaluation. Anamnestic response was defined as an increase in inhibitor titre after aPCC treatment. The increase was calculated on the inhibitor titre present at the onset of the therapy with aPCC. The assessment of anamnestic response was performed by the clinicians of each single centre. Since FAIR is a registry, no special protocols have been provided for patient management.

Statistical analysis included all 56 enrolled patients. Baseline characteristics and the treatment of the patients are summarized in Table 1.

	Total *N* (%)	FEIBA® only *N* (%)	Days Mean (SD)	FEIBA® + Anti-fibrinolytics* *N* (%)	Days Mean (SD)
Patients	56 (100·0)	21 (37·5)	11·6 (±9·1)	35 (62·5)	9·7 (±9·5)
Cause of AHA†					
Idiopathic	29 (51·8)	9 (16·1)	12·4 (±4·6)	20 (35·7)	11·4 (±11·3)
Malignancy	9 (16·1)	3 (5·4)	5·7 (±6·4)	6 (10·7)	6·8 (±3·0)
Autoimmune diseases	8 (14·3)	1 (1·8)	23 (na)	7 (12·5)	8·1 (±5·8)
Pregnancy	4 (7·1)	4 (7·1)	7·0 (±8·1)	0 (0·0)	na
Other	11 (19·6)	9 (13·2)	10·3 (±7·4)	2 (6·4)	8·5 (±7·1)
Bleeds	101 (100·0)	61 (60·4)	11·6 (±9·1)	40 (39·6)	9·7 (±9·5)
Major bleed‡	39 (38·6)	22 (21·8)	12·0 (±11·6)	17 (16·8)	9·9 (±9·6)
Site of bleed‡					
Deep Muscle	35 (34·7)	20 (19·8)	10·3 (±9·8)	15 (14·9)	11·5 (±8·8)
Cutaneous	37 (36·6)	18 (17·8)	13·1 (±10·3)	19 (18·8)	9·4 (±11·2)
Gastrointestinal	8 (7·9)	7 (7·0)	9·3 (±8·7)	1 (0·9)	6 (na)
Urinary	14 (13·9)	10 (9·9)	8·2 (±6·8)	4 (5·0)	6·7 (±4·0)
Respiratory	7 (6·9)	6 (5·9)	11·6 (±8·3)	1 (1·0)	5 (na)

Table 1. *Baseline characteristics and the treatment of the FAIR patients. °No patients used anti-fibrinolytics only. *Patients with more than one condition (Total >100%). §Assessment performed on 101 total bleeds.*

FEIBA® as first-line therapy was used in 82.2% of cases, with a mean dose of 72.6±26.6 IU/kg. Treatment was continued for a median of 8 days (IQR 1-48) and FEIBA® was evaluated as effective in 96.4% of bleeds. Antifibrinolytic agents were used in 39.6% of treated bleeds, based on both a clinical assessment and the evaluation of bleeding severity, more frequent in the prospective group (p=0.0339). 57.1% of patients treated with antifibrinolytic drugs showed serious co-morbidity. Among them, 40% presented severe cardiovascular diseases (myocardial infarction, ischemic stroke and ischemic cardiomyopathy). The sites and severity of bleeding were not significantly different between the total population of the FAIR registry and the group treated with the combined aPCC therapy. All the bleeds treated with double therapy required shorter treatment duration (mean reduction 16.3%). The combined therapy was well tolerated, and no thromboembolic events were reported. 89.3% of patients received at least one immunosuppressive therapy to eradicate the inhibitors. Low-dose aPCC for short-term prophylaxis to prevent bleeding relapses was initiated in 26.8% of the patients after the first episode, while 73.2% of them received no further treatment (p= 0.0048). The mean dose of aPCC for prophylaxis was 54.2±23.0 IU/kg. Prophylaxis lasted an average of 20.5±17.6 days, with an infusion frequency mean of 24 hours. Bleeding relapses were significantly higher in the patients who had no prophylactic treatment with FEIBA®($p<0.05$). The anamnestic response was reported in 6/101 (5.9 %) bleeding treatments. The median inhibitor titre increase was 9.3 BU (IQR 0.6-41.8) after a median of 6 days

(IQR 2-19) from therapy commencement. No differences were observed in the duration of treatment, severity of bleeding and outcome among either the patients who had an anamnestic response or the remaining ones. During the treatment with FEIBA®, no thromboembolic events were reported. Eight patients died.

After the EACH2 registry[4], FAIR is the largest study on the use of FEIBA® in the treatment of AHA, but unlike EACH2 almost half of the patients were prospective. The FAIR registry included a population with a median age of 69.9 years, younger than in the FEIBHAC[5]and EACH2 registries, but older than in the American study[6], and comparable with the French study[7].The efficacy of aPCC as a first-line therapy in AHA is consistent with the data reported by Knoebl et al[4]. However, the FAIR registry is the first study that also highlighted a positive clinical response to the combination of aPCC and antifibrinolytic agents even though these outcomes need to be confirmed in adequate, larger clinical trials.

One of the main problems in the management of patients with AHA is bleeding relapse after the first episode, which is above 20%[8]. The FAIR registry showed that short-term prophylaxis prevented most bleeding relapses (90.6%) occurred in patients without prophylaxis.

An anamnestic response to the treatment of the first bleeding episode was reported in 4/56 patients (7.1%), while inhibitor titre increased in 2 patients. These data

confirm the report by Baudo et al[8]. In our case, the patients who presented an anamnestic response to aPCC were not treated for a longer period of time than the others and did not need a higher amount of FEIBA. They did not show more severe bleeding or worsening outcome than the remaining patients.

Differently from the EACH2 registry[5,8], in which 4.8% of the patients treated with FEIBA® experienced a thrombotic event, in the FAIR registry none of the patients had this side effect. The overall mortality among the FAIR patients treated with aPCC was 14.3%, lower than in the other registries[8]. The FAIR registry showed interesting results that may be used in clinical practice, but controlled trials are needed to confirm the data obtained.

References

1. Kessler C.M., Knobl P. Acquired haemophilia: an overview for clinical practice. European Journal of Haematology 2015; 95 (Suppl 81): 36-44
2. Zanon E., Milan M., Gamba G et al.Activated prothrombin complex concentrate (FEIBA®) for the treatment and prevention of bleeding in patients with acquired haemophilia: A sequential study. Thrombosis Research, 2015 Dec; 136 (6): 1299-1302
3. Schulman S., Kearon C., Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005; 3: 692–4

4. Knoebl P., Marco P., Baudo F., et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Journal of Thrombosis and Haemostasis 2012; 10: 622–31
5. Borg J.Y., Négrier C., Durieu I., Dolimier E., Masquelier A.M., Lévesque H.; FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia2015 May; 21(3): 330-7
6. Sallah S. Treatment of acquired haemophilia with factor eight inhibitor by passing activity. Haemophilia 2004; 10: 169–73
7. Goudemand J. Treatment of bleeding episodes occuring in patients with acquired haemophilia with FEIBA: the French experience. Haemophilia 2004; 10 (Suppl 3): 70
8. Baudo F., Collins P., Huth-Kühne A., Lévesque H., Marco P., Nemes L., Pellegrini F., Tengborn L., Knoebl P.; EACH2 Registry Contributors. Management of bleeding in acquired hemophilia results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012; 120: 39–46

CHAPTER 4

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

---

Ezio Zanon, Samantha Pasca, Alessandra Borchiellini, Corrado Lodigiani, Angelo Claudio Molinari, Chiara Ambaglio, Federica Valeri, Paola Stefania Preti, Paolo Moscatelli, Paolo Simioni

Blood Transfus 2020 Jul;18(4): 312-321 doi: 10.2450/2020.00006-20 PMID:32698943

Abstract

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 are reported in the literature. Here we report the largest registry on the use of rpFVIII for the AHA treatment.
Aim: The objective of this retrospective study was to describe the efficacy and the safety of susoctocog-alfa for AHA.
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 4 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, but without any complications.
Conclusions: 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 found to be clinically insignificant

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 to treating bleeding caused by AHA as soon as possible in first-line therapy with bypassing agents, as activated prothrombin complex concentrate (aPCC) or activated recombinant FVII (rFVIIa), or with susoctocog-alfa, a recombinant porcine FVIII (rpFVIII); moreover, plasmaderived FVIII concentrates can be an option for patients at high thromboembolic risk, especially in the presence of a low-titre inhibitor (<5.0 BU)[2-4]. 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 as the other FVIII products usually used in the haemophilia treatment. The efficacy of sustoctocog-alfa has been proven in the 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 which 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. Tarantino et al.[7] in their clinical experience reported that the haemostatic effect was achieved using loading doses of rpFVIII 100 IU/kg (6/7 patients), and subsequent doses of rpFVIII between 50-100 IU/Kg, lower than recommended. Similarly, two more groups reported clinical efficacy of rpFVIII in AHA associated to bleeding at much lower doses than are currently recommended[8,9]. Until now no other studies or reports on use of Obizur® in clinical practice are 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.

Patients and Methods

Patients

We have collected the cases of nine patients diagnosed with acquired haemophilia A and treated with rpFVIII (Obizur® - Takeda Pharmaceutical Co.) in five Italian Haemophilia Centres (Padua, Genoa, Turin, Pavia and Rozzano).

Methods

Retrospective, multicenter real world case series.

Bleeding: according to the 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 hemoglobin levels of 20 g/L or more or leading to transfusion of two or more units of whole blood or red cells.
Acute bleeding resolution: assessed clinically in terms of bleeding tendency, size of hematoma, stability of Hb/Hct and resolution of pain caused by the haematoma[11].
Short-term prophylaxis: aPCC administered at a lower dosage from acute bleeding resolution to at least 1 week according to clinical decision and based on the data from the FAIR Registry[12,13].
Due to the nature of this report (multicenter, retrospective), the laboratory and medical parameters were not centralized or standardized, all data were collected following the clinical decision for each different subject.

Results

Nine cases of patients diagnosed with AHA and treated with susoctocog-alfa were collected and summarized in Table 1 and Table 2.
Case-1: A 77-year-old man presenting multiple valve insufficiency (tricuspid, mitral and aortic) with EF 51%, diabetes, previously non-ST elevation myocardial infarction (NSTEMI) and abdominal aortic aneurysm

presented at an Emergency Department (ED) with dizziness and upper limb weakness. An intracranial haemorrhage which required neurosurgery was diagnosed by angio-CT-scan. The intervention was performed 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 based on a prolonged 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 8 hours. An immune-suppressive therapy (IST) with corticosteroids 1.0 mg/kg/day and cyclophosphamide 1.5 mg/kg/day 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 was 180.0%, and subsequent doses of 50 IU/Kg of susoctocog-alfa every 12 hours were given for five days (mean porcine FVIII activity 87%). A prophylaxis with low dose aPCC 25 IU/kg/bid was subsequently initiated to prevent bleeding relapses and 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 hospitalization the patient underwent a tracheostomy under an effective haemostatic coverage with a single bolus of susoctocog-

alfa 200 IU/kg. The choice of this dosage of rpFVIII was due to the lack of data available about surgical treatment therefore the dosage used was that suggested by technical product sheet.

Case-2: A 68-year-old man, smoker, presenting arterial hypertension, diabetes, chronic obstructive pulmonary disease (COPD), previous myocardial infarction, chronic renal failure, gastritis, and iatrogenic hypothyroidism was hospitalized 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 and presenting a head and a left shoulder trauma. Laboratory findings showed an aPTT ratio = 2.94, 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, right face and periorbital region. Plasmatic human FVIII level was 2% and a human inhibitor titre 55.0 BU/ml. The patient was immediately treated with aPCC 80 IU/kg every 12 hours, tranexamic acid 10 mg/kg/day, and corticosteroids 1.0 mg/kg/day. 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 hours 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 hospitalized 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 (10x10cm). An AHA was then suspected and confirmed by a prolonged aPTT (65 sec); a plasmatic human FVIII level of 0.3% and a human inhibitor titre of 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 hours for a further two days. A 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. IST with corticosteroids 1.0 mg/Kg/day and cyclophosphamide 1.5 mg/Kg/day was started after AHA diagnosis; the inhibitors had completely disappeared 35 days later. During hospitalization the patient was tested for cancer and autoimmune diseases, 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, when the plasmatic human FVIII level was 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 hospitalized for haematuria and spontaneous haematoma in the right leg. Coagulation analyses showed a prolonged aPTT of 75 sec; a human FVIII level of 1.5%; a human FVIII inhibitor titre of 8.0 BU/ml, and a Hb of 5.8 g/dl. The patient was diagnosed with AHA, and immediately treated with six red blood cell (RBC) bags, corticosteroids 1.5 mg/kg/day, Cyclophosphamide 2.5 mg/kg/day, 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 hours. But still in this case the patient continued to need transfusion support due to persistent haematuria and to the appearance of haemartrosis in the left knee. aPCC treatment was stopped two days later and a treatment with rpFVIII 100 IU/kg every 12-24 hours was started, when aPTT was 72.9 sec and FVIII level 3%. The porcine FVIII peak reached immediately after the first

infusion of Obizur® was 58.0%. 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 10 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, a plasmatic human FVIII of 0.3%, and a human FVIII inhibitor titre of 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/day and cyclophosphamide 1.5 mg/kg/day was immediately prescribed to eradicate the inhibitors. Despite the recommended initial dose of concentrate is 200 IU/Kg, in this case we decided to treat the patient with a lower dosage due to a concomitant presence of an acute coronary syndrome, thus ensuring a plasmatic

FVIII level (>50%) but preventing it from reaching too high and potentially dangerous peaks. Ten days later the haemostatic treatment with rpFVIII was reduced to 25.0 IU/Kg/bid. 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 hypochondrium. 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 thirty minutes 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/tid. A second infection due to Enterococcus Faecalis, immediately treated with a combined antibiotic therapy worsened the clinical condition of our patient. 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 a human FVIII of 4.3%, a human inhibitor titre of 144.0 BU/ml and the appearance of a low titre (1.5 BU/ml) inhibitors against rpFVIII. The

treatment with Obizur® was stopped 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 10 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 history of renal failure, acute coronary syndrome (ACS), atrial fibrillation, MGUS, rheumatic polymyalgia and suspected lung cancer, on treatment with apixaban, had a first hospitalization in an otorhinolaryngology (ORL) department due to mouth bleeding, where an aPTT prolongation was found, 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 hospitalization 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%. Other three doses of Obizur®, 28 IU/kg each, were needed to solve subcutaneous bruising, and maintaining 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 anxious syndrome was admitted to ED due to epistaxis lasting some months, and a large ileo-psoas haematoma. The patient was also treated for a few days with NSAIDs to treat a chest and lumbar pain, and with cephalosporins to treat bronchitis. Due to the suspect 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 hours, later increasing to every 4 hours, 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 a 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 control 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 (1989), rheumatoid arthritis in treatment with corticosteroids and

hydroxychloroquine, and coronary artery disease was admitted to an ED for a right lower limb muscle haematoma and transfused with three blood units. A little later the hematoma also expanded to the left lower limb, and a diagnosis of AHA was performed (human FVIII <1%; human FVIII inhibitor 292.0 BU/ml). An immediate treatment with rFVIIa 90 µg/kg every 4 hours was started and subsequently increased to every three hours 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 hours) 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.

Case-9: An 84-old-man presenting bullous pemphigoid who was a former smoker, was admitted to the ED for a large haematoma in the left superior limb, 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 hospitalized again due to the appearance of

large haematomas in the lower limbs, thorax and face. A diagnosis of AHA was then performed (human FVIII 1.0%; human FVIII inhibitor 128.0 BU/ml), corticosteroids 1.0 mg/kg/d and rFVIIa 90 µg/kg every 6 hours, subsequently increased to every 4 hours, was immediately started. The patient was also transfused with five blood units, but despite all these treatments the TC-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, and 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 which 66.7% of them following 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[14], 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 due 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 5 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 lead 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 without clinical significance.

In our report almost all patients were males, similar to the cases reported by Tarantino and Stemberger[7,9]; but very different from the other data reported in the large studies in which the subjects were almost equally divided between males and females[12,15-17], this is surely 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 presenting some co-morbidities as reported in the largest registries[15-19] on acquired haemophilia A.

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 as reported in the other registries and studies[7, 14-19].

Many bleeds were spontaneous, and mainly involving muscle or skin. Intracranial haemorrhage and haemarthrosis, both occurred in only one patient. The

average delay of the diagnosis was 16 days, ranging from one to sixty days, but it did not affect patient outcomes, unlike what was observed by Tarantino et al[7]. rpFVIII was used as first line therapy in a third of patients. In the remaining patients the bypassing agents were the first line treatment, but in the majority of cases their use was at a dosage lower 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. Conversely, there are no thromboembolic risks with the use of rpFVIII in these patients, which can then be safely used at the recommended dosage or at a dosage of 100 IU/kg, as already reported by some authors[7-9]. In our study the median initial bolus was 100 IU/kg (range 50-200 IU/kg), lower than the dose used in the registration trial[6] (6), but similar to what was reported by Tarantino, Martin and Stemberger[7-9]. This dosage allowed us to obtain a porcine FVIII peak between 50.0 and 180.0%, and therefore to obtain a valid haemostasis in our patients allowing bleeding resolution. Subsequent doses were infused at 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 an immunosuppressive treatment with corticosteroids, where cyclophosphamide was added in the 89% of

cases. Despite 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 experiencing no complications. No thromboembolic events were reported during treatment and follow-up. AHA recurrence occurred in over 20% of patients with a first bleeding episode, the moment there are no guidelines to prevent it, but 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. The dosages, the timing of infusions and the treatment duration were different, based on the single clinical decision, no statistical evaluation can be performed due to small numbers of treated subjects. No recurrences were reported in this retrospective study during one year of mean 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 an FVIII activity level measure is available in real time, like specialized hemophilia centers, rpFVIII could be given in a personalized approach, using much more lower

doses than recommended, avoiding supraphysiologic FVIII levels that may put the patient at risk for thrombosis and obtaining consistent savings in resources.

Only two patients developed low-titre inhibitors against rpFVIII, but without 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 the patients who can benefit from such a regimen.

Tables

	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	14	Haematoma evacuation	Tracheostomy
Case 2	M	68	Oncologic	Hypertension; diabetes; COPD	MI; renal failure; gastritis; hypothyroidism	Face; shoulder; hematorax	ED	7	None	None
Case 3	M	79	Idiopathic	COPD; diabetes	Ischemic cardiopathy; carothid stenosis; vasculopathy	Ileo-psoas	ED	NA	None	Colonoscopy; Gastroscopy
Case 4	M	72	Idiopathic	COPD	None	Haematuria; leg; knee haemartrosis	ED	11	None	None
Case 5	M	81	Autoimmune; oncologic	NSTEMI; vasculopathy	Right breast cancer	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	Inferior 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

Table 1. *Baseline characteristics of AHA patients. AA: aortic aneurysm; ICH: intracranial haemorrhage; (N)STEMI: (non)ST-elevation myocardial infarction; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; ACS: acute coronary syndrome; MGUS: monoclonal gammopathy of undetermined significance; CAD: coronary artery disease ED: emergency department; IMD: internal medicine department; NA: not available*
**: patient on anticoagulant treatment*

	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

Table 2. *Summary of AHA treatments. CS: corticosteroids; Cyp: Cyclophosphamide; rFVIIa: recombinant FVII activated; aPCC: activated prothrombin complex concentrate; NA: not available*

References

1. Kessler CM, Knobl P. Acquired haemophilia: an overview for clinical practice. Eur J Haematol 2015; 95 (Suppl 81): 36-44
2. Franchini M, Castaman G, Coppola A, et al, and the AICE Working Group. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. Blood Transfus 2015; 13: 498-513
3. Pasca S, De Angelis V, Milan M, Zanon E. Can the plasmaderived factor VIII still play a role in the treatment of acquired hemophilia A at the time of new drugs? Blood Coagul Fibrinolysis 2018; 29: 417-42
4. Zanon E, Milan M, Brandolin B, et al. High dose of human plasma-derived FVIII-VWF as first-line therapy in patients affected by acquired haemophilia A and concomitant cardiovascular disease: four case reports and a literature review. Haemophilia 2013; 19: e50-3

5. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017; 92: 695-705
6. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia 2015; 21: 162-70
7. Tarantino M, Cuker A, Hardesty B, et al. Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients. Haemophilia 2017; 23: 25-32
8. Martin K, Kasthuri R, Mooberry MJ, et al. Lower doses of recombinant porcine factor VIII maintain excellent haemostatic efficacy. Haemophilia 2016; 22: e549-51
9. Stemberger M, Mohnle P, Tschop J, et al. Successful bleeding control with recombinant porcine factor VIII in reduced loading doses in two patients with acquired haemophilia A and failure of bypassing agent therapy. Haemophilia 2016; 22: e472-4
10. Schulman S, Kearon C. Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb. Haemost 2005; 3: 692-4
11. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009; 94: 566-75
12. Zanon E, Pasca S, Santoro C, et al; Activated Prothrombin Complex Concentrate (FEIBA®) in Acquired Hemophilia A: a large multicentre Italian study - the FAIR Registry; Br J Haematol. 2019 Mar; 184 (5): 853-8.
13. Zanon E, Pasca S, Siragusa S, Napolitano M, Santoro C, Mameli L, Rocino A; FAIR Low dose of aPCC after the initial treatment in acquired haemophilia A is useful to reduce bleeding relapses: Data from the FAIR registry. Study Group.Thromb Res 2019 Feb; 174: 24-6

14. Turkantoz H, Konigs C, Knobl P, et al. Cross-reacting inhibitors against recombinant porcine factor VIII in acquired hemophilia A: Data from the GTH-AH 01/2010 Study. J ThrombHaemost 2020; 18: 36-43
15. Knoebl P, Marco P, Baudo F, et al. EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J ThrombHaemost 2012; 10: 622-31
16. Borg JY, Négrier C, Durieu I, et al. FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French ' FEIBA d ans l 'hémophilie A acquise' (FEIBHAC) registry. Haemophilia 2015; 21: 330-7
17. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, et al. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol 2003; 121: 21-35
18. Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. ThrombHaemost 1981; 45: 200-3
19. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007; 109: 1870-7
20. Pasca S, Ambaglio C, Rocino A, et al. FAIR Study Group. Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry. J Thromb Thrombolysis 2019; 47: 129-33

CHAPTER 5

Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry

---

*Samantha Pasca, Chiara Ambaglio, Angiola Rocino, Cristina Santoro, Isabella Cantori, Ezio Zanon; for the *FAIR Study Group*

J Thromb Thrombolysis2019 Jan;47(1):129-133doi: 10.1007/s11239-018-1750-y PMID:30267246

Abstract

Background: Antifibrinolytics combined with aPCC are not routinely administered to patients with acquired hemophilia A due to increased thrombotic risk. This association normalizes clot stability, and improves the efficacy of therapy, but can increase the risk of severe side effects. Due to these premises, it has always raised doubts and perplexities in the clinics.

Aim and Methods: We now report the data of the "FEIBA® on acquired haemophiliaA Italian Registry (FAIR Registry), a retrospective-prospective study that included 56 patients. This is the first study that assessed the clinical response of the combination of aPCC and antifibrinolytic agents in patients with acquired haemophilia A.

Results: A total of 101 acute bleeds were treated with aPCC. Antifibrinolytic agents were used in the treatment of 39.6% of total bleeds, based on both, a clinical assessment, and an evaluation of bleeding. Twenty-five of the 30 patients (57.1%) treated with antifibrinolytic drugs showed serious co-morbidity. Among them, 40% presented severe cardiovascular diseases. All bleeds treated with combined therapy had a shorter duration of treatment (mean reduction 16.3%). All the treated patients presented a good tolerability, and no arterial or venous thromboembolic events were reported.

Conclusion: In our retrospective registry the combination of antifibrinolytics and aPCC appears safe and effective in the treatment of patients with AHA,

especially in the case of severe and life-threatening bleeding, but this hypothesis needs to be confirmed in adequate, larger clinical trials.

Introduction

Acquired hemophilia 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 hemostasis[1]. The incidence of AHA is estimated about 1-1.5 per millions of people per year[2]. 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 first line therapy with bypassing agents, as activated prothrombin complex concentrate (aPCC) or activated recombinant FVII (rFVIIa), or with recombinant porcine FVIII (rpFVIII), recently marketed in our Country. Normal haemostasis must be immediately achieved, and the inhibitor eradication should be quickly performed with corticosteroids alone or with corticosteroids and cyclophosphamide. If these recommended treatments fail or are contraindicated, patients should be treated with rituximab[3]. The risk for thromboembolic events among patients treated with bypassing agents has increased. Tranexamic acid in association with bypassing agents normalizes clot stability, and improves the efficacy of therapy, but further increases the risk of severe side effects. The current guidelines suggest the use of topic solutions of antifibrinolytics only to treat oral or skin bleeding[3]. Due to these premises the combined use of antifibrinolytics and bypassing agents in the patients with AHA has always raised doubts and perplexities in the clinics. The EACH2 registry[4] reported the use of antifibrinolytic drugs in 18% of

cases, but no other data were reported about the type of treated bleeding, the characteristics of patients, and the associated bypassing agent, rFVIIa or aPCC.

At this moment only one study reported the outcomes of the combined use of these drugs in a patient with acquired disorder[5]. In this report, six total patients were evaluated, but five of them had congenital haemophilia A. Also, the other published studies presented only cases of subjects affected by inherited haemophilia. In their prospective crossover study, Tran et al.[6]evaluated the combined use of tranexamic acid and bypassing agents in a group of six patients with haemophilia A and inhibitors compared with a group of five healthy subjects. Clinical and laboratory results were positive, and no adverse events were reported. Data similar were observed by Windyga et al.[7] in patients with haemophilia A and inhibitors presenting mucosal or dental bleeding and treated with a combined therapy of aPCC and antifibrinolytics.

The "FEIBA® on acquired haemophilia A Italian Registry (FAIR Registry) is the first study that assessed the clinical response of the combination of aPCC and antifibrinolytic agents in patients with acquired haemophilia A.

Methods

The FAIR study is a retrospective-prospective registry that included patients with acquired haemophilia A

treated with aPCC (FEIBA®) at 12 Italian Haemophilia Centres. Data collection started in December 2012.

Retrospective group: all patients ≥ 18-years-old, treated with aPCC for AHA in the previous ten years (from January 2003 to December 2012).

Prospective group: all consecutive patients ≥ 18-year-olds who received a diagnosis and were treated with aPCC, from January 2013 to December 2015.

The study protocol was approved by each institution's Ethical Committee and was conducted in accordance with the principles of the Declaration of Helsinki and with local laws and regulations. All patients provided written informed consent. In the case of retrospective patients who died before data collection data started, the informed consent was signed by a family member.

All patients were assessed for 1) demographic and baseline characteristics such as sex, age at diagnosis, body weight, diagnosis and clinical conditions; 2) descriptive characteristics of bleeding episodes (site, cause and severity); 3) treatment of AHA (time, dosage, outcome of therapy); 4) laboratory parameters (Factor VIII concentration and inhibitor titre); 5) bleeding resolution and bleeding relapses; 6) adverse events (AE), serious adverse events (SAE), drug-related AE and AE requiring study discontinuation.; 7) cardiovascular co-morbidities (atrial fibrillation, myocardial infarction, ischemic heart disease, stroke, hypertension, other)
According to the ISTH guidelines, major bleeding episodes were defined as symptomatic bleeding into 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 levels of 20 g/L or more or leading to transfusion of two or more units of whole blood or red cells. The resolution of acute bleeding was assessed clinically, considering bleeding tendency, the size of haematoma, the stability of Hb/Hct and resolution of pain caused by the haematoma[9].

All the events occurring in the 4 weeks following resolution of the qualifying bleeding episode were recorded. A "bleeding relapse" was defined as any bleeding event occurred into the previous site or a different site within a month after the resolution of the first episode.

Antifibrinolytics were administered exclusively based on a clinical evaluation. No specific protocol was established to determine how these drugs had to be administered.

Results

Fifty-six patients were enrolled, equally divided between males and females, 31 in the retrospective group, and 25 in the prospective one. One-hundred and one acute bleeds were reported, all treated with aPCC, 65.3% of which in the retrospective group. Spontaneous bleeding episodes were 84.1%, major bleeds were 39 (38.6%), and 71.3% involved muscles or skin.

Antifibrinolytic agents were used in the treatment of 39.6% of total bleeds, based on both, a clinical assessment, and an evaluation of bleeding. Retrospective patients (48.4%) had two or more bleeding events, higher than reported in the other group ($p<0.05$). Twenty-five of the 30 patients (57.1%) treated with antifibrinolytic drugs showed serious co-morbidity. Among them, 40% presented severe cardiovascular diseases (myocardial infarction, ischemic stroke, ischemic cardiomyopathy). The sites and severity of bleeding were not significantly different between the total population of the FAIR registry and the group treated with combined aPCC and antifibrinolytic therapy. Complete data are presented in Table 1.

All bleeds treated with combined therapy (40/101) had a shorter duration of treatment (mean reduction 16.3%) up to a median of 7 days (IQR 1-48). Combined therapy was well tolerated, and no thromboembolic events were reported during treatment or during follow-up.

Antifibrinolytics were administered exclusively based on a clinical evaluation. During the study no specific protocol was established to determine how these drugs had to be administered. Tranexamic acid was used in all the patients treated with a combined therapy.

Discussion

Activated Prothrombin Complex Concentrate (FEIBA®) is a multicomponent therapeutic agent that contains FII, FVII, FIX, and FX coagulation proteins,

which have activities targeting different sites of the coagulation cascade. The exact mechanism of action of aPCC is unknown, although it may be related to one or more of the active clotting factors and their ability to bypass the FVIII inhibitor. In some in vitro studies, a FXa–like substance or a complex of FVIII:Ag, FIXa, and phospholipid have been hypothesized as the active principles, which is only minimally inhibited by the auto-antibodies. These multiple modes of action make aPCC able to maintain the procoagulant process, necessary for haemostasis in the congenital or acquired haemophiliac patients with inhibitors[9]. Due to this mechanism of action that activates the coagulation cascade, the sudden appearance of thromboembolic events is the greatest risk for patients treated with aPCC. In fact, the EACH2 Registry[4] reported 4.8% of thromboembolic episodes developed among 63 patients treated with FEIBA®. Data however not confirmed in the French Registry[10], in which no thromboembolic events were observed.

Tranexamic acid is an antifibrinolytic drug that exerts its action inhibiting activation of plasminogen, and reducing the plasminogen conversion to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant FV and FVIII. Tranexamic acid also inhibits the plasmin activity, but higher doses are required to reduce plasmin formation. Headache, abdominal pain, backache, and diarrhoea are the common side effects of this drug, while pulmonary embolism or deep vein thrombosis are not frequent. Despite this, the association with another drug that acts on the coagulation cascade can greatly

increase the thromboembolic risk. This leads clinicians to use caution in associating aPCC and antifibrinolytics, especially in the case of patients with acquired haemophilia. In fact, these subjects are often elderly with severe co-morbidities that make them more susceptible to cardiovascular or cerebrovascular events, as it happens in the general population. Acquired haemophilia is only a transient state that does not put the patient away from venous or arterial thromboembolic diseases. Conversely, until recently it was thought that patients with congenital haemophilia had a lower risk of cardiovascular events due to their permanent hypocoagulable state, but now different reports have showed that also the subjects presenting coagulation defects can be affected by these diseases[11-14].

The FAIR registry is the first study that assessed the clinical response to the combination of aPCC and antifibrinolytic agents in patients with AHA. In our FAIR registry, 39.6% of total bleeding episodes were treated with tranexamic acid, more frequently in the prospective patients ($p<0.05$). Antifibrinolytics agents were also used in patients with severe cardiovascular diseases, about 6% had had a previous ischemic stroke, and 3% myocardial infarction. All the treated patients presented a good tolerability, and no arterial or venous thromboembolic events were reported. In a review published by Valentino et al.[15] the combined therapy has been considered usable in case of dental procedures or surgeries, or in case of patients who have failed a monotherapy, but almost all the evaluated patients consisted in subjects affected by congenital haemophilia

A, while no data about patients with AHA are clearly available. In the FAIR Registry the combined therapy reduced the treatment duration by 16.3% (mean reduction), up to a median of 7 days. In conclusion, in our experience, the association of aPCC and tranexamic acid appeared to be safe and effective in a group of patients with AHA, presenting in some case severe bleeding and relevant diseases. A relation between the aPCC and antifibrinolytics in a combined therapy and a reduction in the times for the bleeding resolution could also be suggested.

Even though we believe antifibrinolytics could be used routinely in the treatment of patients with AHA in association with aPCC, especially in the case of severe and life-threatening bleeding, this hypothesis needs to be confirmed in adequate, larger clinical trials.

ID patient	R/P	Age	Sex	Cause AHA	Bleeding site	Co-morbidity	Dose aPCC (IU/kg)	Frequency (h)	Treatment duration (days)
01	R	74	M	Infection	Cutaneous	Ischemic cardiopathy	81,60	12	2
02	R	69	F	Idiopathic	Retroperitoneal	Hypertension	71,20	8	9
03	R	65	M	RA	Urogenital	Hypertension, diabetes	66,70	8	9
04	R	63	F	MGUS	Respiratory		93,40	12	5
05	R	60	F	Idiopathic	Cutaneous		76,90	12	8
06	R	68	M	Idiopathic	Cutaneous	Hypertension	85,70	24	9
07	R	29	F	Idiopathic	Cutaneous	Hypertension	100,00	12	19
08	R	71	M	RA	Skeletal muscle	MI, ischemic stroke, AA	80,00	12	5
09	R	46	F	Idiopathic	Skeletal muscle	Hypertension	80,00	12	9
10	R	88	F	Infection	Cutaneous	Hypertension	80,00	12	2
11	R	72	M	Idiopathic	1.Urogenital 2.Cutaneous		51,10 51,10	12 12	2 1
12	R	28	F	Idiopathic	Urogenital		50,00	8	5
13	R	74	F	RA	Cutaneous		57,10	24	4
14	R	55	M	RA	1.Skeletal muscle 2. Skeletal muscle	AMV	50,00 50,00	12 12	2 3
15	R	72	M	Idiopathic	Gastrointestinal	PTA (carotid stenosis), AMV	80,00	12	6
16	R	66	F	RA	1. Cutaneous 2. Skeletal muscle		64,90 64,90	8 8	9 10
17	R	77	F	Idiopathic	Cutaneous		66,70	8	8
18	R	76	M	Idiopathic	Cutaneous	Hypertension, diabetes	65,80	48	48
19	P	83	F	Idiopathic	Cutaneous	Hypertension Cerebral vasculopathy	100,00	8	7
20	P	78	F	Idiopathic	Retroperitoneal		87,00	12	25
21	P	56	F	RA, Sjogren	Retroperitoneal		80,00	12	20
22	P	70	M	RA	Retroperitoneal	AF, ischemic cardiopathy, DM2	87,00	12	8
23	P	90	F	Idiopathic	Cutaneous	Hypertension, CRF,PE Ischemic cardiopathy, DM2	83,40	12	4
24	P	86	F	Cancer	Cutaneous	Hypertension	75,00	12	8
25	P	73	F	Idiopathic	Retroperitoneal	Hypertension	90,90	12	12
26	P	57	M	Idiopathic	1.Cutaneous 2. Cutaneous		66,70 66,70	12 48	26 14
27	P	45	F	Cancer	1.Skeletal Muscle 2. Skeletal Muscle		80,60 80,60	12 12	3 4
28	P	54	M	Cancer	Cutaneous	Hypertension	76,90	24	6
29	P	93	M	Cancer	Cutaneous		57,10	8	4
30	P	52	F	Cancer	Urogenital	Hypertension	76,90	12	11
31	P	76	F	Cancer	Cutaneous	ACS (NSTEMI)	63,80	12	9
32	P	80	M	Idiopathic	Cutaneous		100,00	24	4
33	P	75	F	Idiopathic	Skeletal muscle	DM2, cartotid stenosis, hypertension	80,00	12	13
34	P	76	M	Idiopathic	Skeletal muscle	Ischemic Cardiopathy, DM2	53,40	12	31
35	P	77	M	Idiopathic	Cutaneous	Hypertension, ischemic stroke	62,50	12	1

Table 1. *Characteristics of patients treated with a combined therapy aPCC/antifibrinolytics, aPCC treatment scheme, and duration of treatment. R/P: retrospective/prospective. AHA: acquired haemophilia A. RA: Rheumatoid Arthritis. MGUS: Monoclonal Gammopathy Unknown Significance. MI: Myocardial Infarction. AA: Aortic Aneurysm. AMV: aortic Mechanic Valve. PTA: Percutaneous Angioplasty. AF: Atrial Fibrillation. DM2: Diabetes Mellitus type 2. CRF: Chronic Renal Failure. PE: Pulmonary Embolism. ACS: Acute Coronary Syndrome. aPCC: activated Prothrombin Complex Concentrate*

References

1. Kessler CM, Knobl P. Acquired haemophilia: an overview for clinical practice. Eur J Haematol 2015; 95 (Suppl 81): 36-44
2. Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost 2013; 110: 1114-20
3. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017 Jul; 92 (7): 695-705
4. Knoebl P, Marco P, Baudo F et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J ThrombHaemost2012; 10: 622–31
5. Holmström M, tran HT, Holme PA. Combined treatment with aPCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patient with acquired haemophilia A—a two-centre experience. Haemophilia 2012 Jul; 18 (4): 544-9
6. Tran HT, Sørensen B, Rea CJ, et al. Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors. Haemophilia 2014 May; 20 (3): 369-375
7. Windyga J, Stefanska-Windyga E, Odnoczko E, et al.Activated prothrombin complex concentrate in combination with tranexamic acid: a single centre experience for the treatment of mucosal bleeding and dental extraction in haemophilia patients with inhibitors. Haemophilia 2016 Sep; 22 (5): e465-8
8. Schulman S., Kearon C., Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692–4
9. Turecek PL, Váradi K, Gritsch T, et al. FEIBA®: mode of action. Haemophilia 2004; 10 (Suppl. 2): 3–9

10. Borg JY, Négrier C, Durieu I et al.; FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia2015 May; 21(3): 330-7
11. Zanon E, Milan M, Sarolo L et al. Cerebrovascular diseases in haemophiliacs: a real but underestimated risk. Haemophilia 2018 Jan; 24 (1): e3-5
12. Humphries TJ, Rule B, Ogbonnaya A, et al. Cardiovascular comorbidities in a United States patient population with hemophilia A: A comprehensive chart review. Adv Med Sci 2018 Jul 18; 63(2): 329-33
13. Berger K, Schopohl D, Lowe G et al. How to compare cardiovascular disease and risk factors in elderly patients with haemophilia with the general population. Haemophilia 2016 Sep; 22(5): e406-16
14. Minuk L, Jackson S, Iorio A et al. Cardiovascular disease (CVD) in Canadians with haemophilia: Age-Related CVD in Haemophilia Epidemiological Research (ARCHER study). Haemophilia 2015 Nov; 21(6): 736-41
15. Valentino LA, Holme PA. Should anti-inhibitor coagulant complex and tranexamic acid be used concomitantly? Haemophilia 2015; 21: 709–14

CHAPTER 6

pdFVIII/VWF may be an alternative treatment for old medical patient with acquired haemophilia A and systemic vascular disease?

Giovanni Barillari, Samantha Pasca

Transfus Apher Sci 2013 Feb; 48(1): 59-62 doi: 10.1016/j.transci.2012.08.005 PMID:23026792

Abstract

Acquired Haemophilia is a severe, rare, and potentially life-threatening bleeding that affects both, males and females with an incidence of 1.5 cases/million/year. Mucocutaneous haemorrhages or haematomas are typical expression of this disease because of a FVIII activity decrease and a FVIII inhibitors presence, differently from congenital haemophilia. We report a case of a 71-year-old-man, who presented with spontaneous haematomas and severe anaemia and suffered from vascular disease. At admission all haemostatic and laboratory data were diagnostic for idiopathic AHA. Treatment with by-passing agents such as rFVIIa was contraindicated because of the risk of thromboembolic events. Despite the administration of FVIII concentrates in AHA is recommended only in patients with inhibitor titre < 5.0 BU, physicians decided for the use of pdFVIII/vWF in this patient associated with corticosteroids. One month later FVIII was within normal range and inhibitors were disappeared. In our case pdFVIII/vWF resulted a safe and effective alternative for the treatment of acquired haemophilia A patient at high thromboembolic risk.

Introduction

Acquired Haemophilia (AH) is a severe, rare, and potentially life-threatening bleeding in which mortality from haemorrhages has been reported in up to 22% of cases[1]. This syndrome affects both, males, and females with an incidence about 1 to 4 cases/million/year[2]. In almost of 50% of cases AH is secondary to pregnancy/delivery, autoimmune disorders, onco-haematology or neoplastic diseases, drugs, or infections[3-6], however aetiology is unknown in the remaining part of cases, and it occurs without family and personal history of bleeding. Diagnosis of AH is often difficult cause a low number of cases. Mucocutaneous haemorrhages or haematomas are typical expression of this disease because of a FVIII activity decrease and a FVIII inhibitors presence, differently from congenital haemophilia. Haemarthroses are not frequent in patients with AH[6,]. International guidelines recommend treating early AH with by-passing agents such as activated recombinant FVII (rFVIIa) or activated prothrombin complex concentrates (aPCCs) and, if these products are not available or the FVIII inhibitor titre is slow (<5 BU), with recombinant FVIII (rFVIII) or plasma-derived FVIII (pdFVIII). To ensure normal haemostasis, immediate inhibitor eradication should be performed with corticosteroids or with a combined modality approach, including corticosteroids and alkylating agents (mainly cyclophosphamide). Only if these recommended treatments fail or are contraindicated, the patients may be treated with rituximab[6-8].

Case report

We report a case of a 71-year-old-man, who presented with spontaneous haematomas and severe anaemia. His past medical history consisted of: 1) previous thromboendoarterectomy of left carotid artery; 2) previous aorto-iliac by-pass; 3) acute myocardial infarction and consequent coronary artery by-pass graft (CABG) on October 2008, six months before onset of acquired coagulopathy and vascular cervical myelopathy with sensory and motor deficit in the right lower limb. Neither personal nor family history of haemorrhages or inherited coagulation disorders or autoimmune diseases had been reported

Plasma-derived FVIII (pdFVIII) used in this case was: Fanhdi® (Grifols Italia S.p.A., Ghezzano, Pisa, Italy), a doubly virus-inactivated highly purified VWF/FVIII complex concentrate.

Immunosuppressive treatment, in order to eradicate inhibitors, was made with prednisone (Deltacortene®, Bruno Farmaceutici S.p.A., Roma, Italy) and cyclophosphamide 100 mg/day (Endoxan®, Baxter Italia S.p.A., Lurago d'Erba – Como, Italy).

The patient was admitted to Emergency Department (University Hospital of Udine) in April 17th2009 with serious haemorrhagic muco-cutaneous syndrome that had begun 15 days before with extensive haematomas on face, left arm and supra-pubic region and followed by anaemia due to decrease of 4.0 g/dl of Hb and due to the confirmed prolongation of aPTT ratio. At hospitalisation the patient was transfused with 600 ml of fresh frozen plasma (FFP) and 2 units of packed red

blood cells (RBC). Clinical and laboratory findings at admission, before haemostatic treatment, were Hb: 10.3g/dl; WBC 9.05 $x10^3/\mu L$; Plt 319 $x10^3/\mu L$; INR: 1.12; aPTT ratio: 2.38; FVIII activity: 2.5%; FVIII inhibitor: 28 BU; FIX activity: 145%; FXI activity: 70%; vWFAg: 148%; AT: 72%; Fibrinogen: 654 mg/dl; Protein C: 80%; Protein S: 60%. Haemostatic data were diagnostic for idiopathic AHA. On April 18th the therapy for treatment of AHA was started. As this patient suffered from vascular disease, treatment with by-passing agents such as rFVIIa was contraindicated because of the risk of thromboembolic events. Despite the administration of FVIII concentrates in AHA is recommended only in patients with inhibitor titre < 5.0 BU, based on the design and on the preliminary experience of the "Resist Study", we decided for the administration of pdFVIII/VWF 100 IU/kg to control bleeding and to contribute to the induction of immunotolerance against clotting FVIII. Immunosuppressive treatment with prednisone was added to pdFVIII/vWF therapy in order to eradicate inhibitors. On April 24th, cyclophosphamide 100 mg/day was further added to enhance the immunosuppressive action on FVIII inhibitor. Duration of treatments and dosages are shown in Table 1.

Date	Day	pdFVIII/VWF IU/day or IU/bid	Prednisone mg/day	Cyclophosphamide mg/day
18 Apr 09 – 23 Apr 09	1	4000 IU/bid	75 mg/day	
24 Apr 09 – 30 Apr 09	7	3000 IU/bid	75 mg/day	100 mg/day
01 May 09 – 06 May 09	8	3000 IU/bid	50 mg/day	100 mg/day
07 May 09 – 10 May 09	14	4000 IU/day	50 mg/day	100 mg/day
11 May 09 – 29 May 09	18	4000 IU x 3/weekly	50 mg/day	100 mg/day
30 May 09 – 15 Jun 09	23	STOP	50 mg/day	100 mg/day
16 Jun 09 – 09-Jul 09	58		25 mg/day	50 mg day
10 Jul 09 – 16 Sep 09	82		12.5 mg/day (3 days/week)	STOP
17 Sep 09 – 11 Dec 09*	148		5 mg/day (3days/week)	
	180		STOP	

Table 1. *Outline of pdFVIII/VWF administration and immunosuppressive therapy (in grey follow-up). *Last visit of follow-up*

This AH treatment strategy was found to be effective so that subsequent checks evidenced a decrease of inhibitors associated with a simultaneous increase of FVIII activity (Figure 1). The patient discharged on May 15th (day +28). Haemostasis was normalized (INR: 1.07; aPTT ratio: 1.20; Hb: 12.1 g/dl; FVIII activity: 64%) and inhibitors dramatically decreased to 1.1 BU. The complete disappearance of the inhibitors was observed on the day +42. Cyclophosphamide and corticosteroids were discontinued respectively on day +82 and on day +180. At follow-up normal levels of FVIII and absence of FVIII inhibitors were confirmed.

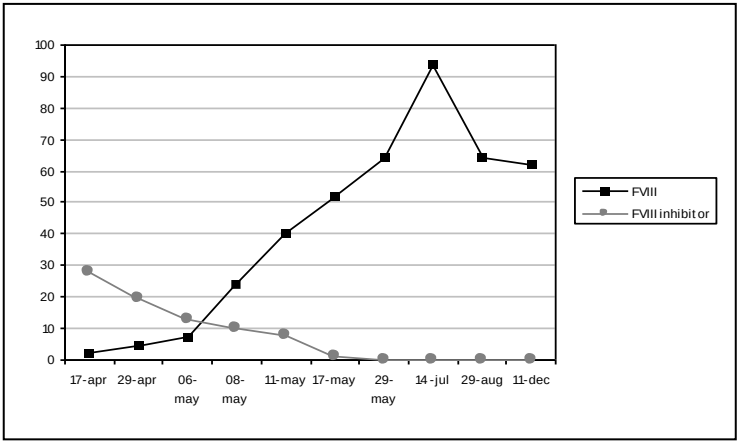

Figure 1. *FVIII:C increase and FVIII inhibitor eradication after pdFVIII/vWF administration*

Discussion

Congenital haemophilia affects males on the maternal side, the number of affected persons worldwide is estimated to be about 400000 and 80-85% is represented from haemophilia A, caused by a deficiency of coagulation factor VIII. Conversely acquired haemophilia affects both, males, and females, appears in adult age without presence of inherited coagulation disorders or autoimmune disease[3]. If not early diagnosed and treated AH can be fatal. In our case the patient had never experienced bleeding problems, personal and family history was negative for autoimmune diseases or coagulation disorders. Previous analyses of blood coagulation parameters were always normal. The sudden appearance of large haematomas in

many parts of the body, followed by anaemia, prolongation of the aPTT, decrease of FVIII activity and presence of FVIII inhibitors led doctors to diagnose an idiopathic AH. Published guidelines[1,3-5] consider two steps in the management of AH: 1. early treatment and prophylaxis of bleedings; 2. inhibitor eradication.

For treatment and following prophylaxis, the correct choice should be the use of by-passing agents such as rFVIIa or PCCs, but in our case the patient suffered from vascular diseases and the risk of venous thromboembolism was very high, treatment with by-passing agents was contraindicated.

Use of pdFVIII is normally recommended only in patients with low inhibitor FVIII titre (<5.0 BU). In our case, although the patient presented a rather high inhibitor titre at the moment of diagnosis (28 BU) but based on the design and the preliminary experience of the "Resist Study" [9] and other published studies[10,11], the contraindication to the use of by-passing agents led the physicians to treat the patient with pdFVIII/vWF. rFVII was strictly used in case of major bleeding, while pdFVIII/vWF was administered as an immunomodulatory agent, independently of inhibitor titre, following the clinical findings[12,13]. Based on showed immunomodulatory effects in patients with congenital haemophilia and inhibitors, we evaluated the hypothesis that this same effect could also apply to patients with acquired haemophilia. Furthermore, the thrombotic risk associated with pdFVIII/vWF is estimated to be lower than that observed with rFVIIa or aPCC[14,15]. This therapy resulted safe and effective, its duration may be shorten and may improve the success

rate of treatment[10]. Haemorrhages and haematomas quickly vanished. To eradicate inhibitors, published studies and international guidelines establish, as a treatment of choice, the use of corticosteroids alone or the combined therapy corticosteroids/cyclophosphamide. Normally after 6-8 weeks of treatment, inhibitors might be removed but, if it doesn't happen, subsequent treatment with cyclosporine or rituximab is recommended[1,16].

In our case the patient was treated initially with prednisone alone and, one week later, when the FVIII inhibitor was still present, the cyclophosphamide was added to improve the immunosuppressive action. The delayed administration of cyclophosphamide in this patient was due to avoid the potential risk of febrile neutropenia induced by chemotherapy greater in the elderly if compared with people under 65 years[17,18]. Moreover, unlike rFVIII, pdFVIII concentrates contain vWF which has been postulated to exert an immunomodulate role on FVIII[12,13].

At discharge coagulation and haemostatic parameters were normalized and inhibitors were almost vanished.

Successfully, at discharge, coagulation and haemostatic parameters were normalized and inhibitors were eliminated, no worsening or recurrence of the underlying severe cardiovascular disease was observed. pdFVIII/vWF can be a valid, safe and effective alternative for the treatment of AH in patients with vascular diseases and VTE risk in which the use of by-passing agents is contraindicated. pdFVIII/vWF may also allow saving the immunosuppressive therapy

avoiding cytotoxic agents and have also proven to be effective at doses of induction of immunotolerance.

References

1. Hay CRM. The 2000 United Kingdom Haemophilia Centre Doctors'Organisation (UKHCDO): Inhibitor Guidelines. Pathophysiol Haemost Thromb, 2002; 32 (Suppl 1): 19-21
2. Gheisari R, Bomke B, Hoffman T et al. Clinical features and outcome of acquired haemophilia A. Hämostaseologie, 2010; 30: 156-61
3. Collins P, Baudo F, Huth-Kühne A et al. Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. BMC Research Notes, 2010; 3: 161
4. Huth-Kühne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Lévesque H, Mingot Castellano ME, Shima M, St-Louis J. International recommendations on the diagnosis and treatments of patients with acquired hemophilia A. Haematologica, 2009; 94 (4): 566-75.
5. Collins PW. Management of acquired haemophilia A. J ThombHaemost, 2011; 9 (Suppl 1): 226-35
6. Shetty S, Bhave M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. Autoimm Rev, 2011; 10: 311-6
7. Giangrande P. Acquired Hemophilia. Treatment of Hemophilia, Dec 2005, nr. 38.
8. Franchini M. Rituximab in the treatment of adult acquired hemophilia A: a systematic review. Crit Rev Oncol Hematol, 2007; 63 (1): 47-52
9. Gringeri A. vWF/FWIII concentrates in high-risk immunotolerance: the RESIST Study. Haemophilia, 2007 Dec; 13 Suppl. 5: 73-7

10. Kurth MAH, Di Michele D, Sexauer C et al. Immune tolerance therapy utilizing factor VIII/von Willebrand factor concentrate in haemophilia A patients with high titre factor VIII inhibitors. Hemophilia, 2008; 14: 50-5
11. Greninger DA, Saint-Remy JM, Jacquemin M et al. The use of factor VIII/von Willebrand factor concentrate for immune tolerance induction in haemophilia A patients with high-titre inhibitors: association of clinical outcome with inhibitor epitope profile. Haemophilia, 2008 Mar; 14 (2):295-302
12. Kreuz W. The role of VWF for the success of immune tolerance induction. Thomb Res, 2008; 122 (Suppl 2): S7-12
13. Lillicrap D. The role of immunomodulation in the management of factor VIII inhibitors. Hematology Am Soc Hematol Educ Program.2006:421-5
14. Aledort LM: Comparative thrombotic event incidence after infusion of recombinant factorFVIIa versus factor VIII inhibitor bypass activity. J Thromb Haemost, 2004; 2: 1700-8
15. Franchini M, Lippi G. von Willebrand factor and thrombosis. Ann Hematol. 2006 Jul; 85 (7):415-23
16. Aggarwal A, Grewal R, Green RJ et al. Rituximab for autoimmune haemophilia: a proposed treatment algorithm. Haemophilia, 2005; 11: 13-19
17. Klastersky J, Awada A, Paesmans M et al. Febrile neutropenia: a critical review of the initial management. Crit Rev Oncol Hematol, 2011 Jun; 78 (3):185-94
18. Hosmer W, Malin J, Wong M. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. Support Care Cancer, 2011; 19: 333-41

CHAPTER 7

Acquired haemophilia A, concomitant acute myocardial infarction and urgent major surgery: how to successfully treat a critical patient with rpFVIII (Obizur®)

Ezio Zanon, Samantha Pasca, Luca Spiezia, Francesco Poletto, Simone Gherardi, Paolo Simioni

Thromb Res 2020 Nov; 195:125-127 doi: 10.1016/j.thromres.2020.07.012 PMID:32683151

Abstract

Association of acute myocardial infarction (AMI) and acquired haemophilia A (AHA) is extremely rare, and very difficult to treat, if the patient then presents several serious comorbidities and must undergo an urgent major surgery, the correct choice of haemostatic therapy is essential to avoid potentially life-threatening adverse events for the patient. The recombinant porcine FVIII (rpFVIII) is considered, together with the bypassing agents, as first-line therapy for the AHA, but compared to these it presents a reduced thromboembolic risk which makes it safer in patients who already present at the onset of haemorrhagic event an underlying cardiovascular disease. Haemorrhagic and thrombotic events are always to be taken into consideration in the case of surgery, but in the case of patients with concomitant acquired haemophilia the risk of having serious bleeding has further increase. Today there have been no reports of surgeries carried out under Obizur® coverage.

We are reporting the successful case of an elderly critical patient with acquired haemophilia A and concomitant myocardial infarction, treated with rpFVIII and in which an urgent major surgery under coverage of this dug was performed for the first time.

Case Report

The association of acute myocardial infarction (AMI) and acquired haemophilia A (AHA) is extremely rare. Foley et al. reported a case of a 78-old man hospitalized for acute coronary syndrome (ACS), initially treated with enoxaparin, clopidogrel, aspirin, and statins, and in which an AHA was diagnosed later after the activated partial thromboplastin (aPTT) ratio remained high despite the suspension of the anticoagulant treatment, without any previous clinical manifestation. Routledge et al.[2] instead reported the case of a 64-old-woman in which an inferior ST elevation myocardial infarction (STEMI) with complete heart block appeared nine months after the AHA onset, when the acquired bleeding disorder was in partial remission. Our case is the first in which a symptomatic AHA and an AMI occurred together. In these cases, the treatments are particularly difficult because it's known that the use of by-passing agents could be associated to arterial o venous thrombosis[3], while the use of anticoagulants to treat the concomitant acute myocardial infarction can aggravate the bleeding. The recombinant B-domain deleted porcine FVIII (rpFVIII) is considered together with bypassing agents as first-line therapy for the treatment of bleeds in patients with acquired haemophilia A[4]. The advantage of this drug is that it can be easily measured in the plasma with the one stage assay, and its efficacy has been proven in the OBI-1 Study[5]. If the thromboembolic risk due to bypassing use is always present[3] no cases of thrombosis has been reported due to rpFVIII. The use of this concentrate in case of patients with acquired haemophilia A (AHA)

and concomitant cardiovascular diseases is then safer, as also reported by Owen et al[6]. Surgery is always at haemorrhagic risk, but in case of a subject with AHA this risk is very increased. In literature, in addition to the cases of patients with congenital haemophilia undergoing surgery[7,8], there have been no reports of surgeries carried out under coverage of Obizur® in subjects with AHA. The complete resolution of the AHA provides for the eradication of the autoantibodies against the endogenous FVIII that has formed, and which is the basis of acute bleeding in patients suffering from this acquired disorder. Corticosteroids alone or corticosteroids/cyclophosphamide are usually used to obtain the eradication, but if these treatments fail or are contraindicated, the patients should be treated with rituximab[9].

We are reporting a case of an elderly man with AHA and concomitant acute myocardial infarction, undergoing an urgent abdominal major surgery.

Our 81-years-old patient was initially hospitalised due to an acute non-ST elevation myocardial infarction (NSTEMI) and severe anaemia (5.7 g/dl). At admission, he presented also large subcutaneous haematomas in the lower and upper limbs, and in the soft palate. Laboratory analyses immediately performed showed a Troponin I 2.92 ng/ml (range 0-0.34 ng/ml), due to NSTEMI, and a prolonged aPTT ratio of 2.10 (normal range 0.8-1.20). A concomitant presence of an AHA was then suspected and subsequently confirmed by plasmatic FVIII level <1% (range 60-160%) and inhibitor titre of 110 BU/ml. Given the concomitant

presence of AHA, the cardiologists decided not to perform a coronary angiography, but to put the patient on treatment with statins, ACE-inhibitors, and beta-blockers. His medical history also reported: previous right (2010) and left (2018) breast ductal carcinoma; carotid vasculopathy; and rheumatoid arthritis. An initial treatment with rpFVIII 50.0 IU/kg/tid was then started to solve the severe life-threatening bleeding, while an immunosuppressive treatment (IST), prednisone/cyclophosphamide, was immediately prescribed to eradicate the inhibitors. Ten days later the haemostatic treatment with rpFVIII was reduced to 25.0 IU/Kg/bid to maintain a sufficient haemostasis (FVIII: 20-30%) in a subject with a recent AMI, while the IST was maintained. Twenty-five days from AHA diagnosis, the patient began to complain of pain in the right hypochondrium, initially treated only with drugs. Thirteen days later, the relapsing pain led the patient to surgery due to the presence of an empyema of the gallbladder, with bilious effusion in the abdominal cavity, as reported by the CT-scan (Figure 1).

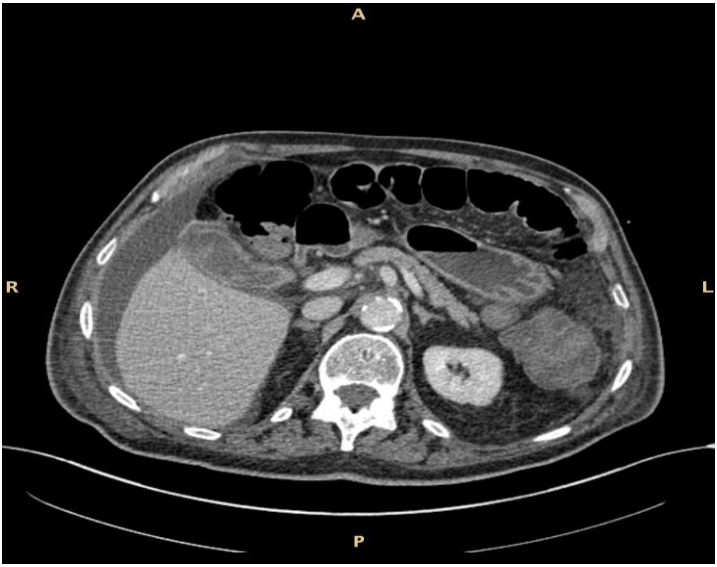

Figure 1. *The abdominal CT-scan that revealed an empyema of the gallbladder, with bilious effusion in the abdominal cavity.*

The cholecystectomy was performed under rpFVIII coverage at dosage of 87.5 IU/kg, a single bolus administered thirty minutes before surgery, followed by 62.5 IU/kg/tid for two days and by 37.5 IU/kg/tid for another week. In Figure 2 we have reported the FVIII levels reached during the initial treatment with rpFVIII and maintained during surgery and the post-operative period.

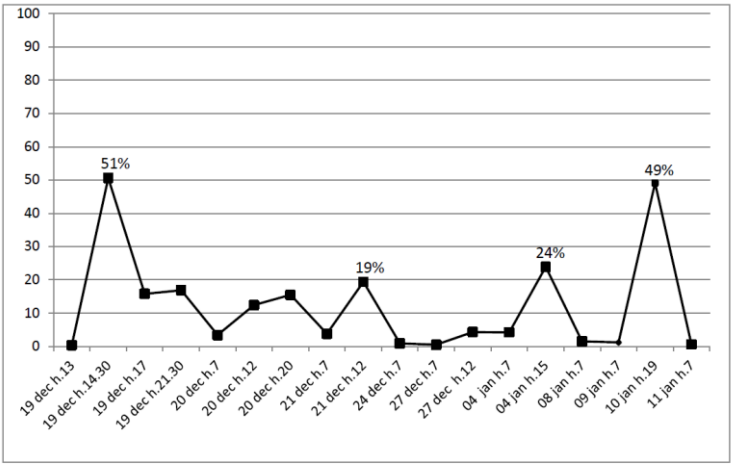

Figure 2.a

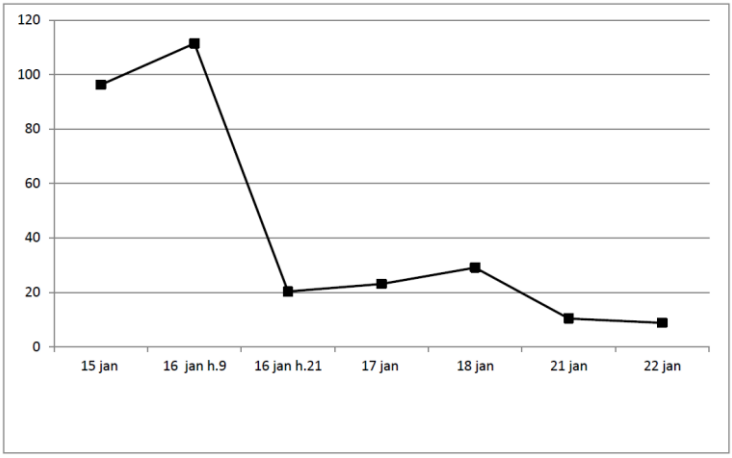

Figure 2.b

Figure 2. *a) The FVIII levels (one-stage assay) reached during the initially treatment for acquired haemophilia A; 2.b) The FVIII levels (one-stage assay) maintained during the surgery (January 15) and the post-operative period, performed under coverage of rpFVIII*

The patient was stabilized when he was discharged from the surgical division and transferred again to our medical department. The treatment with rpFVIII was then reduced to 25.0 IU/kg/tid. A dual infection by enterococcus faecalis and candida albicans occurred fifteen days after surgery, and worsened the clinical condition of our patient, solved subsequently with a combined antifungal/antibiotic therapy. The treatment with rpFVIII was further reduced to 25.0 IU/kg/day only to maintain the haemostasis, and reducing the bleeding risk, always present in this patient, in which plasmatic FVIII and inhibitor titre were still 4.3% and 144 BU/ml respectively. During this period the patient did not experienced bleeding, but a check of the coagulation parameters showed the presence of a low-titre (1.5 BU/ml) allo-antibodies against rpFVIII. The therapy with susoctocog-alfa was stopped, and a new prophylactic treatment with a low-dose activated prothrombin complex concentrate (aPCC) 40.0 IU/day was then started. Although haemostasis was maintained with these treatments, the inhibitors to human FVIII had not yet been eradicated (139 BU/ml), and FVIII remained very low (3.2%), it was therefore decided to undertake a therapy with rituximab 375 mg/sqm/weekly. Three weeks later, before the last infusion of rituximab, the plasmatic FVIII level and the inhibitor titre reached 43.0% and 2.8 BU/ml respectively. The patient was then discharged and addressed to scheduled follow-up visits. The planned control performed two weeks after the end of the treatment with rituximab highlighted that the inhibitor reached 1.3 BU/ml and the FVIII was within normal

range (100.9%). A therapy with prednisone 50 mg/day was then maintained to allow complete inhibitor eradication to be achieved. Once a normal haemostasis was reached (138 days after diagnosis), the patient underwent a left mastectomy, followed by chemo-radiotherapy. The patient no experienced any adverse events during the surgery and the post-surgical period. Planned follow-ups subsequently performed, confirmed the complete resolution of AHA.

At diagnosis of AHA our patient presented a severe anaemia associated with a NSTEMI which made the use of by-passing agents difficult. Even if in the FAIR Registry no thromboembolic events were reported also in case of concomitant use of aPCC and antifibrinolytics in patients with severe cardiovascular diseases[10]; in the EACH 2 Registry the thromboembolic events occurred in the 3.6% of patients treated with by-passing agents[3]. With this controversial background we have chosen to treat our elderly and already infarcted patient with susoctocog-alfa, since the use of this concentrate has allowed a better monitoring of the therapy and reduced the thromboembolic risk. Despite the recommended initial dose of concentrate is 200 IU/kg[5], we have decided to treat the patient with a lower dosage due to concomitant presence of an AMI, thus ensuring a sufficient plasmatic FVIII level, but preventing him from reaching too high and potentially dangerous peaks.

In literature only few cases of patients with congenital haemophilia A undergoing surgery under rpFVIII coverage has been published[7,8], while ours is the first real-world report that deals with the history of an AHA

patient undergoing a major surgery under successfully susoctocog-alfa coverage.

De-novo inhibitor development against rpFVIII is a complication described in the 17.9% of treated patients, as reported by Kruse-Jarres et al[5]. Our patient also developed a low-titre allo-antibodies to susoctocog-alfa, which was then stopped and replaced with a low-dose of aPCC to maintain a minimal haemostasis during the concomitant treatments.

The auto-antibodies eradication had not been obtained despite the concomitant IST, therefore after having resolved other clinical problems, we have decided to use the rituximab, as second line strategy[9].

In conclusion we have described a very complicated case of an elderly man affected by AHA and other severe co-morbidities, in which different therapeutic strategies were adopted: 1) susoctocog-alfa to solve acute bleeding and as a haemostatic coverage during major surgery; 3) aPCC at prophylactic dosage to replace rpFVIII and to maintain haemostasis; 4) rituximab to definitively eradicate human inhibitors and solve AHA.

References

1. Foley PW, Pepperell D, Kazmi R, Curzen NP. Unsuspected acquired haemophilia in a patient with myocardial infarction. J R Soc Med. 2004 Nov;97(11):542-3
2. Routledge DJ, Fraser D, Thachil J, Nash MJ. Management of a myocardial infarction in a patient with classical acquired

haemophilia patient in partial remission. Haemophilia. 2015 Nov;21(6): e494-6
3. Baudo F, Collins P, Huth-Kühne A, et al.; EACH2 Registry Contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012; 120: 39–46
4. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017 Jul; 92 (7): 695-705
5. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. Haemophilia 2015; 21: 162–70
6. Owen M, Gidley G, Horn EH. Treatment of acquired haemophilia with recombinant porcine factor VIII: A successful strategy in a patient with unstable angina. Haemophilia. 2019 Mar; 25 (2): e94-7
7. Ruan GJ, Mao JJ, Sytsma TT, et al. Continuous infusion of recombinant porcine factor VIII for neurosurgical management of intracranial haemorrhage in a patient with severe haemophilia A with factor VIII inhibitor. Haemophilia2020 May;26(3): e141-4
8. Croteau SE, Abajas YL, Wolberg AS, et al. Recombinant porcine factor VIII for high-risk surgery in paediatric congenital haemophilia A with high-titre inhibitor. Haemophilia. 2017 Mar; 23 (2): e93-8
9. Zeng Y, Zhou R, Duan X, Long D. Rituximab for eradicating inhibitors in people with acquired haemophilia A. Cochrane Database Syst Rev. 2016 Jul 8;7: CD011907
10. Pasca S, Ambaglio C, Rocino A, et al. Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry. J Thromb Thrombolysis 2019 Jan; 47 (1): 129-33

CHAPTER 8

Low dose of aPCC after the initial treatment in acquired hemophilia A is useful to reduce bleeding relapses: data from the FAIR Registry

Ezio Zanon, Samantha Pasca, Sergio Siragusa, Marisanta Napolitano, Cristina Santoro, Lucia Mameli, Angiola Rocino; for the FAIR Study Group

Thromb Res 2019 Feb; 174:24-26doi: 10.1016/j.thromres.2018.12.006 PMID:30551040

Abstract

Background: Bypassing agents are the first line therapy in patients with acquired haemophilia A (AHA). Activated prothrombin complex concentrate (aPCC) proved to be effective as initial treatment, but 20% of patients (pts) had relapses. aPCC as short-term prophylaxis to reduce subsequent bleeds is still not clear.
Aim: To evaluate whether a short-term prophylaxis with low dose of aPCC can reduce bleeding relapses after initial AHA treatment, maintaining safety
Methods: The FAIR Registry is a retrospective-prospective study started on December 2012, that collected data on all pts with AHA treated with aPCC in 12 Italian Hemophilia Centers. All statistical analyses were carried out in the 56-pts included in the registry.
Results: 31 retrospective and 25 prospective pts were evaluated.101 bleeds requiring treatment were reported, 84.1% spontaneous, 71.3% involving muscles or skin. Major bleeds were 38,6%. Low dose aPCC as short-term prophylaxis was started after the first resolved episode in 15/56 pts, 58% of whom prospective, in a mean dose of 54.2±23.0 IU/kg, higher (61.4±23.4 IU/kg) in the prospective group than in the retrospective one (44.3±19.7 IU/kg) and it was continued up to a mean of 20.5±17.6 days, similar in both groups. A total of 32 bleeding relapses were reported, 87.5% in the retrospective group. Only 9.4% occurred during short-term prophylaxis ($p<0.05$). In our Registry no thromboembolic events were found

Conclusion: Initial AHA treatment with aPCC proved to be highly effective, but a consecutive low dose as short-term prophylaxis seems to demonstrate a significant reduction in bleeding relapses maintaining safety.

Letter to Editor

Acquired haemophilia A (AHA) is a rare auto-immune disorder due to the sudden appearance of an inhibitory antibody against plasmatic factor VIII (FVIII). The annual incidence of AHA has been reported to be 1-1.5 per million in the general population, equally divided between males and females. The diagnosis is often delayed due to the onset of hemorrhagic episodes in subjects without known coagulation defects, and, in some cases, treatment of bleeding can be inadequate. This disease usually leads to severe bleeding, mainly occurring in soft tissues, as muscles or skin. Unlike inherited hemophilia, in AHA the hemarthroses are very rare[1]. Morbidity and mortality associated with AHA are high, especially in elderly patients with severe previous co-morbidities. An immediate haemostatic control is necessary to reduce the risk of severe sequelae or death in patients with AHA. The International Guidelines[2] recommend the use of bypassing agents as recombinant activated FVII (rFVIIa) or activated prothrombin complex concentrate (aPCC) as first-line treatment of bleeds, and in recent years, also the use of recombinant porcine FVIII (rpFVIII).

When these products are not available, or the auto-antibodies titre is low (<5 BU), AHA may be treated with FVIII concentrates[3]. Safety and efficacy of these different haemostatic agents was proven to be similar. Despite the high rate of success of bypassing agents in the treatment of acute bleeding, relapses occurred in over 20% of patients with a mean period of recurrence of 14 days[4]. This result underlines how the initial

treatment period with a bypassing drug is not sufficient to solve AHA.

At the present time there are no guidelines on how to prevent the risk of recurrence and relapses of bleeding in patients presenting acquired haemophilia. In a previous Italian study[5] a short-term prophylaxis with lower doses of aPCC, after first-line therapy, was proven to be effective in reducing bleeding relapses. In this report a lower dose administration of aPCC subsequent to the acute bleeding resolution was used until the auto-antibodies titre was reduced by more than 50% of the baseline level. This strategy decreased the relapses in patients with AHA. Another recent study published by Árokszállási et al.[6] showed that a prophylaxis with aPCC in a dose of 30–60 U/kg, on two or three days a week, and continued until the inhibitor disappeared, was effective to avoid the recurrence of bleeding.

We now report the data on "short-term prophylaxis" after the acute bleeding obtained in our study named FEIBA® in the Acquired hemophilia Italian Registry (FAIR Registry).

The FAIR study is a retrospective-prospective registry that included fifty-six patients with AHA, 31 retrospective and 25 prospective, treated with aPCC at 12 Italian Haemophilia Centres.

The study protocol was approved by each institution's Ethical Committee and was conducted in accordance with the principles of the Declaration of Helsinki and with local laws and regulations.

All events occurring in the 4 weeks following resolution of the qualifying bleeding episode were collected. The

acute bleeding resolution was assessed clinically, considering bleeding tendency, the size of hematoma, the stability of Hb/Hct and the resolution of pain caused by the hematoma.
A "bleeding relapse" was defined as any bleeding event occurred into the previous site or a different site within a month after the resolution of the first episode.
Short-term prophylaxis was defined as aPCC administered at a lower dosage, after resolution of an acute bleeding episode, for at least one week according to a clinical decision. Short-term prophylaxis was administered based on the clinical evaluation and bleeding severity of each patient and performed by local physicians. Since the FAIR is a registry, no special protocols have been provided for patient management after the acute treatment period.

Due to the small sample of patients, all comparative statistics were performed using the Fisher's Exact Text ($p<0.05$).
Statistical analysis included all data of the 56 enrolled patients, mean age at AHA diagnosis was 69.9±15.1 years, similar between the two groups: 1) patients treated with short-term prophylaxis, and 2) patients without short-term treatment. Among the overall population, idiopathic AHAs (29 patients, 51.8%) was the most common aetiology, followed by the presence of autoimmune diseases. Malignancy was more frequent in the prospective patients, but no significant difference was reported between subjects treated (15.4%) or not treated (14.6%) with short-term prophylaxis.
Totally 101 bleeding episodes were reported, 20 (19.8%) in the short-term prophylaxis group. 84.1% of

bleedings were spontaneous; 39 (38.6%) were major bleedings, 7 of these occurred in the group treated with short-term prophylaxis; 71.3% involved muscles or skin. Thirty-six patients (64.3%) had only one bleed. Only two patients included in the short-term prophylaxis group had two bleeds each.

FEIBA® as first line therapy was used in 82.2% of cases, with a median dose of 72.6±26.6 IU/kg, higher in the groups subsequently treated with short-term prophylaxis (76.1±22.7IU/kg. The median frequency of infusion was 12 hours (IQR 0-84), similar in both groups. FEIBA® was evaluated as effective in 96.4% of bleeds. Fifty patients (89.3%) received at least one immunosuppressive therapy to eradicate the inhibitors. (All these patients received corticosteroids, and prednisone in 41 cases). Combined immunosuppressive therapy was performed in 31 patients: 21 patients received cyclophosphamide, 6 rituximab, and 4 patients azathioprine. For the remaining 6 patients data were not available. Rituximab was used only in one patient included in the group treated with prophylaxis; cyclophosphamide in 53.4% of this group, and in 37.2% of the other one; azathioprine was used only in the retrospective patients included in the group without short-term treatment.

Low-dose aPCC for short-term prophylaxis to prevent bleeding relapses was initiated after the first episode in 26.8% of patients, while 73.2% received no further treatment (p= 0.0048). Mean dose of aPCC for prophylaxis was 54.2±23.0 IU/kg, higher in the prospective group (61.4±23.4 IU/kg) than in the retrospective one (44.3±19.7 IU/kg). Prophylaxis lasted

an average of 20.5±17.6 days, with an infusion's frequency mean every 24 hours (range 12-72 hours). Bleeding relapses resulted significantly higher in the patients without prophylactic treatment with FEIBA®. Complete data including patient demographics and baseline characteristics, as sex, age, FVIII:C and inhibitor titre are presented in Table1.

During acute and prophylactic treatment with FEIBA®, neither thromboembolic events nor myocardial infarction nor disseminated intravascular coagulation was reported. Eight patients died, equally divided in the two groups; none related to treatment with aPCC.
The FAIR Registry is a large multicenter study on the use of FEIBA® in the treatment of AHA, in which almost half of the patients was prospective, and the first which considers the outcomes of the short-term prophylaxis with aPCC after first line therapy.
Currently there is no evidence or specific guidelines on the use of aPCC in preventing bleeding relapses in patients with AH A. Two reports, published some years ago, showed the effective use of a short prophylaxis with this bypassing drug. In the first Grünewald et al.[7] reported the use of a reduced dose of aPCC in a population of patients previously treated for a severe muscle-skeletal bleeding, with anaemia and acquired auto-antibodies against FVIII, while Kang et al.[8]showed a case of a young woman treated with a very low dose of FEIBA® after the resolution of acute event. In the 2015, another nonrandomized, prospective, Italian study[5]performed on 18 subjects with AHA showed that a short-term prophylaxis with a low-dose of aPCC started subsequently to the acute bleeding resolution

was effective to prevent the relapses. In this study a regular and continuous administration of aPCC was initiated and continued independent of severity of initial bleeding and stopped when the inhibitor titre fell below 50% of the baseline level. This choice was arbitrary and based on the perception that such decrease in the titre of FVIII inhibitor may be considered as an indicator of the response to immunosuppressive therapy, able therefore to predict the reduction in the risk of bleeding relapse. The same cut-off used in our Registry seems to confirm this hypothesis. Among the 18 evaluated patients, only 7 were treated on prophylaxis with FEIBA®, while the remaining 11 have constituted the control group. No relapses occurred in the prophylaxis group, conversely six relapses were reported in the control group, without prophylactic treatment with aPCC. A recent study published by Árokszállási et al.[6] showed that a prophylaxis with aPCC in a dose of 30–60 U/kg, the lowest effective therapeutic dose used for acute treatment, on two or three days a week, and continued until the inhibitor disappeared, was effective to avoid the recurrence of bleeding. In this study only two of the eleven patients treated with a low regimen of aPCC presented haematuria, in both cases due to previous urinary tract defects or diseases, the remaining nine have not experienced any bleeding. In all these published reports no thromboembolic complication was developed during the aPCC prophylaxis. In our study thromboembolic risk was further reduced using lower doses of aPCC than the acute treatment. The prevention of bleeding episodes through prophylaxis with FEIBA®was also approved and recognized to be

effective in patients with congenital haemophilia A and inhibitors[9].

In our FAIR study, the median initial dose of FEIBA® was not different from that used in the other registries[4], but the median duration of treatment was twice that of the recent French study[10]. The low dose short-term prophylaxis with aPCC was started on 15 patients, with a mean duration of treatment of 24 days. A total of 32 relapses occurred on patients included in the study, among these the 90.6% were reported in patients without prophylaxis. Although the costs of treatment resulted initially increased due to the higher consumption of aPCC in the patients treated with short-term prophylaxis, in the long-term these are reduced by the fewer days of hospitalization, the fewer severe events requiring further treatment and by the lower number of sequelae.

Our study showed that a short-term prophylaxis with FEIBA® started immediately after an acute episode resolution was proven to be effective to prevent relapses, and safe. The randomized controlled trials should be necessary to define the appropriate dose of aPCC and the appropriate duration of treatment.

Demographic and clinical data of the patients	Prophylaxis group $n = 15$	Non prophylaxis group $n = 41$	P value (< 0.05)
Age at diagnosis (years; mean, SD)	69.4 ± 17.1	70.0 ± 14.6	–
Sex: M/n (%)	46.7	51.2	–
Group:			
- Retrospective	7/15	24/41	0.547
- Prospective	8/15	17/41	
Total bleeds/patients	24/15	77/41	0.702
Patients with one bleed (pts/n)	9/15	26/41	–
Patients with two or more bleeds (pts/n)	6/15	15/41	–
FVIII:C at diagnosis (%; mean, SD)	5.4 ± 6.7	5.8 ± 11.0	–
Inhibitor titre at diagnosis (BU/ml; mean, SD)	15.9 ± 13.6	15.3 ± 13.8	–
aPCC initial dose (IU/kg; mean, SD)	76.1 ± 22.7	72.0 ± 27.5	–
Treatment duration (days; mean, SD))	11.8 ± 6.5	9.6 ± 9.7	–
aPCC prophylaxis dose (IU/kg; mean, SD)	54.2 ± 23.0	–	na
Prophylaxis duration (days; mean, SD)	17.9 ± 15.9	–	na
Relapses (r/R)	3/32	29/32	0.0016

Table1. *Demographic and clinical data of the patients. n: number of patients each group. r: number of relapses each group. R: total*

number of relapses. SD: standard deviation. M: male. IU: international units. aPCC: activated prothrombin complex concentrate. pts: patients

References

1. Kessler CM, Knobl P. Acquired haemophilia: an overview for clinical practice. Eur J Haematol 2015; 95 (Suppl 81): 36-44
2. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017 Jul; 92(7): 695-705
3. Pasca S, De Angelis V, Milan M, et al. Can the plasmaderived FVIII still play a role in the treatment of acquired haemophilia A at the time of new drugs? Blood Coagul Fibrinolysis2018 Jul;29(5):417-22
4. Baudo F, Collins P, Huth-Kühne A, et al.; EACH2 Registry Contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012; 120: 39–46
5. Zanon E, Milan M, Gamba G et al. Activated prothrombin complex concentrate (FEIBA®) for the treatment and prevention of bleeding in patients with acquired haemophilia A: a sequential study. Thromb Res, 2015 Dec; 136 (6): 1299-1302
6. Árokszállási A, Rázsó K, Ilonczai P, et al. A decade-long clinical experience on the prophylactic use of activated prothrombin complex concentrate in acquired haemophilia A: a case series from a tertiary care centre. Blood Coagul Fibrinolysis2018 Apr;29(3):282-7
7. Grünewald M, Beneke H, Güthner C, et al.Acquired haemophilia: experiences with a standardized approach. Haemophilia, 2001; 7: 164–9
8. Kang E, Kim HG, Lee JH, et al. Acquired hemophilia successfully treated with activated prothrombin complex concentrate and immunosuppressant combination: a case report. Blood Coagul. Fibrinolysis, 2012, 23: 669–72

9. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. N. Engl. J. Med, 2011; 365: 1684–92
10. Borg JY, Négrier C, Durieu I et al.; FEIBHAC Study Group. FEIBA in the treatment of acquired haemophilia A: results from the prospective multicentre French 'FEIBA dans l'hémophilie A acquise' (FEIBHAC) registry. Haemophilia. 2015 May; 21(3):330-7

CHAPTER 9

Emicizumab in acquired hemophilia A: pros and cons of a new approach to the prevention and treatment of bleeding

---

Samantha Pasca, Ezio Zanon, Pier Mannuccio Mannucci, Flora Peyvandi

Blood Transfusion 2023 Feb 7
doi: 10.2450/2023.0247-22. Online ahead of print.

Abstract

Emicizumab, a monoclonal bispecific antibody that mimics the function of activated factor VIII (FVIII), is currently licensed for prophylactic use in patients with congenital hemophilia A with and without inhibitors. Acquired hemophilia A (AHA) is a very rare bleeding disorder that equally affects males and females and is due to the development of autoantibodies that inhibit FVIII activity in plasma. Therapeutic options for patients with AHA currently include eradication of the inhibitor with immunosuppressive treatments and management of acute bleeding with bypassing agents or recombinant porcine FVIII. More recently, several reports have described the off-label use of emicizumab in patients with AHA and a phase 3 study is ongoing in Japan. The aim of this review, in addition to describe the 73 reported cases, is to highlight the pros and cons of this novel approach to the management of bleeding in AHA.

Introduction

Emicizumab, a bispecific monoclonal antibody that mimics the procoagulant function of activated factor VIII (FVIIIa) by binding activated factor IX and factor X, plays an important role in the prophylactic treatment of patients with congenital hemophilia A with or without FVIII inhibitors[1]. Acquired hemophilia A (AHA) is a very rare bleeding disorder that equally affects males and females, with an estimated prevalence of 1.5 cases per million patient years due to the development of autoantibodies that inhibit FVIII activity in plasma. In almost half of the cases AHA is secondary to cancer, autoimmune diseases, infections and occurs frequently in elderly people, with an additional peak in women at the time of pregnancy and parturition. The dual goal of treatment is the control of bleeding and autoantibody eradication. FVIII bypassing agents and recombinant porcine FVIII (rpFVIII) are first-line therapies at the time of bleeding and immunosuppressive drugs are concomitantly administered in the attempt to eradicate the inhibitory autoantibody and restore plasma FVIII levels[2]. Several recent reports described the off-label use of emicizumab in patients with AHA, and a phase 3 study (AGEHA) is ongoing, with preliminary data presented in abstract form[3]. With this background we chose to collect and review the available literature on this topic, with the purpose to highlight the pros and cons of this novel approach to the management of AHA.

Methods

This review has been created following the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) model[4]. Literature search included clinical studies, case reports, reviews, abstracts, and all scientific articles concerning AHA treated with emicizumab on PubMed until September 2022. The key terms "acquired haemophilia A", "acquired hemophilia A", "emicizumab" were used for the search, linked with the boolean operator AND terms such as "treatment, therapy". In the query box, these terms were searched only within the titles and/or abstracts of the articles. Publications that met the following criteria were included in this review: 1) articles/abstracts concerning patients with AHA treated with emicizumab; 2) articles/abstracts written in English. Thus, a total of twelve manuscripts and six abstracts dealing with this topic were considered for this review, with the main findings summarized in table 1.

Results

- *Prophylaxis of bleeding*

The prophylactic use of emicizumab was implemented by a number of authors after the control of bleeding was obtained with FVIII bypassing agents.

An early report in 2019 of Möhnle et al.[5], described the case of an 83-year-old man diagnosed with AHA, multiple comorbidities (Table) and on long-term

treatment with direct oral anticoagulants. He was initially successfully treated with rpFVIII for bleeding and corticosteroids for immunosuppression but owing to bleeding recurrence and increase in inhibitor titer rpFVIII was replaced by recombinant activated factor VII (rFVIIa). Because bleeding persisted despite the decrease of the inhibitor titer, emicizumab was administered at an initial dosage of 3.0 mg/kg followed by additional weekly doses of 1.5 mg/kg. This treatment was continued for a total of 36 days and allowed hospital discharge with no further bleeding nor thrombotic complications.

Al-Baana et al.[6] reported the case of an elderly woman with atrial fibrillation on anticoagulant therapy and a recent history of gastrointestinal bleeding secondary to warfarin who, after anticoagulant discontinuation, was admitted to hospital owing to anemia and multiple hematomas. Plasma FVIII activity <1% and the inhibitor titer > 100 BU led to diagnose AHA. Initially treated with activated prothrombin complex concentrate (aPCC) 50 IU/kg every 12 hours for 2 weeks with a prompt control of bleeding, at discharge she was started on prophylaxis with emicizumab, initially at a dosage of 3.0 mg/kg/week for one month and next 1.5 mg/kg/week for another month. No further bleeds nor adverse events were recorded.

Hess et al.[7] reported the case of a 91-year-old man with several concomitant diseases (Table) admitted to hospital for anemia owing to macroscopic hematuria. After obtaining a diagnosis of AHA (FVIII level <1%, inhibitor titer 44 BU/ml), he was treated with rFVIIa

90μg/kg every two hours for 24 hours, promptly halting hematuria. Following the onset, a week later of an ileo-psoas hematoma, rFVIIa was restarted and bleeding stopped again. At hospital discharge this bypassing agent was replaced by prophylaxis with emicizumab at a loading dose of 3.0 mg/kg/week for four weeks and a maintenance dose of 1.5 mg/kg every two weeks. The patient was monitored for six months without bleeding nor adverse events.

Dane et al.[8] reported the case of a 72-year-old man with a history of bullous pemphigoid associated to AHA with a high-titer FVIII inhibitor refractory to multiple immunosuppressive regimens. To control acute bleeding, he was initially treated with aPCC, then continued as prophylaxis owing to the persistence of the bleeding tendency. After two years of this continued regimen, the patient was hospitalized for chest pain and non-ST-segment elevation myocardial infarction and a percutaneous coronary intervention (PCI) was carried out under the cover of aPCC, continued at discharge for bleeding prophylaxis. After 15 weeks he was hospitalized again for re-stenosis despite dual antiplatelet treatment. A drug-eluting stent was deployed under rpFVIII coverage followed by continuous prophylaxis, first with aPCC and then with emicizumab 3.0 mg/kg/week together with dual anti-platelet treatment. The patient underwent uneventfully a second PCI and was transitioned to prophylaxis with emicizumab 1.5 mg/kg/week for a month. Follow-up after five months recorded no hemorrhage nor any cardiac event.

Chen et al.[9] described four patients with AHA and multiple comorbidities (Table). Hospitalized for acute bleeding they were first treated with rpFVIII and then, following the onset of anti-porcine FVIII antibodies, with rFVIIa and rituximab for immunosuppression with a satisfactory response. Prior to hospital discharge all patients were put on long-term prophylaxis with emicizumab, 3.0 mg/kg/week for 4 doses followed by 1.5 mg/kg/week (mean 22 doses). Only one of them required a new hospitalization due to a promptly resolved traumatic bleeding, no thromboembolic episodes was reported nor other adverse events.

Yates et al.[10] described an 83-old-man with comorbidities (Table), who first presented as outpatient for fatigue attributed to anemia and treated with one unit of red blood cells (RBC). A few days afterwards he was hospitalized due to an abdominal wall hematoma and large ecchymoses in the lower limbs, so that AHA was suspected, laboratory confirmed and a combined treatment with rFVIIa, tranexamic acid, prednisone and cyclophosphamide was started. However, bleeding continued with a decline in hemoglobin. Tranexamic acid was then stopped and replaced with aPCC, cyclophosphamide was also stopped owing to thrombocytopenia and rituximab started. rFVIIa was discontinued following hemoglobin stabilization, aPCC dosage was reduced and ultimately stopped when he developed atrial fibrillation. Prophylaxis of bleeding recurrence with emicizumab was initiated at hospital discharge, but 5 days later he was re-admitted with an altered mental status, left gluteal and thigh hematomas, orthostatic hypotension and hemoglobin dropping, so

that rFVIIa was resumed. The patient was ultimately discharged and maintained on emicizumab prophylaxis 1.5 mg/kg every two weeks for 224 days, with no reported bleeding recurrence nor thromboembolic events.

Escobar et al.[11] described two cases, a woman of 57 years and a man of 90 years, treated with two different dosage regimens of emicizumab: the standard protocol with a loading dose of 3.0 mg/kg/week for four doses followed by a maintenance of 1.5 mg/kg/week, and the so-called Texas protocol with a loading dose of 1.5 mg/kg/week for two weeks and a maintenance of 1.5 mg/kg once every 21 days. Both regimens were effective to prevent bleeding and apparently safe, but no additional data are available.

Gelbenegger et al.[12] described a recent case of a 75-year-old male with Covid-19 and a previous history of ST-elevation myocardial infarction with coronary stenting, hypertension, hyperlipidemia and an infrarenal aortic aneurysm in dual antiplatelet treatment, admitted to their hospital for pain in the left groin that revealed an iliacus muscle hematoma. Dual antiplatelet therapy was temporarily stopped, but without bleeding resolution. A diagnosis of AHA was then performed, and the patient was first put on prophylaxis with rFVIIa, followed by emicizumab (in second day after diagnosis) 3.0 mg/kg/week for six weeks followed by emicizumab 1.5 mg/kg every 2-4 weeks until bleeding resolution. No bleeding, no thromboembolic events were reported. Antiplatelet treatment with clopidogrel was restarted as soon as the FVIII level exceeded 50%.

- *Treatment of acute bleeding*

Emicizumab as second-line treatment of acute bleeding was described in a few manuscripts or abstracts.

Hansenne & Hermans[13] reported the case of a 73-year-old man with several co-morbidities and chose to use emicizumab to stop bleeding after two unsuccessful approaches, first with RBC units and then with rFVIIa. There was no more bleeding nor any adverse event.

Al-Banaa et al.[14] described a 79-year-old man with multiple comorbidities (Table), including atrial fibrillation on anticoagulant treatment (apixaban 2.5 mg/bid), type 2 diabetes and rheumatoid arthritis. Admitted to hospital for acute muscle and skin bleeding with anemia, he was first treated with RBC and rFVIIa with no clinical response. After AHA was diagnosed (FVIII activity <1% and an inhibitor titer of 627 BU/ml), treatment with rpFVIII and corticosteroids was started. Bleeding stopped notwithstanding the development of inhibitory antibodies against porcine FVIII and allowed patient discharge. Two weeks later new hematomas appeared, and the inhibitor titer had raised to 749 BU/ml. Owing to a difficult intravenous access and a complex living situation during the Covid-19 pandemic, subcutaneous emicizumab was initiated as second-line strategy with the goal to first treat and then prevent bleeds (3.0 mg/kg/week for four weeks, followed by 3.0 mg/kg every two weeks). Bleeding stopped, but the patient experienced an asymptomatic acute non-occlusive proximal deep vein thrombosis in the left leg, that led to prescribe again the previously

stopped anticoagulant and reduce the dosage of the emicizumab maintenance regimen (1.5 mg/kg every two weeks).

Knoebl et al.[15] described a series of 12 cases (6 men and 6 women) with AHA and severe bleeding treated upfront with immunosuppressive therapies to eradicate the inhibitor (mean titer 22.3 BU/ml). Only 8 of them were treated upfront with bypassing agents, subsequently also administered to the four remaining cases. Due to insufficient clinical responses and poor control of bleeding, emicizumab was started in all cases with a loading dose of 3.0 mg/kg/week for four weeks, maintained with two or three additional doses and then followed by a dose reduction to 1.5 mg/kg for four weeks until plasma FVIII levels exceeded 10% following immunosuppression. Emicizumab was effective to stop bleeding in all cases. However, a 79-year-old female developed a minor stroke on day 16 after starting emicizumab during a concomitant treatment with rFVIIa (90 μg/kg) and a male patient died albeit for causes related to his pre-existing clinical conditions. A preliminary update of this case series extended to 20 patients were recently reported[16], confirming the previous findings.

The role of emicizumab as second line therapy of acute bleeding was also reported by Latef et al.[17]. They described the history of a middle-aged woman with HIV who, after being hospitalized multiple times for AHA unresponsive to the treatment of bleeding with bypassing agents, was started on emicizumab, with the combined goal of acute treatment of bleeding and

continuous prophylaxis. Bleeding stopped, the patient was no longer hospitalized during the next three years of follow-up and no adverse events were reported.

The case of a 21-year-old woman with a history of multi-site autoimmune disease was reported by Flommersfeld et al.[18]. Diagnosed in 2016 with AHA following uncontrolled bleeding after minor skin surgery she was immediately treated with rFVIIa. All subsequent immunosuppressive treatments failed to eradicate the autoantibody and, due to persistent bleeding, rFVIIa was continued. An attempt to induce immune tolerance with a combination of immunoadsorption, intravenous immunoglobulins, immunosuppression, and high-dose FVIII replacement was then carried out. However, due to the relapse of bleeding a new course of rFVIIa was started. Six months later the patient was started on prophylactic emicizumab at the conventional dosage indicated for congenital hemophilia. Bleeding resolved and no further treatment was necessary until a couple of months later bleeding occurred following a dental extraction and required treatment with rFVIIa for one week.

Hansenne & Hermans[13] reported the first-line use of emicizumab for the acute treatment of bleeding in a 93-year-old man with metastatic adenocarcinoma hospitalized with multiple hematomas due to AHA (FVIII 1%; FVIII inhibitors 11.0 BU/ml). On the day of admission, he was treated with methyl prednisone and emicizumab 3.0 mg/kg/week for four doses, followed by 3.0 mg/kg every two weeks totaling four additional

doses. No bleeding nor thromboembolic events were reported during follow-up.

Crossette-Thambiah[19] described three cases that occurred in the post-partum period after BNT162b2 (Pfizer) SARS-CoV-2 vaccination. Two of them had a complete response after treatment with by-passing agents and corticosteroids, but the third case was refractory to such multiple drugs as by-passing agents, rpFVIII, corticosteroids and azathioprine. Subcutaneous emicizumab 3.0 mg/kg weekly for four weeks followed by 3.0 mg/kg every two weeks was then started, bleeding stopped and during the next 10 months no thrombotic events were observed.

Happaerts & Vanassche[20] reported a case of AHA in a 75-year-old-man that occurred after Vaxzevria ChAdOx1-S Sars-CoV-2 vaccination with the concomitant relapse of bullous pemphigoid. A combined treatment with rFVIIa, rituximab, methylprednisolone and emicizumab 3.0 mg/kg/week for two doses was started with the goal to stop multiple hematomas and eradicate the autoantibody.

A series of 11 patients (5 males and 6 females) treated with emicizumab and rituximab was reported by Chen et al.[21]. Eight of them had bled in multiple sites and 6 were previously treated with rFVIIa, while in 5 emicizumab was immediately started as first line therapy. Bleeding was stopped and 8 cases achieved inhibitor eradication. During a median follow-up of 13.9 months only one patient bled but no thrombotic,

microangiopathic nor infectious complications were recorded.

- *Phase 3 clinical trial*

All the data so far reported stem from case reports or case series and emicizumab has been used off-label. Shima et al.3 recently presented the preliminary results of the first multicenter, single-arm, phase 3 clinical trial (AGEHA) carried out in Japan to investigate safety, efficacy, pharmacokinetics, and pharmacodynamics after the subcutaneous administration of emicizumab in AHA. Their early analysis involved 12 patients on unspecified immunosuppression who were prophylactically treated with emicizumab at 6.0 mg/kg on day 1 at 3.0 mg/kg on day 2 and then at 1.5 mg/kg/week from day 8 onwards. Emicizumab was discontinued when FVIII levels became higher than 50%. Overall, five bleeds occurred during prophylaxis but none of them was a major episode at variance with as many as 27 bleeds in the historical period before emicizumab. Furthermore, a patient experienced an asymptomatic deep vein thrombosis. Shima et al.[3] stated that these data suggest a favorable risk-benefit profile for emicizumab in AHA, but that additional data are warranted. Following the results of the AGEHA study, in June 2022 the Japanese Ministry of Health, Labor and Welfare chose to extend the approval of emicizumab to include its prophylactic use to prevent or reduce bleeding in patients with AHA, that is designated as an intractable disease in Japan. Noteworthy, the dosage

regimen employed (6 mg/kg on day 1, 3 mg/kg on day 2 and then 1.5 mg/kg weekly) is different from those used in congenital hemophilia A, perhaps with the goal to accelerate the achievement of a circulation steady state of the medication and thus an earlier clinical response[22].

Discussion

Our perusal of these reports indicates that short- or long-term prophylaxis aimed to prevent bleeding appears to be the main clinical situation for a favorable use of emicizumab in patients with AHA, because all reports, including AGEHA, demonstrated that this medication used at various dosage regimens was efficacious in the prevention of bleeding. To date, in patients with AHA there are no specific recommendations regarding the adoption of prophylaxis in order to prevent bleeding episodes at a time when immunosuppression has not yet restored plasma FVIII levels. However, a few reports did indicate that aPCC started soon after an acute bleeding episode managed to prevent recurrences[23,24]. At variance with the aPCC, the route of administration of emicizumab is subcutaneous, thus favoring prophylactic home treatment. Furthermore, the possibility of reaching a therapeutic steady state thanks to the achievement of a constant drug concentration in the circulation should be able to attain hemostatic competence in patients with AHA when endogenous FVIII activity is still low, and the risk of bleeding is looming large before immunosuppression is attained.

The use of emicizumab as second line of treatment of acute bleeds or as a rescue asset may be a therapeutic option in patients presenting with not yet eradicated FVIII inhibitor when they develop frequent and/or life-threatening bleeds. Overall, six cases using this monoclonal antibody as first therapeutic choice were identified in this review. Other drugs are authorized and largely used for the primary treatment of acute bleeding in AHA, i.e., FVIII bypassing agents and rpFVIII, because they are immediately able to stop bleeding with no need to wait until emicizumab becomes effective. Recombinant porcine FVIII has the additional advantage of being monitored in the laboratory by means of FVIII assays.

On the other hand, it must be pointed out that the conditions frequently associated with the occurrence of AHA, i.e., older age, pregnancy and puerperium and cancer, are characterized by an increased risk of thrombosis. Therefore, it is necessary to take this risk into consideration and personalize management with the most suitable and least risky approach. The high thromboembolic risk associated with the treatment of patients with AHA was previously highlighted by the EACH2 study[25], in which 4.8% of thromboembolic episodes developed among patients treated with aPCC and 2.9 % in those treated with rFVIIa, no thrombotic events being reported with the less frequently used rpFVIII[26,27]. During the pivotal and post marketing studies on emicizumab in congenital hemophilia A, thirteen confirmed episodes of arterial or venous thrombosis (VTE) and four of thrombotic microangiopathy (TMA) were described[28]. Six of them

(4 TMA; 2 VTE) occurred during the concomitant use of aPCC, and three after the application of intravascular devices. Furthermore, in the frame of the post-marketing surveillance of emicizumab implemented by the license holder, among a total of 56 thrombotic complications in more than 11.400 cases treated in 100 different countries 7 occurred in patients with AHA in the frame of the off-label use of emicizumab[29]. In the present review, despite the limited number of cases so far reported (totaling 73), three thromboembolic events (two DVT and a minor stroke) were described, and a patient died during treatment with emicizumab, albeit for causes apparently unrelated to the medication.

All in all, the message stemming from this review is a word of caution for clinicians who plan to employ emicizumab in AHAs, considering the high thrombosis risk in the most frequent categories of potentially treatable patients, i.e., older people and women during pregnancy and puerperium. Particular attention should also be paid to monitoring the patients endogenous FVIII levels3, because emicizumab should be discontinued to reduce the risk of thromboembolic events when, owing to successful immunosuppression, plasma levels exceed 50%. Despite the limited real-world data and the need for caution and careful monitoring of patients outlined in this review, emicizumab begins to play a role in the therapeutic setting of AHA, and the reasons for its choice are different, as summarized by Poston et al.[30]. In the USA-based experience, thirty-two hematologists responded to a questionnaire regarding their experience with the management of AHA. Overall, they had treated in the

last five years 358 patients, 40 of them with emicizumab, almost all as a second line choice. This medication was chosen for convenience of the subcutaneous administration route in comparison with other hemostatic agents given intravenously, insufficient response to them, desire to minimize the period of immunosuppression or failed immunosuppression.

Table 1. *Manuscripts and abstracts considered in this review, characteristics of 73 patients and their management. M: male; F: female; AHA: acquired hemophilia A; DVT: deep vein thrombosis; CS: corticosteroids; RTX: rituximab; VTE: venous thromboembolism; IG: intravenous immunoglobulin; rpFVIII: recombinant porcine factor VIII; rFVIIa: recombinant activated factor VII; aPCC: activated prothrombin complex concentrate; BPA: unspecified bypassing agents; AE: adverse events; FXIII: factor XIII; PCI: Percutaneous coronary intervention; CVD: cardiovascular disease; RBC: red blood cells; MGUS: monoclonal gammopathy of undetermined significance; HIV: human immunodeficiency virus; ITI: immune tolerance induction; INH: inhibitor.*

Reference	Patient	Co-morbidities	Emicizumab (dosage/timing)	Immunosuppression	Previous treatments	Outcomes
Shima et al., 2022 (3) Phase 3 study	12 pts	No information	6 mg/kg (day 1), 3 mg/kg (day 2) + 1.5 mg/kg/wk (from day 8 onwards)	Yes, not specified	None	10/12 bleeding stopped, no AE 1 DVT 5 minor bleeds in 2 pts
Möhnle et al., 2019 (5)	1 M, 83 yrs	Heart failure, atrial fibrillation, chronic kidney disease, previous VTE events	3.0 mg/kg (one dose) + 1.5 mg/kg for two doses (day 7 and day 20 after the first dose)	CS, RTX, IG	rpFVIII, rFVIIa PCC, FXIII concentrate, Fibrinogen	Bleeding stopped after emicizumab, no AE.
Al-Banaa et al., 2019 (6)	1 F, 87 yrs	Atrial fibrillation	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk (at least two months)	No information	aPCC	Bleeding stopped, no AE
Hess et al., 2020 (7)	1 M, 91 yrs	Atrial fibrillation, mitral valve stenosis, prostate hypertrophy	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/2wk (at least six months)	CS, cyclosporine	rFVIIa	Bleeding stopped, no AE
Dane et al., 2019 (8)	1 M, 72 yrs	Bullous pemphigoid, coronary artery disease, PCI	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk (five months)	Multiple immunosuppressive medications	aPCC, rpFVIII	Bleeding stopped, no AE, Second PCI
Chen et al., 2021 (9)	3 M, 1 F (mean age 66 yrs)	Multiple comorbidities (CVD, diabetes, MGUS, dementia)	3.0 mg/kg/wk (4 wks) + 1.5 mg/kg/wk (mean 22 doses)	RTX (all patients) + CS (1 M patient) + cyclophosphamide (1 M patient and 1 F patient)	rpFVIII (all patients) + rFVIIa (1 F patient)	Bleeding stopped, no AE
Yates et al., 2022 (10)	1 M 83 yrs	Atrial fibrillation, low grade lymphoproliferative disorder	Not specified	CS, cyclophosphamide, RTX	rFVIIa aPCC	Bleeding stopped (multiple RBC transfusions), no AE
Escobar et al., 2020 (11)	1 M, 90 yrs 1 F, 57 yrs	Multiple co-morbidities	M (Texas protocol): 1.5 mg/kg/wk (two doses) + 1.5mg/kg/wk (21 days) F (standard protocol): 3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk	Not available	No information	Bleeding stopped, no AE
Gelbenegger et al., 2022 (12)	1 M, 75 yrs	Covid-19, hypertension, hyperlipidemia and an infrarenal aortic aneurysm. Previous STEMI	3.0 mg/kg/wk (3 wks) + 1.5 mg/kg every 2–4 weeks until complete remission	CS	rFVIIa	Bleeding stopped, no AE
Hansenne & Hermans 2021 (13)	1 M 73 yrs 1 M 93 yrs	Gout, hypertension, prostate cancer	3.0 mg/kg/wk + 6.0 mg/kg once 3.0 mg/kg/wk (4 doses) + 3.0 mg/kg/2wk (4 doses)	CS, cyclophosphamide, RTX	rFVIIa	Bleeding stopped, no AE
Al-Banaa et al., 2021 (14)	1 M 79 yrs	Rheumatoid arthritis, diabetes	3.0 mg/kg/wk (4 wks) + 3.0 mg/kg/2wk 1.5mg/kg/2wk (reduced after DVT)	CS	rpFVIII	Bleeding stopped, an asymptomatic DVT
Knöbl et al., 2021 (15)	6 M, 6 F (median 74 yrs)	Multiple co-morbidities (cancer, neurological disorders, gastrointestinal diseases, etc.)	3.0 mg/kg/wk (2-3 doses) + 1.5 mg/kg/3wk	10/12 CS, 12/12 RTX, 1/12 cyclophosphamide	rFVIIa	Bleeding stopped, a minor stroke during emicizumab with concomitant rFVIIa. One death
Knöbl et al., 2022 (16)	20 pts (11 M, 9 F) (median age 79 yrs)	No information	3 mg/kg/wk (4 wks) + 1.5 mg/kg/2-4 wks intervals	CS, RTX	rFVIIa	Bleeding stopped, no AE
Latef et al., 2022 (17)	1 F, middle-age	HIV	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk	CS, cyclophosphamide	BPA (AHA refractory)	Bleeding stopped, no AE
Flommersfeld et al., 2019 (18)	1 F 21 yrs	Multi-site autoimmune disease	3.0 mg/kg/wk (4 wks) + 1.5 mg/kg/wk	CS, cyclophosphamide, monoclonal antibodies	rFVIIa ITI	Bleeding initially stopped, no AE. Bleeding after dental extraction
Crossette-Thambiah et al., 2022 (19)	1 F	Post-partum, Sars-Cov2 vaccination	3.0 mg/kg/wk (4 wks) + 3.0 mg/kg/2 wks	CS, azathioprine	rpFVIII, BPA	Bleeding stopped, no AE
Happaerts & Vanassche, 2022 (20)	1 M 75 yrs	Bullous pemphigoid, Sars-Cov-2 vaccination	3.0 mg/kg two doses	CS, RTX	rFVIIa (concomitant)	Bleeding stopped, no AE
Chen et al., 2022 (21)	11 pts (5 M, 6 F) (median age 77 yrs	Multiple concomitant diseases	3.0 mg/kg/ week (4 weeks)	RTX	6 rFVIIa	Bleeding stopped, no AE One bleeding relapse

References

1. Holstein K, Albisetti M, Bidlingmaier C, et al; 'Ständige Kommission Hämophilie' (Haemophilia board) of the German, Swiss Austrian Society for Thrombosis Haemostasis Research (GTH). Practical Guidance of the GTH Haemophilia Board on the Use of Emicizumab in Patients with Haemophilia A. Hamostaseologie 2020 Dec; 40 (5): 561-71
2. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017; 92: 695-705
3. Shima M, Amano K, Ogawa Y, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in patients with acquired hemophilia A: primary analysis results from a phase III study (AGEHA). Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2022: London, UK; OC 40.2
4. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009 Jul 21; 339: b2535
5. Möhnle P, Pekrul I, Spannagl M, et al. Emicizumab in the treatment of acquired haemophilia: a case report. Transfus Med Hemother 2019 Apr; 46 (2): 121-3
6. Al-Banaa K, Alhillan A, Hawa F, et al. Emicizumab use in treatment of acquired hemophilia A: a case report. Am J Case Rep 2019 Jul 18; 20:1046-8
7. Hess KJ, Patel P, Joshi AM, Kotkiewicz A. Utilization of emicizumab in acquired factor VIII deficiency. Am J Case Rep. 2020 May 7; 21: e922326
8. Dane KE, Lindsley JP, Streiff MB, et al. Successful use of emicizumab in a patient with refractory acquired hemophilia A and acute coronary syndrome requiring percutaneous coronary intervention. Res Pract Thromb Haemost. 2019 Apr 9; 3 (3): 420-3
9. Chen SL, Ellsworth P, Kasthuri RS, et al. Emicizumab reduces re-hospitalization for bleeding in acquired haemophilia A. Haemophilia 2021 Jul; 27 (4): e585-8

10. Yates SG, Webb CB, Sarode R, et al. Utilization of emicizumab in acquired hemophilia A: A case report. TransfusApher Sci 2022 May; 11:103457
11. Escobar M, Aboshady I, Montanez N. Prophylactic potential of standard and modified emicizumab prophylaxis in 2 patients with acquired hemophilia: a case report. Proceedings of the 28th Virtual Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2020: Milan, Italy; PB0791
12. Gelbenegger G, Traby L, Rahimi N, Knöbl P. Management of acquired haemophilia A in severe Covid-19: Haemostatic bridging with emicizumab to keep the balance between bleeding and thrombosis. J Clin Pharmacol 2022 Nov 11 [Online ahead of print].
13. Hansenne A, Hermans C. Emicizumab in acquired haemophilia A: about two clinical cases and literature review. Ther Adv Hematol 2021 Aug 28; 12: 20406207211038193
14. Al-Banaa K, Gallastegui-Crestani N, von Drygalski A. Anticoagulation for stroke prevention after restoration of haemostasis with emicizumab in acquired haemophilia A. Eur J Case Rep Intern Med 2021 Nov 11; 8 (11): 002984
15. Knoebl P, Thaler J, Jilma P, et al. Emicizumab for the treatment of acquired hemophilia A. Blood 2021 Jan 21; 137 (3): 410-9
16. Knoebl P, Thaler J, Jilma P, et al. Emicizumab for the treatment of acquired hemophilia A: an update of the Vienna experience. Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2022: London, UK; PB0002
17. Latef TJ, Bhardwaj P, Bilal M. Refractory acquired haemophilia A in a patient with HIV treated with emicizumab. Blood Coagul Fibrinolysis 2022 Mar 1; 33 (2): 138-40
18. Flommersfeld S, Slonka J, Bieberle I, et al. Successful control of bleeding with emicizumab in aquiredhaemophilia A: a case report [abstract]. Proceedings of the 63rd Annual Meeting of the Society

of Thrombosis and Haemostasis Research (GTH); 2019: Berlin, GER; P01-1
19. Crossette-Thambiah C, Arachchillage D, Laffan M. Post-partum acquired haemophilia A in the COVID era – building the case for emicizumab? Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2022: London, UK; PB0007
20. Happaerts M, Vanassche T. Acquired hemophilia following COVID-19 vaccination: Case report and review of literature. Res PractThrombHaemost 2022 Sep 9; 6 (6): e12785
21. Chen EC, Gibson W, Temoczko P, et al. Emicizumab for the treatment of acquired hemophilia A: Retrospective review of a single-institution experience. Haemophilia. 2022 Sep 26. doi: 10.1111/hae.14664. [Online ahead of print]
22. Nishiki H, Suzuki N, Kobayashi R et al. Efficacy and Safety of Emicizumab Prophylaxis in Patients with Acquired Hemophilia a Who Were Deemed Ineligible for Immunosuppressive Therapy: Additional Data from the Ageha Study. Proceedings of the 64th Congress of the American Society of Hematology; 2022: New Orleans, USA: American Society of Hematology, OC1153
23. Árokszállási A, Rázsó K, Ilonczai P, et al. A decade-long clinical experience on the prophylactic use of activated prothrombin complex concentrate in acquired haemophilia A: a case series from a tertiary care centre. Blood Coagul Fibrinolysis 2018 Apr; 29 (3): 282-7
24. Zanon E, Pasca S, Siragusa S, et al. Low dose of aPCC after the initial treatment in acquired haemophilia A is useful to reduce bleeding relapses: Data from the FAIR registry. Thromb Res 2019 Feb; 174: 24-6
25. Knoebl P, Marco P, Baudo F et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J ThrombHaemost2012; 10: 622–31

26. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant) porcine sequence in subjects with acquired haemophilia A. Haemophilia 2015; 21: 162–70
27. Zanon E, Pasca S, Borchiellini A, et al. Susoctocog-alfa (Obizur ®) in the treatment of nine elderly patients with acquired haemophilia A: an Italian multicentre real-world experience. Blood Transfus 2020 Jul; 18 (4): 312-21
28. Lee L, Moreno K, Kuebler P, et al. Summary of thrombotic or thrombotic microangiopathy events in persons with hemophilia A taking emicizumab. Proceedings of the National Hemophilia Foundation (NHF) Bleeding Disorders Virtual Conference 2020: Atlanta, USA; PB003
29. Howard M, McKinley D, Sanabria F, et al. Evaluation of the Safety of Emicizumab Prophylaxis in Persons with Hemophilia A: An Updated Summary of Thrombotic Events and Thrombotic Microangiopathies [abstract]. Blood 2021; 138 (Suppl 1): 3186.
30. Poston J, Kruse-Jarres. The use of emicizumab for acquired hemophilia A at US hemophilia treatment centers. Proceedings of the 29th Congress of the International Society on Thrombosis and Haemostasis (ISTH); 2021: Philadelphia, USA; PB0431

CHAPTER 10

Summary and general discussion

Acquired hemophilia A (AHA) is a rare, autoimmune bleeding disease characterized by a deficiency of coagulation FVIII secondary to autoantibodies directed against specific epitopes, which cause the accelerated neutralization and clearance of FVIII from plasma. AHA is extremely rare in children, presents a first peak in young women during pregnancy or puerperium, and becomes significantly more frequent in elderly people after 65 years old. AHA is a serious disease not only due to the incidence of severe bleeding, but also due to the high mortality, estimated to exceed 20% in older patients with other comorbidities.

In almost half of the cases the cause of AHA is idiopathic, while in the remaining 50% it is attributable to underlying diseases or clinical conditions, the main ones of which are shown in Table 1.

DISEASES OR CLINICAL CONDITIONS	CHARACTERISTICS
Oncologic diseases	Multiple myeloma, lymphomas, monoclonal gammopathy of uncertain significance (MGUS), myelofibrosis, myelodysplasia.
Rheumatic diseases	Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's Syndrome, Goodpasture's Syndrome, Temporal

	Arteritis, Myasthenia Gravis, Thyroiditis, Multiple Sclerosis
Dermatological diseases	Psoriasis, pemphigus
Pregnancy or Puerperium	Within 1-4 months of delivery or miscarriage
Drugs	Some beta-lactam antibiotics, chloramphenicol, sulfonamides, clopidogrel, nonsteroidal anti-inflammatories (NSAIDs), fludarabine, interferon alpha
Other Diseases	Asthma, chronic obstructive pulmonary disease, acute hepatitis

***Table 1**. Diseases and clinical conditions associated to AHA (adapted from AICE Recommendations 2020)*

Typical onset manifestations of AHA, present in over 70% of cases, are large muscle and skin hematomas which generally affect the lower and upper limbs and the trunk, and which can cause severe anemization and/or compression of vessels and nerves (compartment syndrome). Other hemorrhagic manifestations may occur in the soft tissues, in the genitourinary tract or in the mucous membranes. Unlike congenital hemophilia, hemarthrosis or the feared intracranial hemorrhages are very rare.

An important role in the timely diagnosis of AHA is played by the laboratory (Figure 1) which must be able to exclude the presence of heparin, of other anticoagulant drugs (e.g. DOACs) and of Lupus Anticoagulant (LA), all associated to lengthening of the aPTT. The mix test, easily performed in most laboratories, aids in rapid diagnosis.

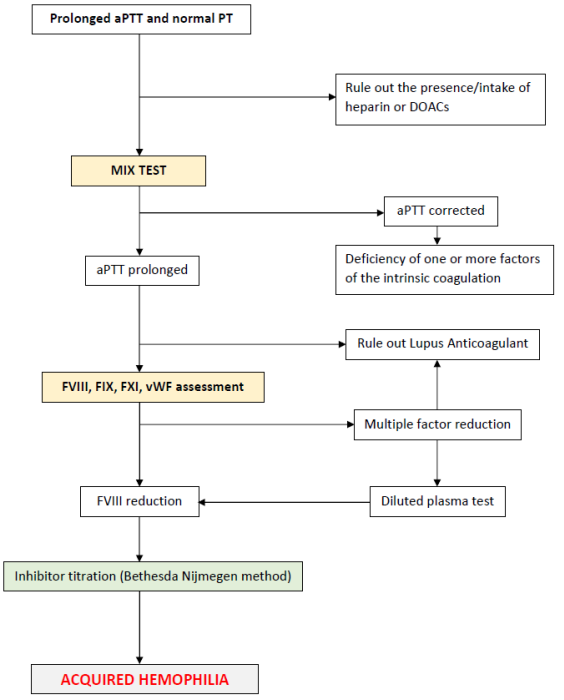

Figure 1. *Algorithm for the laboratory diagnosis of AHA (adapted from AICE Recommendations 2020)*

The management of a patient with AHA is complex, therefore it requires an in-depth knowledge of the disease, the most appropriate treatments and short- and long-term follow-ups. To help clinicians, there are precise algorithms that describe a differentiated clinical-diagnostic path for the hemophilia treatment centers (Figure 2), used to managing people with congenital and/or acquired bleeding disorders, and for peripheral hospitals (Figure 3) less accustomed to dealing with such emergencies.

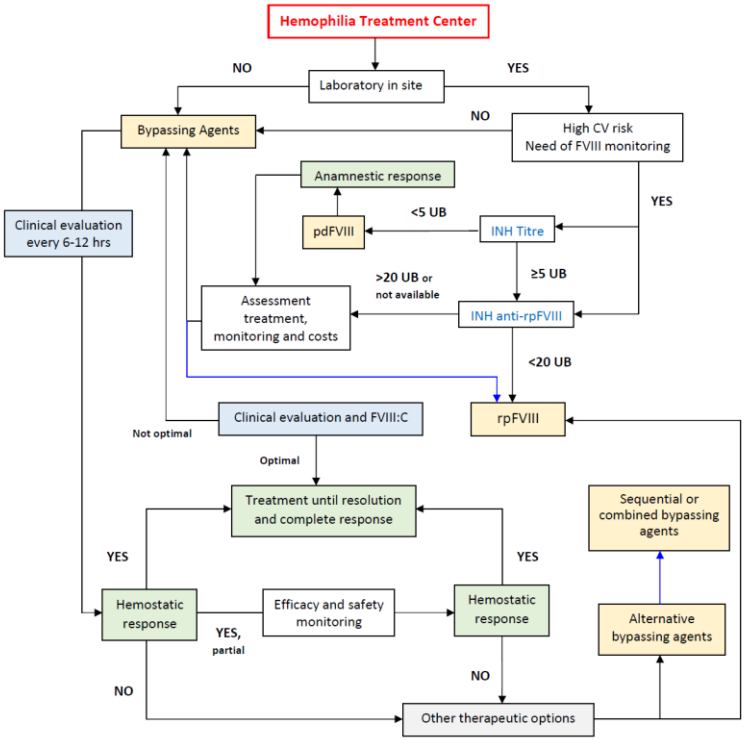

Figure 2. *Algorithm for AHA management at Hemophilia Treatment Centers (adapted from AICE Recommendations 2020)*

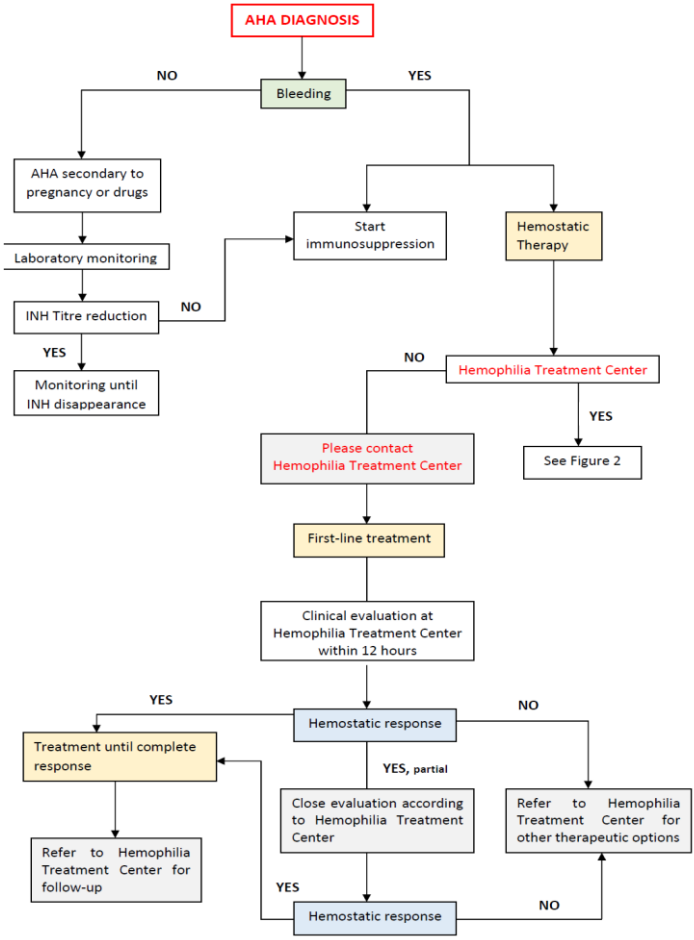

Figure 3. *Algorithm for AHA management at different hospitals (adapted from AICE Recommendations 2020)*

National and international guidelines recommend intervening as soon as possible to resolve bleeding and to eradicate inhibitors. Nowadays there are several possibilities of anti-hemorrhagic treatment, illustrated here in Table 2, while the immunosuppressive therapy is represented by corticosteroids alone, corticosteroids associated to cyclophosphamide or, in case of fail of these drugs, rituximab.

TREATMENTS	DOSAGE	ADVANTAGES	DISADVANTAGES
rpFVIII (Obizur®)	Initial dose of 200 IU/Kg, subsequent doses based on clinical response and FVIII levels (performed 30' and 3 hours after infusion) to be maintained depending on the type of hemorrhage, usually infusions every 4-12 hours	Easy monitoring and efficacy	Possible anti-rpFVIII development; not available in some hospitals; high costs, needing laboratory h.24.
rFVIIa (NovoSeven®)	90-120 µg/Kg every 2-3 hours until achieving secure hemostasis, then at longer intervals	Easily available in all hospitals; efficacy; small infusion volume	No validated monitoring; risk of events arterial or venous thrombosis; short half-life (2-3 hours)
aPCC (Feiba®)	50-100 IU/Kg every 8-12h. Do	Easily available in all hospitals;	No validated monitoring; risk

	not exceed 200 IU/ kg /day	efficacy	of events arterial or venous thrombosis; high volume of infusion
pdFVIII or pdFVIII/vWF	Variable based on bleeding severity, inhibitor titer, infusion mode (single boluses or continuous infusion)	Easily available in all hospitals; efficacy (especially in case of low-titer inhibitors); easy monitoring	Possible anamnestic response; need for high doses; daily laboratory control

Table 2 *Different treatments for AHA, dosage, advantages, and disadvantages (adapted from AICE Recommendations 2020)*

Patients with AHA often remain hospitalized for a long time, usually in internal medicine wards, requiring many treatments, those specific to this bleeding disorder, but also those necessary to cure their underlying diseases, sometimes very complex therapies consisting of biological drugs, such as for example belimumab for the treatment of lupus, enteracept for rheumatoid arthritis or imanitib for some forms of leukemia. Clinicians must therefore be constantly trained in order to better manage these patients. Periodic training meetings, managed by experts from hemophilia centers, would be necessary to ensure peripheral hospital staff have minimal skills in managing the AHA. Medical and graduate schools should also include the AHA in their courses in order to provide students and young doctors with the basics so that they are not unprepared if they are faced with one of these cases.

The main goal that we set ourselves in the study presented in **Chapter 2** was to evaluate whether plasma-derived products could still have a role in the treatment of AHA and possibly highlight which patients could benefit from this therapy. Two different groups of patients with different inhibitor titers were treated with pdFVIII, with and without von Willebrand factor (vWF), in an immunotolerance regimen or in continuous infusion. Some patients also had underlying diseases at high thromboembolic risk which made treatment with bypassing agents more critical. All treatments resulted ineffective stopping of bleeding, but the duration was markedly shorter in the case of pdFVIII/vWF used in continuous infusion, similar to that obtained with bypassing agents or with rpFVIII. Conversely to what is recommended in international guidelines[1,2], plasma-derived concentrates were also effective in patients who already had a high titer of inhibitors at the onset of AHA. This may therefore be a valid therapeutic option in many patients, especially when first-line drugs for the management of AHA are lacking.

The efficacy and safety of aPCC in the acute treatment of AHA is the subject of **Chapter 3**. The FAIR study is a multicenter Italian study involving 12 hemophilia centers, the data collection covered a period of 10 years and a total of data from 56 patients were collected. The aPCC was used as first-line therapy in 82.2% of subjects, while it was effective in 96.4% of cases, the latter data being consistent with that reported in the EACH2[3,4], but unlike what is reported in this registry, in

the FAIR study no patient experienced side effects using this drug.

The efficacy of a new recombinant B-domain deleted porcine FVIII (rpFVIII)was proven in the OBI-1 Study[5], in which the positive response to treatment was achieved in all enrolled patients within 24 hours from the first dose. This drug was then licensed in Italy in 2016. The real-world use of susoctocog-alfa in the treatment of patients with AHA was described in **Chapter 4**. Nine different cases were described, 88.9% were males, mean age 78.7 years. 44.4% were idiopathic AHAs. Seven patients presented muscular bleeding, one intracranial hemorrhage and the remaining hematuria with concomitant knee hemarthrosis. Seven patients also presented concomitant diseases, among these 71.4% were cardiovascular. Susoctocog-alfa as first line therapy was used in one third of cases. In contrast to the recommended loading dose of 200.0 IU/kg[5], the median loading dose used in this study was 100.0 IU/kg; median subsequent doses were 50 IU/kg with a median frequency of 12 hours and with a median number of doses of 8, data similar to those reported in other studies[6,7]. Treatment was continued for a median of 4 days (IQR 1-32).The inhibitor against rpFVIII was not tested before treatment with susoctocog-alfa, only two patients developed a low titer rpFVIII-inhibitor. rpFVIII was considered effective and safe in all cases and was associated with antifibrinolytics in 22.2% of cases.

The concomitant use of antifibrinolytics and aPCC were detailed and discussed in **Chapter 5**. Antifibrinolytic

drugs exert their action inhibiting activation of plasminogen and reducing the plasminogen conversion to plasmin. Headache, abdominal pain, backache, and diarrhea are common side effects of these drugs, while pulmonary embolism or deep vein thrombosis are rare. Despite this, the association with another drug that acts on the coagulation cascade can greatly increase the thromboembolic risk. This leads clinicians to use caution in combining aPCC and antifibrinolytics, especially in the case of patients with AHA. Only rare reports are in fact available in literature[8]. In the detailed sub-analysis of the FAIR study 40/101 acute bleeds were overall treated with a combined use of aPCC and antifibrinolytics; there were 19/35 bleeds in the prospective group and 21/66 in the retrospective one, showing a statistically significant difference ($p<0.05$). In 35 patients in whom the combined treatment was used, two of them had a previous ischemic stroke, while other one had a history of myocardial infarction. In these subjects, the treatment duration was reduced (mean reduction 16.3%) up to a median of 7 days (IQR 1-48). Good tolerance to combined therapy and no thromboembolic events were reported during the study, also in subjects with severe cardiovascular diseases, suggesting that the combined use of aPCC and antifibrinolytics has a reasonable safety.

In **Chapter 6** we reported the case of a 71-year-old-man, who presented with spontaneous hematomas and severe anemia, and had a medical history of thromboendoarterectomy of the left carotid artery; aorto-iliac by-pass; acute myocardial infarction with consequent coronary artery by-pass graft (CABG) and

vascular cervical myelopathy with sensory and motor deficit in the right lower limb. He did not have a personal or family history of inherited coagulation disorders or autoimmune diseases. Idiopathic AHA was diagnosed at admission to hospital needing an immediate treatment to solve bleeding. At the time of this case report, only bypassing agents were available for the treatment of AHA, but their use in this subject with severe cardiovascular disease was risky. Despite the high titer of the inhibitor (28 BU/ml) and the lack of recommendations[1,2], we still decided to use pdFVIII/vWF in combination with corticosteroids. The bleeding resolved and one month after the start of treatment the FVIII plasma level returned to normal, and the inhibitor disappeared. No relapses occurred in the following months. This treatment has therefore proved to be a valid therapeutic alternative in a very complex patient.

In **Chapter 7** the attention is focused on the case of an elderly patient with many comorbidities including bilateral breast cancer and rheumatoid arthritis, who presents in hospital for acute myocardial infarction, severe anemia (5.7 g/dl) and extensive mucocutaneous hematomas. After the first emergency treatments for the ischemic heart disease, the patient was transfused with packed red blood cells to restore the hemoglobin level, and subsequently an AHA was diagnosed. The patient was immediately treated with cyclophosphamide/corticosteroids and a bolus of rpFVIII 100IU/Kg, followed by rpFVIII 50IU/Kg/tid; the bleeding resolved within 72h. One month later the patient had to undergo an emergency cholecystectomy

under cover with susoctocog-alfa 50IU/Kg/tid, without any complications. This was the first real-world case reported in the literature of an AHA patient undergoing surgery under rpFVIII coverage, while only few cases of subjects with congenital hemophilia A and inhibitors were available[9,10].

One of the major problems in managing the patient with AHA is the risk of relapse, which is around 20% of treated cases[4] and is more likely within a month of resolution of the first episode. The use of low-dose aPCC as post-acute treatment prophylaxis is the topic of **Chapter 8**. The efficacy of this prophylactic regimen had already been described in a previous Italian study[11]for a small number of patients, now the larger FAIR study has confirmed these results. Only three of the thirty-two total relapses occurred in the group of patients treated in prophylaxis with aPCC. However, further studies would be necessary to better define the most appropriate dosage of aPCC to be used and the duration of treatment.

A possible new therapeutic option for the treatment of AHA may derive from the use of emicizumab, a bispecific monoclonal antibody that mimics the action of FVIII, currently approved only for the treatment of hemophilia A with or without inhibitors[12,13]. In **Chapter 9** we reviewed the available literature regarding the use of emicizumab in AHA. From the analysis it clearly emerges that this drug finds its best use in short and long-term prophylaxis, the efficacy in preventing further bleeding has in fact emerged in all the publications analyzed. Given the need for a period of at least four

weeks to reach steady state and full efficacy, emicizumab is not widely indicated as first-line treatment of the acute event.

Furthermore, the level of FVIII must be constantly monitored in patients with AHA treated with emicizumab, in fact when it exceeds 50% the risk of thromboembolic events significantly increases.

In conclusion, with this thesis we wanted to underline the importance of not underestimating a disease such as acquired hemophilia, which is still today the cause of high mortality and, at the same time, we wanted to make an overview of the treatments currently available or under study.

References

1. Franchini M, Castaman G, Coppola A, et al;and the AICE Working Group. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. Blood Transfus. 2015 Jul;13(3):498-513
2. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol 2017; 92: 695-705
3. Knoebl P., Marco P., Baudo F., et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Journal of Thrombosis and Haemostasis 2012; 10: 622–31
4. Baudo F., Collins P., Huth-Kühne A., Lévesque H., Marco P., Nemes L., Pellegrini F., Tengborn L., Knoebl P.; EACH2 Registry Contributors. Management of bleeding in acquired hemophilia results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012; 120: 39–46
5. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine

sequence, in subjects with acquired haemophilia A. Haemophilia 2015; 21: 162-70
6. Tarantino M, Cuker A, Hardesty B, et al. Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients. Haemophilia 2017; 23: 25-32
7. Martin K, Kasthuri R, Mooberry MJ, et al. Lower doses of recombinant porcine factor VIII maintain excellent haemostatic efficacy. Haemophilia 2016; 22: e549-51
8. Holmström M, tran HT, Holme PA. Combined treatment with aPCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patient with acquired haemophilia A—a two-centre experience. Haemophilia 2012 Jul; 18 (4): 544-9
9. Ruan GJ, Mao JJ, Sytsma TT, et al. Continuous infusion of recombinant porcine factor VIII for neurosurgical management of intracranial haemorrhage in a patient with severe haemophilia A with factor VIII inhibitor. Haemophilia 2020 May; 26 (3): e141-4
10. Croteau SE, Abajas YL, Wolberg AS, et al. Recombinant porcine factor VIII for high-risk surgery in paediatric congenital haemophilia A with high-titre inhibitor. Haemophilia2017 Mar; 23 (2): e93-8
11. Zanon E, Milan M, Gamba G et al. Activated prothrombin complex concentrate (FEIBA®) for the treatment and prevention of bleeding in patients with acquired haemophilia: A sequential study. Thromb Res, 2015 Dec; 136 (6): 1299-302
12. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med 2017 Aug 31; 377 (9): 809-18
13. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med 2018 Aug 30; 379 (9): 811-22

Impact Paragraph

Acquired hemophilia is a rare autoimmune disease whose incidence is inexorably destined to increase over the years.

The average age of the population has grown from around 50 years in the 1950s to 74 years today and is still growing. This leads to an increase of an elderly population often affected by numerous comorbidities, including those form the cardiovascular tract, such as atrial fibrillation and heart failure, pulmonary system, such as chronic bronchitis and asthma, autoimmune disorders such as rheumatoid arthritis, or oncological diseases, all requiring pharmacological care and treatments. Underlying diseases and drugs account for 50% of non-idiopathic AHA cases, while age over 65 years appears to be another risk factor for developing this bleeding disorder.

These patients who present to the hospital with extensive hematomas and anemia are subjects without a family or personal bleeding history, therefore the diagnosis of AHA becomes difficult and may be delayed for many days, causing a similar delay in starting the necessary treatments. Other reasons for such delay are comorbidities and/or the use of antithrombotic medication. Unlike what happens in the case of congenital hemorrhagic diseases, where well-identified patients are immediately referred to specific treatment centers for acute and prophylactic therapies, in case of acquired hemophilia, patients after a first visit to an emergency room, are hospitalized in general internal medicine departments where clinicians are not always able to recognize this autoimmune hemorrhagic disorder

in time. Given the potentially life-threatening consequences of delayed diagnosis and treatment, the impact of timely management has substantial impact. The guidelines therefore recommend prompt intervention to stop bleeding and eradicate inhibitor.

It is therefore necessary to train these specialists who can be the first to meet subjects affected by AHA to immediately understand the signs and symptoms of the disease and to immediately request those laboratory tests that can help to correctly frame the patient.

In the case of AHA, the severity of the bleeding does not always correlate with the level of FVIII present in the circulation and with the inhibitor titer, so it is necessary to subject the patient to periodic checks over a long period of time.

Patients with AHA should be monitored after discharge to prevent relapse, but these follow-ups should preferably be performed at hemophilia centers where the laboratory is able to evaluate both plasma coagulation FVIII and inhibitor titers, while doctors are able to promptly intervene in case of need.

Today there are several first-line drugs for the treatment of AHA such as rFVIIa, aPCC and rpFVIII, but often these are only available in large hospitals where there is a congenital hemophilia treatment center, while in smaller peripheral hospitals these expensive products are not always available, or if they are, it occurs with a certain delay, after a specific purchase request.

Given these difficulties and given the costs associated with treatment, clinicians must nevertheless be informed

that the use of plasma-derived concentrates can also be effective in stopping acute. They must know which are the most suitable drugs for this type of therapy and the method of administration. The cost of treatment with different anti-hemostatic drugs to solve the acute AHA bleeding in Italy is reported in table 1. The example is based on a man/woman, weight 70 kg, needing a treatment for seven days. Mean IU or mg were derived from published studies and registries.

	Cost (€)/IU (or mg)	IU (or mg)/Kg/week	Treatment Cost (€)
rpFVIII (Obizur®)	3.882	56,000	217,392
rFVIIa (NovoSeven®)	971.2	353	342,833
aPCC (Feiba®)	1.224	73,500	89,964
*pdFVIII or pdFVIII/vWF	0.771	60,000	46,260

* Continuous infusion

In the future, especially for the prophylactic treatment necessary to prevent dangerous relapses, estimated at around 20% of cases after the first acute episode, there may be more often a place for emicizumab, which is a bispecific monoclonal antibody that has been quite

successfully applied in congenital hemophilia. However, it is not an easy-to-manage drug; its interference with some laboratory tests, the need for a loading dose to achieve full efficacy, the associated thromboembolic risk, especially when plasma FVIII levels tend to rise, suggest the use of this drug should be confined to experts in the treatment of congenital hemophilia, who can best oversee the advantages and disadvantages of emicizumab.

Information and training are therefore the basis of the treatment of acquired hemophilia, necessary so that this disease is increasingly easily recognized and correctly managed, which may reduce related mortality to zero.

Curriculum Vitae

Samantha Pasca is native to Forni di Sopra (Udine), a small town nestled in the Dolomites of Friuli Venezia Giulia, a north-eastern region of Italy. She obtained her master's degree in biology, Molecular Biology curriculum, at the end of the 90's at the University of Trieste (Italy). She then began her post-graduate internship at the Laboratory of Molecular Biology and Viral Research, Transfusion Medicine Unit of the University Hospital of Udine (Italy), and subsequently moved to the Department for Bone Marrow Transplantation, where she collaborated with the Hematology Clinic of the same hospital.

In 2009 she began to deal with coagulation diseases at the Hemorrhagic and Thrombotic Diseases Center in Udine (Italy), initially as study coordinator of the pivotal trials on direct-acting oral anticoagulants. She then earned her Medical Degree at the University of Udine (Italy), which allowed her to begin her clinical activity. From September 2016 she moved to the Hemophilia Center of the Padua University Hospital (Italy), where in addition to clinical activity, she collaborated in the drafting and management of several national and international clinical studies on patients suffering from acquired and congenital hemorrhagic diseases. She was awarded a PhD in Clinical and Experimental Sciences, curriculum Hematological and Geriatric Sciences, at the University of Padua, while completing her specialization in Clinical Pathology and Clinical Biochemistry at the same University. She has also spent a few months as a visiting doctor at the

Hemophilia and Thrombosis Center “Angelo Bianchi Bonomi”, Fondazione IRCSS Ca’ Granda Ospedale Maggiore Policlinico of Milan (Italy).

The clinical studies carried out over the years and all the research activities have resulted in over a hundred of manuscripts and about seventy abstracts, all published in scientific peer-reviewed international journals.

List of published manuscripts

1. Pasca S, Zanon E, Mannucci PM, Peyvandi F. Emicizumab in acquired hemophilia A: pros and cons of a new approach to the prevention and treatment of bleeding. Accepted Blood Transf, December 2022.
2. Pasca S, Linari S, Tagliaferri A, Santoro C, Zanon E; for the EMO.REC study group. Very high risk of intracranial hemorrhage in adult mild hemophilia patients and severe outcomes: sub-analysis of the EMO.REC Registry. Tromb Res, October 2022.
3. Pasca S.Concizumab as a subcutaneous prophylactic treatment option for patients with hemophilia A or B: a review of the evidence and patient's perspectives. J Blood Med 2022 Apr 16; 13:191-199
4. Pasca S, Linari S, Tagliaferri A, et al. Very high risk of intracranial hemorrhage in adult mild hemophilia patients and severe outcomes: sub-analysis of the EMO.REC Registry. Submitted Thromb Res, Sep 2022.
5. Gualtierotti R, Pasca S, Ciavarella A, et al.Updates on Novel Non-Replacement Drugs for Hemophilia Pharmaceuticals 2022; 15 (10): 1183
6. Di Minno MND, Napolitano M, Giuffrida AC, et al. Diagnosis and treatment of chronic synovitis in patients with haemophilia: consensus statements from the Italian Association of Haemophilia Centres. Br J Haematol 2022 Feb;196 (4): 871-83
7. Pasca S, Fasolato S, Polese L, Zanon E A woman hemophilia carrier with life-threatening esophageal varices and a severe hemophiliac male: a comparison between two different case reports and a brief description of literature. J J Gastro, Vol.2 April 2022
8. Zanon E, Pasca S, Demartis F., et al. Intracranial haemorrhage in haemophilia patients is still an open issue: the final results of 10-yr Italian (AICE) EMO.REC Registry.J Clin Med 2022 Apr 1; 11 (7):1969
9. Zanon E, Pasca S, Sottilotta G., et al A multicenter, real-world experience with recombinant FXIII for the treatment of patients with FXIII deficiency: from pharmacokinetics to clinics – The Italian FXIII Study. Blood Transf, October 2022
10. Cortesi PA, Di Minno G, Zanon E, et al. Real-world clinical outcomes and replacement factor VIII consumption in patients with

haemophilia A in Italy: a comparison between prophylaxis pre and post Octocog alfa (Kovaltry®). J Clin Med 2022 Jun 15; 11 (12): 3434
11. Pasca S, Zanon E. Albumin-fusion recombinant FIX in the management of people with hemophilia B: an evidence-based review. Pasca Submitted Drug Des Devel Ther, 2022 Sep 15; 16: 3109-16
12. Boccalandro EA, Begnozzi V, Garofalo S, Pasca S, Peyvandi F. The evolution of physiotherapy in the multidisciplinary management of persons with haemophilia (PWH): a scoping review. Submitted Haemophilia, 2022 Sep 27. Online ahead of print.
13. Pasca S, Cojutti PG, Pea F, Zanon E. The pharmacokinetics of recombinant FXIII (catridecacog) from the MENTOR™2 trial to a Real-World study: a head-to-head comparison. Submitted J Thromb Throbolysis, 2022 Sep 12. Online ahead of print.
14. Pasca S, Santoro C, Ambaglio C, et al. Comparison among three different bleeding scores and the Thrombin Generation Assay to assess the haemorrhagic phenotype in patients with FVII deficiency. BTVB, May 2022, Vol. 2
15. Cojutti PG, Zanon E, Pasca S, Pea F; Italian FXIII Study Group.Real-Life Population Pharmacokinetics of Recombinant Factor XIII and Dosing Considerations for Preventing the Risk of Bleeding in Patients with FXIII Congenital Deficiency. Clin Pharmacokinet 2021 Oct 31
16. Zanon E, Pasca S, Radossi P, et al. rFVIII single-chain in an Italian population of hemophilia A patients: the Veneto experience. Hemonline 2021
17. Frizziero A, Finotti P, Costantino C, Pasca S, Zanon E. Rehabilitation management of a triceps surae muscle injury in a young male with haemophilia A and high-titre inhibitors. Acta Biomed. 2021 Apr 30; 92 (S1): e2021118
18. Coluccia A, Marchesini E, Giuffrida AC, et al.; AICE MECCOVID-19 Study Group. Addressing the impact of SARS-CoV-2 infection in persons with congenital bleeding disorders: The Italian MECCOVID-19 study. Haemophilia 2021 Jul; 27 (4): e575-8
19. Franchini M, Coppola A, Santoro C, et al. ABO Blood Group and Inhibitor Risk in Severe Hemophilia A Patients: A Study from the Italian Association of Hemophilia Centers. Semin Thromb Hemost

2021 Feb; 47 (1): 84-9
20. Bacci C, Cerrato A, Zanette G, Pasca S, Zanon E. Regenerative Surgery with Dental Implant Rehabilitation in a Haemophiliac Patient. TH Open. 2021 Mar 16;5(1): e104-e106
21. Pasca S, Zanon E. Lights and shadows of the new therapies for haemophilia treatment in the Covid-19 era. Blood Transfus 2021 Jan; 19 (1): 73-6
22. Pasca S, Zanon E. Haemophilia A/B carriers: haemorrhagic burden of disease and open issues. E. Blood Transfus 2020 Nov; 18 (6): 496-7
23. Zanon E, Tosetto A, Radossi P, Pasca S, et al. Treatment With Efmoroctocog Alfa (Elocta®) in Hemophilia: A Case Series.Clin Management Issues, Oct 2020.
24. Zanon E, Pasca S, Campello E, et al. How haemophilia A impacts Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) treatment: a case report. J Thromb Thrombolysis 2020 Nov; 50 (4):795-8
25. Zanon E, Pasca S, Spiezia L, et al. Acquired haemophilia A, concomitant acute myocardial infarction and urgent major surgery: how to successfully treat a critical patient with rpFVIII (Obizur®). Thromb Res 2020 Nov; 195: 125-7
26. Zanon E, Pasca S, Borchiellini A, et al. Susoctocog-alfa (Obizur®) in the treatment of nine elderly patients with acquired haemophilia A: an Italian multicentre real life experience Blood Transfus 2020 Jul;18(4):312-321
27. Pasca S, Zanon E. Savings without changing how to use the *MyPKfit*® device to improve treatment strategies in a cohort of patients with haemophilia A. Thromb Res 2019 Nov; 183: 1-3
28. Santagostino E, Riva A, Cesaro S, et al; the HEVA Study Group. Consensus statements on vaccination in patients with haemophilia – Results from the Italian haemophilia and vaccination (HEVA) project. Haemophilia 2019 Jul; 25 (4): 656-67
29. Zanon E, Tagliaferri A, Pasca S, eta l. Physical activity improved by adherence to prophylaxis in an Italian population of children, adolescents, and adults with severe haemophilia A: the SHAPE Study. Blood Transfus 2019 Jun 5: 1-6
30. Zanon E, Pasca S, Pollio B, et al. Immune Tolerance Induction with moroctocog-alpha (Refacto/Refcto AF) in a population of Italian haemophilia A patients and high-titre inhibitors: data from REF.IT

Registry. Haemophilia 2019 Nov; 25 (6): 1003-10
31. Zanon E, Pasca S, Bertomoro A, et al. Spontaneous recurrent intracranial haemorrhage in a woman with type 2B von Willebrand disease: a clinical case and a brief literature review. Haemophilia 2019 Jul; 25 (4): e282-5
32. Zanon E, Pasca S. Intracranial haemorrhage in children and adults with haemophilia A and B: a literature review of the last 20 years. Blood Transfus 2019 Feb; 4: 1-7
33. Zanon E, Pasca S,Siragusa S, et al; for the *FAIR Study Group. Low dose of aPCC after the initial treatment in acquired hemophilia A is useful to reduce bleeding relapses: data from the FAIR Registry.Thromb Res 2019 Feb; 174:24-26
34. Zanon E, Pasca S, Radu CM, et al. Tailored prophylaxis with rFXIII (NovoThrirteen®) in a young girl with severe FXIII deficiency and previous cephalohematoma. Haemophilia 2019 May; 25 (3): e206-8
35. Pasca S, Ambaglio C, Rocino A, et al; for the *FAIR Study Group. Combined use of antifibrinolytics and activated prothrombin complex concentrate (aPCC) is not related to thromboembolic events in patients with acquired haemophilia A: data from FAIR Registry. J Thromb Thrombolysis, 2019 Jan; 47 (1): 129-33
36. Zanon E, Pasca S, Salmaso L, Macellari E. Music is a rainbow: effects of musicotherapy on haemophiliac children. Medico e Bambino, Febbraio 2019
37. Zanon E, Pasca S, Simioni P. The sudden and unexpected appearance of inhibitors in a previously treated severe haemophilia B patient (PTP) after the switch to albutrepenonacog alpha. Haemophilia, 2018 Sep; 24(5): e372-5
38. Zanon E, Milan M, Pasca S Immune Tolerance (ITI) Rescue with turoctocog-alfa in a poor risk hemophilia a young-child with inhibitors: a history of a success. Blood Coagul Fibrinolysis, 2018 Jul; 29(5): 465-6
39. Milan M, Pasca S, sarolo L, et al. Managing a rare brain tumor in haemophilia patient: the two-faces Janus of the coagulation side. J Blood Res, 2018 30 Jun
40. Pasca S, De Angelis V, Milan M, Zanon E. Can the plasmaderived play a role in the treatment of acquired haemophilia A at the time of the new drugs? Blood Coagul Fibrinolysis, 2018 Jul; 29 (5): 417-22

41. Zanon E, Pasca S, Milan M, et al. Activated prothrombin concentrate (FEIBA®) in acquired hemophilia A: a large multicenter Italian study - the FAIR Registry. Br J Haematol, 2019 Mar; 184 (5): 853-5
42. Zanon E, Milan M, Sarolo L, Pasca S. Cerebrovascular diseases in hemophiliacs: a real, but underestimated risk. Haemophilia, 2018 Jan; 24 (1): e3-5
43. Barco S, Pomero F, Di Minno MND, et al. Clinical course of patients with symptomatic isolated superficial vein thrombosis: the ICARO follow-up study.J ThrombHaemost2017 Nov; 15 (11): 2176-83
44. Pasca S, Milan M, Sarolo L, Zanon E. PK-driven prophylaxis versus standard prophylaxis: when a tailored treatment maggio be a real and achievable cost-saving approach in children with severe hemophilia A. Thromb Res, Sep 157: 58-63
45. Barillari G, Springolo F, Pasca S, et al. Cesarean surgery or vaginal delivery in a pregnant woman with homozygous FXI deficiency and FXI level <1%? This the question! Minerva Ginecologica 2016 Aug; 68 (4): 476-7
46. Frasson S, Gussoni G, Di Micco P, et al RIETE Investigators. Infection as cause of immobility and occurrence of venous thromboembolism analysis of 1635 medical cases from the RIETE Registry. J Thromb Thrombolysis 2016 Apr; 12 (8); 1122-9
47. Poli D, Antonucci E, Dentali F, et a;the Italian Federation of Anticoagulation Clinics (FCSA) Intracranial hemorrhage recurrence on vitamin K antagonist: severity of the first episode and HASBLED score fail to identify high-risk patients from the CHIRONE study. Blood Coag Fibrinolysis, 2017 Jan; 28 (1): 62-5
48. Franchini M, Di Perna C, Santoro C, et al; Italian Association of Haemophilia Centres. Cancers in Patients with von Willebrand Disease: A Survey from the Italian Association of Haemophilia Centres.Semin Thromb Hemost 2016 Feb; 42 (1): 36-41
49. Jiemenez D, de Miguel-Diez J, Guijarro R, et al; RIETE Investigators. Trends in the Management and Outcomes of Acute Pulmonary Embolism: analysis from the RIETE Registry. J Am Coll Cardiol 2016 Jan19; 67 (2): 162-70
50. Agnelli G, Gitt AK, Bauersachs R and PREFER study group. The management of acute venous thromboembolism in clinical practice-study rationale and protocol of the European PREFER in VTE

Registry. Thombosis J 2015 Oct 21; 13:41
51. Giorgi-Pierfranceschi M, Di Micco P, Cattabiani C, et al; RIETE Investigators. Platelet count and major bleeding in patients receiving vitamin K antagonists for acute thromboembolism findings from real world clinical practice. Medicine (Baltimore) 2015 Nov; 94 (47): e1915
52. Pasca S, Venturelli U, Bertone A, Barillari G. Direct Oral Anticoagulants for Very Elderly People with Atrial Fibrillation: Efficacy and Safe Enough? Clin Appl Thromb Hemost2017 Jan;23 (1): 58-63
53. Pomero F, Di Minno MN, Tamburini Premunian E, et al. A clinical score to rule out the concomitant presence of deep vein thrombosis in patients presenting with superficial vein thrombosis: The ICARO study.Thromb Res. 2015 Nov; 136 (5): 938-42.
54. Spiezia L, Campello E, Trujillo-Santos J, et al; RIETE Investigators.The impact of disseminated intravascular coagulation on the outcome of cancer patients with venous thromboembolism. Blood Coagul Fibrinolysis. 2015 Sep; 26 (6): 709-11
55. Ageno W, Riva N, Schulman S, et al. Long-term Clinical Outcomes of Splanchnic Vein Thrombosis: Results of an International Registry. JAMA Intern Med. 2015 Sep;175 (9): 1474-80
56. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al; RIETE Investigators. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Ann Am Thorac Soc. 2015 Aug; 12 (8): 1122-9
57. Baumann Kreuziger L, Cote L, Verhamme P, et al; RIETE Investigators. A RIETE Registry analysis of recurrent thromboembolism and hemorrhage in patients with catheter-related thrombosis. J Vasc Surg Venous Lymphat Disord 2015 Jul; 3 (3): 243-50
58. Rosa-Salazar V, Trujillo-Santos J, Díaz Peromingo JA, et al; RIETE Investigators. A prognostic score to identify low-risk outpatients with acute deep vein thrombosis in the upper extremity. J Thromb Haemost 2015 Jul; 13 (7): 1274-8
59. Farge D, Trujillo-Santos J, Debaurdau P, et al; RIETE Investigators. Fatal events in cancer patients receiving anticoagulant therapy for venous thromboembolism. Medicine (USA)2015 Aug; 94 (32): e1235

60. Mahé I, Sterpu R, Bertoletti L, et al; RIETE Investigators Long-Term Anticoagulant Therapy of Patients with Venous Thromboembolism. What Are the Practices? PLoS One 2015 Jun 15; 10 (6): e0128741
61. Antonucci E, Poli D, Tosetto A, et al; START-Register. The Italian START-Register on Anticoagulation with Focus on Atrial Fibrillation. PLoS One. 2015 Maggio 22; 10 (5): e0124719
62. Schulman S, Zondag M, Linkins L, Pasca S, et al. Recurrent venous thromboembolism in anticoagulated patients with cancer: management and short-term prognosis. J Thromb Haemost. 2015 Jun; 13 (6): 1010-8
63. Ageno W, Poli D, Testa S, et al; Italian Federation of Anticoagulation Clinics (FCSA).Safety of vitamin K antagonist treatment for splanchnic vein thrombosis: a multicenter cohort study. J Thromb Haemost 2015 Jun; 13 (6): 1019-27
64. López-Reyes R, Nauffal D, Ballester M, et al; RIETE investigators. Venous thromboembolism in patients immobilised at home. Eur Respir J. 2015 Jun; 45 (6): 1728-31
65. Dello Russo P, Damante G, Pasca S, et al. Thrombophilic mutations as risk factor for retinal vein occlusion: a case-control study. Clin Appl Thromb Hemost. 2015 May; 21 (4): 373-7
66. Ageno W, Samperiz A, Caballero R, et al; RIETE investigators. Duration of anticoagulation after venous thromboembolism in real world clinical practice. Thromb Res. 2015 Apr; 135 (4): 666-72
67. Pesavento R, Amitrano M Trujillo-Santos J, et al, RIETE Investigators. Fondaparinux in the initial and long-term treatment of venous thromboembolism. Thromb Res 2015 Feb; 135 (4): 666-72
68. Martín-Martos F, Trujillo-Santos J, Barrón M, et al; RIETE Investigators.Gender differences in cancer patients with acute venous thromboembolism. Thromb Res. 2015 Feb;135 Suppl 1: S12-5
69. Trujillo-Santos J, Lozano F, Lorente MA, et al; RIETE Investigators. A prognostic score to identify low-risk outpatients with acute deep vein thrombosis in the lower limbs. Am J Med. 2015 Jan; 128 90 (1): e9-15
70. Blanco-Molina A, Enea I, Gadelha T, et al; RIETE Investigators. Sex differences in patients receiving anticoagulant therapy for venous thromboembolism. Medicine (Baltimore). 2014 Oct; 93

(17): 309-17
71. Cote LP, Greenberg S, Caprini JA, et al; RIETE Investigators.Outcomes in neurosurgical patients who develop venous thromboembolism: a review of the RIETE registry. Clin Appl Thromb Hemost. 2014 Nov; 20 (8): 772-8
72. Silvestri F, Pasca S, Labombarda A, et al. Safety of fondaparinux in the prevention of venous thromboembolism in elderly medical patients: results of a single-center, retrospective study. Minerva Med 2014 Jun; 105 (3): 221-8
73. Lozano F, Trujillo-Santos J, Barrón M, et al; RIETE Investigators. Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. J Vasc Surg 2014 May; 59 (5): 1362-7
74. Maestre A, Trujillo-Santos J, Visoná A, et al; RIETE Investigators. D-dimer levels and 90-day outcome in patients with acute pulmonary embolism with or without cancer.Thromb Res. 2014 Mar; 133 (3): 384-9
75. Büller HR, Décousus H, Grosso MA et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. Hokusai-VTE Investigators, N Engl J Med. 2013 Oct 10;369(15):1406-15
76. Lecumberri R, Alfonso A, Jiménez D, et al; RIETE investigators. Dynamics of case-fatalilty rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism. Thromb Haemost. 2013 Oct; 110 (4): 834-43
77. Di Micco P, Ruiz-Giménez N, Nieto JA, et al; RIETE investigators. Platelet count and outcome in patients with acute venous thromboembolism. Thromb Haemost. 2013 Nov; 110 (5): 1025-34
78. Bertoletti L, Quenet S, Laporte S, et al; RIETE Investigators. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: data from the RIETE registry. Respir Res. 2013 Jul 18; 14:75
79. Nieto JA, Solano R, Trapero Iglesias N, et al; RIETE Investigators. Validation of a score for predicting fatal bleeding in patients receiving anticoagulation for venous thromboembolism. Thromb Res 2013 Aug; 132 (2): 175-9
80. Trujillo-Santos J, Schellong S, Falga C, et al; RIETE Investigators. Low-molecular-weight or unfractionated heparin in venous

thromboembolism: the influence of renal function. Am J Med. 2013 May; 126 (5): 425-434
81. Silvestri F, Pasca S, Labombarda A, et al. Safety and efficacy of thromboprophylaxis with fondaparinux in elderly acutely ill medical patients with renal impairment: a retrospective single center study. Italian J Med, Maggio 2013
82. Otero R, Elías T, Jara L, et al; RIETE investigators.Factors associated with elevated pulmonary arterial pressure levels on the echocardiographic assessment in patients with prior pulmonary embolism. Thromb Res. 2013 May; 131 (5): e191-5
83. Pasca S, Barillari G. When an optimal control of haemostasis is fundamental: a case report of patient with simultaneous acquired FVIII deficiency and venous thromboembolism. Gazzetta Medica Italiana Archivio per le Scienze Mediche 2013 March; 172 (3): 235-9
84. Barillari G, Pasca S. pdFVIII/VWF: an alternative treatment for old medical patient with acquired haemophilia A and systemic vascular diseases. Transfus Apher Sci 2013 Feb; 48 (1): 59-62
85. Gabriel F, Portolés O, Labiós M, et al; RIETE Investigators. Usefulness of thrombophilia testing in venous thromboembolic disease: findings from the RIETE registry. Clin Appl Thromb Hemost 2013 Jan-Feb; 19 (1): 42-7
86. den Exter PL, Gómez V, Jiménez D, et al; Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) Investigators. A clinical prognostic model for the identification of low-risk patients with acute symptomatic pulmonary embolism and active cancer. Chest. 2013 Jan; 143 (1): 138-45
87. Giglia D, Pasca S, Barillari G.Haemophilia in children today (L'emofilia nel bambino di oggi. Medico e bambino 2012; 31: 632-8
88. Tengborn L, Baudo F, Huth-Kühne A, et al; EACH2 registry contributors. Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. BJOG 2012 Nov; 119 (12): 1529-37
89. Rinaldi C, Savignano C, Pasca S, et al. Efficacy and safety of peripheral blood stem cell mobilization and collection: a single-center experience in 190 allogeneic donors. Transfusion. 2012 Nov; 52 (11): 2387-94
90. Nauffal D, Ballester M, Reyes RL, et al; RIETE Investigators.

Influence of recent immobilization and recent surgery on mortality in patients with pulmonary embolism. J Thromb Haemost. 2012 Sep; 10 (9): 1752-60
91. Nuñez MJ, Villalba JC, Cebrián E, et al; RIETE Investigators. Venous thromboembolism in immobilized patients with dementia. Findings from the RIETE registry. Thromb Res. 2012 Aug; 130 (2): 173-7
92. Baudo F, Collins P, Huth-Kühne A, et al; EACH2 registry contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012 Jul 5; 120 (1): 39-46
93. Dentali F, Poli D, Scoditti U, et al. Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study.J Thromb Haemost. 2012 Jul; 10 (7): 1297-302
94. Collins P, Baudo F, Knoebl P, et al; EACH2 registry collaborators. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). Blood 2012 Jul 5; 120 (1): 47-55
95. Becattini C, Agnelli G, Schenone A, et al; WARFASA Investigators.Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012 May 24; 366 (21): 1959-67
96. Riera-Mestre A, Jiménez D, Muriel A, et al; RIETE investigators.Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. .J Thromb Haemost. 2012 May; 10 (5): 751-9
97. Berntorp E, Shapiro AD, Waters J, Astermark J; International Factor IX Treatment Network. The international factor IX treatment network survey. Haemophilia. 2012 May;18 (3): e60-2.
98. Soler S, Delgado C, Ballaz A, et al; RIETE Investigators. Unsuspected pulmonary embolism in patients with cancer. Thromb Res. 2012 Apr;129 Suppl 1: S16-9
99. Di Micco P, Fontanella A, Falvo N, et al; RIETE Investigators. Natural history of patients developing thrombocytopenia while receiving anticoagulant therapy for venous thromboembolism. Int Angiol. 2012 Feb; 31 (1): 92-5
100. Knoebl P, Marco P, Baudo F, et al; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 2012 Apr; 10 (4): 622-31

101. Bertoletti L, Quenet S, Mismetti P, et al; RIETE Investigators.Clinical presentation and outcome of venous thromboembolism in COPD. Eur Respir J. 2012 Apr; 39 (4): 862-8
102. Tzoran I, Saharov G, Brenner B, et al; RIETE Investigators. Silent pulmonary embolism in patients with proximal deep vein thrombosis in the lower limbs. J Thromb Haemost. 2012 Apr; 10 (4): 564-71
103. Barillari G, Pasca S. Continuous infusion of rFVIII: a good choice for mild haemophilic patient undergoing major oncologic surgery and reconstructive plastic surgery. Chirurgia, 2012 Feb; 25 (1): 84-5
104. Barillari G, Pasca S, Erice F, Livi U. Successful double bypass in a patient with severe hemophilia A: a case report. J Thromb Thrombolysis. 2012 Feb; 33 (2): 193-6
105. Barillari G, Pasca S. Acute thrombocytopenia after infusion of an iodinated contrast medium: a case report. J Clin Case Rep 2012, 2: 218
106. Marzoena PJ, Nieto JA, Guil M, et al; RIETE Investigators.Long-term therapy with low-molecular-weight heparin in cancer patients with venous thromboembolism. Thromb Haemost 2012 Jan; 107 (1): 37-43
107. Tagliaferri A, Di Perna C, Santoro C, et al; Italian Association of Hemophilia Centers. Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers. J Thromb Haemost. 2012 Jan; 10 (1): 90-5
108. Barillari G, Pasca S, Barillari A, De Angelis V. Emergency reversal of anticoagulation: from theory to real use of prothrombin complex concentrates. A retrospective Italian experience. Blood Transfus. 2012 Jan; 10 (1): 87-94
109. Muñoz-Torrero JF, Bounameaux H, Pedrajas JM, et al; RegistroInformatizado de la EnfermedadTromboEmbólica (RIETE) Investigators.Effects of age on the risk of dying from pulmonary embolism or bleeding during treatment of deep vein thrombosis. J Vasc Surg 2011 Dec; 54 (6 Suppl): 26S-32S
110. Barillari A, Barillari G, Pasca S. Extended Compression Ultrasound Performed By Emergency Physicians: A Modified Compression Ultrasound Examination To Detect Superficial And Deep Lower Limb Thromboses In The Emergency. J Med Ultrasound, Nov 2011; 19: 103-8.

111. Foramiti S, Biondini E, Bigolin T, Pasca S, Rossi P. Vanishing bile duct syndrome in non-Hodgkin lymphoma: a case report. Minerva Med. 2011 Aug; 102 (4): 345-9
112. Barillari G, Pasca S, Gonano N, Daminato R. Prothrombin complex concentrate such as therapy and prophylaxis in factor X-deficient patient (Friuli variant).Clin Appl Thromb Hemost. 2011 Aug; 17 (4): 332-6
113. Bertoletti L, Righini M, Bounameaux H, eta l; RIETE Investigators. Acute venous thromboembolism after non-major orthopedic surgery or post-traumatic limb immobilisation. Findings from the RIETE registry. Thromb Haemost. 2011 Apr; 105 (4): 739-41
114. Trujillo-Santos J, Casas JM, Casado I, et al; RIETE Investigators.Thirty-day mortality rate in women with cancer and venous thromboembolism. Findings from the RIETE Registry. Thromb Res. 2011 Feb;127 Suppl 3: S1-4
115. Soto MJ, Grau E, Gadelha T, et al; RIETE Investigators.Clinical significance of a negative D-dimer level in patients with confirmed venous thromboembolism. Findings from the RIETE Registry. J Thromb Haemost. 2011 Feb; 9 (2): 407-10
116. Prandoni P, Trujillo-Santos J, Sanchez-Cantalejo E, et al; RIETE Group.Major bleeding as a predictor of mortality in patients with venous thromboembolism: findings from the RIETE Registry. Thromb Haemost 2010 Nov; 8 (11): 2575-7
117. Maestre A, Sánchez R, Rosa V, et al; RIETE Investigators.Clinical characteristics and outcome of inpatients versus outpatients with venous thromboembolism: findings from the RIETE Registry. Eur J Intern Med. 2010 Oct; 21 (5): 377-82
118. Jiménez D, Aujesky D, Moores L, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010 Aug 9; 170 (15): 1383-9
119. Nieto JA, Solano R, Ruiz-Ribó MD, et al; Riete Investigators.Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2010 Jun; 8 (6): 1216-22
120. Turello M, Pasca S, Daminato R, et al. Retinal vein occlusion: evaluation of "classic" and "emerging" risk factors and treatment. J Thromb Thrombolysis. 2010 May; 29 (4): 459-64

121. Trujillo-Santos J, Nieto JA, Ruíz-Gamietea A, et al; RIETE Investigators. Bleeding complications associated with anticoagulant therapy in patients with cancer. Thromb Res. 2010 Apr; 125 Suppl 2: S58-61
122. Blanco-Molina A, Rota LL, Di Micco P, et al; RIETE Investigators. Venous thromboembolism during pregnancy, postpartum or during contraceptive use. Thromb Haemost. 2010 Feb; 103 (2): 306-11
123. Barillari G, Frigo MG, Casarotto M, et al; Italian rFVIIa-PPH Study Group. Use of recombinant activated factor VII in severe post-partum haemorrhage: data from the Italian Registry: a multicentric observational retrospective study. Thromb Res. 2009 Dec; 124 (6): e41-7
124. Lobo JL, Zorrilla V, Aizpuru F, et al; RIETE Investigators. D-dimer levels and 15-day outcome in acute pulmonary embolism. Findings from the RIETE Registry. J Thromb Haemost 2009 Nov; 7 (11): 1795-801
125. Barillari G, Pasca S. Practical use of intermittent pneumatic compression as thromboprophylaxis in neurosurgery. J Neurosurg Sci. 2009 Jun; 53 (2): 45-8
126. Barillari G, Fabbro E, Pasca S, Bigotto E. Coagulation and oxidative stress plasmatic levels in a type 2 diabetes population.Blood Coagul Fibrinolysis. 2009 Jun; 20 (4): 290-6