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Letter to the Editors-in-Chief

# Low dose of aPCC after the initial treatment in acquired haemophilia A is useful to reduce bleeding relapses: Data from the FAIR registry

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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 Haemophilia 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.

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 haemophilia, in AHA the haemarthroses 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 > 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 haemophilia 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

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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 ± 22.7 IU/kg. The median frequency of infusion was 12 h (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 infusions frequency mean every 24 h (range 12–72 h). 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 Table 1.

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 anemia 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 non-randomized, 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 hematuria, 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 were 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

**Table 1**
Demographic and clinical data of the patients. n: number of patient 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.

| 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 |

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.

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