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# 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

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**Abstract**
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. We now report the data of the "FEIBA® on acquired haemophilia A 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. 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. 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.

**Keywords** Acquired haemophilia A · Activated prothrombin complex concentrate · Antifibrinolytics · Thromboembolic risk

## Highlights

- In our study the association of aPCC and antifibinolytics was proved to be effective and safe in patients with acquired haemophilia A
- This combined therapy can be used also in patients with severe cardiovascular diseases
- This combined therapy can reduce the duration of treatment
- This combined therapy presented a good tolerability in all treated patients
- Antifibrinolytics could be used routinely in association with aPCC, especially in the case of severe and life-threatening bleeding, but this hypothesis needs to be confirmed in adequate, larger clinical trials

The members of the FAIR Study Group are listed in the acknowledgements.

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## 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 million of people per year [2]. Morbidity and mortality associated with AHA are high, especially in elderly patients with severe co-morbidities. International guidelines recommend to treat 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 10 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 [8].

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 autoantibodies. 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 are 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 diarrhea 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 thrombembolic 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

**Table 1** Characteristics of patients treated with a combined therapy aPCC/antifibrinolytics, aPCC treatment scheme, and duration of treatment

| 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<br>2.Cutaneous | | 51,10<br>51,10 | 12<br>12 | 2<br>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<br>2. Skeletal muscle | AMV | 50,00<br>50,00 | 12<br>12 | 2<br>3 |
| 15 | R | 72 | M | Idiopathic | Gastrointestinal | PTA (carotid stenosis), AMV | 80,00 | 12 | 6 |
| 16 | R | 66 | F | RA | 1. Cutaneous<br>2. Skeletal muscle | | 64,90<br>64,90 | 8<br>8 | 9<br>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<br>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<br>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<br>2. Cutaneous | | 66,70<br>66,70 | 12<br>48 | 26<br>14 |
| 27 | P | 45 | F | Cancer | 1.Skeletal Muscle<br>2. Skeletal Muscle | | 80,60<br>80,60 | 12<br>12 | 3<br>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 |

*R/P* Retrospective/prospective, *AHA* acquired haemophilia A, *RA* rheumatoid arthritis, *MGUS* monoclonal gammapathy 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

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.

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## Compliance with ethical standards

**Conflict of interest** All authors have read and understood JTT policy on declaration of interests and declare that they have no competing interests.

**Ethical approval** All procedures performed in this study involving human partecipants were in accordance with the ethical standards of the institutional and/or national research and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** All patients enrolled in our retrospective-prospective registry accepted to participate in the study signing the informed consent as requested by Ethical Committees. In the case of retrospective patients who had died before the start of collection data the informed consent was signed by a family member.

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