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Full Length Article

Activated prothrombin complex concentrate (FEIBA®) for the treatment and prevention of bleeding in patients with acquired haemophilia: A sequential study

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ABSTRACT

Despite anti-haemorrhagic therapy with proper doses of activated prothrombin complex concentrate (aPCC, Feiba®), patients with acquired haemophilia A (AHA) have a considerable risk of recurrent bleeding complications. Evidence in support of the benefit-to-risk ratio of prevention strategies with the use of lower doses of aPCC following the end of the initial treatment period is scarce and inconclusive.

We report our experience in the management of 18 consecutive patients with AHA admitted to two Haemophilia centres in Italy. We managed the first 11 according to current guidelines (e.g., with conventional aPCC doses until bleeding resolution). Then, we decided to prolong the treatment beyond bleeding resolution with lower doses of the same concentrate (short-term prophylaxis) in the 7 additional patients. In these patients, the treatment was continued for as long as the titre of FVIII inhibitor was found to decrease by at least 50% when compared to the baseline one.

We observed six relapses of bleeding in patients in whom aPCC was confined to the treatment of the qualifying bleeding episode, and none in patients to whom lower doses were administered until the pre-specified decrease in the titre of FVIII inhibitor was achieved. No patients experienced thrombotic complications during the study period.

Prolonging the treatment with lower doses of aPCC beyond the initial phase in patients with AHA in whom the titre of FVIII inhibitor is still high is likely to safely prevent further bleeding complications.

1. Introduction

Acquired haemophilia A (AHA) is a rare auto-immune disorder caused by an inhibitory antibody directed against circulating coagulation factor VIII. The annual incidence of AHA has been reported to be 1.4 per million [1] in the general population, this rate being similar in males and in females (except in females aged between 15 and 40 years, due to the development of post-partum related AHA) and increasing with age. This disease usually leads to severe bleeding, mainly occurring into soft tissues, muscles and mucosae [2]. Haemostatic control is, therefore, the first priority in the management of AHA.

Consensus guidelines recommend the use of bypassing agents (recombinant activated FVII [rFVIIa, Novoseven®] or activated prothrombin complex concentrate – [aPCC, Feiba®]) as first-line treatment of bleeds [3]. Based on available evidence, no difference has been found between r-FVIIa and aPCC in terms of either efficacy or safety [4].

No standardized protocols on the use of aPCC for the treatment of patients with AHA are available [5,6]. Available findings suggest that a bolus injection between 50 and 100 U/kg-1 body weight every 8 to 12 h up to a maximum of 200 U/kg-1 body weight/day should be administered until haemostasis is achieved [7], usually after a median of 8 doses of aPCC (IQR 3-15) [4].

Based on the results of a recent international registry, 25% of AHA patients are prone to relapse into bleeding with a mean period of recurrence of 14 days (3–45 IQR) [4]. Bleeding relapse was indeed reported in 68 of 269 recruited patients with 99 episodes (mean of 1.5 events/person).

Evidence in support of the benefit-to-risk ratio of prevention strategies with the use of lower aPCC doses following the conclusion of the initial treatment period is scarce and inconclusive [4,8–12].

Here we report our experience in the management of 18 consecutive patients with AHA admitted to two centres in Italy. We managed the first 11 according to current guidelines (e.g., with conventional aPCC doses until bleeding resolution). Then, because of a high rate of bleeding

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relapse in this group, we decided to prolong the treatment beyond bleeding resolution with lower doses of the same concentrates in the 7 additional patients (low dose prophylaxis). In these patients, the treatment was continued until the inhibitor reduced by more than 50% of the baseline level.

2. Methods

We managed the haemorrhagic episodes of 18 consecutive patients with AHA, who were admitted to the Haemophilia Centres of two University Hospitals in Italy (Padua and Pavia) from April 2008 to August 2014 with an episode of acute bleeding. All patients were treated with FEIBA in doses tailored to the severity of bleeding in association with immunosuppressive drugs for eradication of antibodies (i.e., steroids with or without cyclophosphamide, followed by azathioprine or rituximab whenever appropriate) until resolution of bleeding, defined as stability of or increase in haemoglobin levels, pain relief and/or reduction or stability of haematoma [13]. While in the first 11 patients the treatment was discontinued, in the subsequent 7 patients the treatment was prolonged with lower doses (short-term prophylaxis) for as long as the titre of FVIII inhibitor – checked every 5 days - was found to decrease by at least 50% when compared to the baseline one.

After the completion of the treatment period, all patients were followed up for 4 additional weeks. Written informed consent was obtained from all patients and the local ethics committees approved the study. Particularly, all patients were asked to give consent for collection of data during and after treatment. Moreover, they had to sign a consent form for the use of FEIBA (being a plasma derived product) according to internal protocols. Specifically, all patients who underwent prolonged FEIBA treatment were informed about the contraindications of FEIBA and about the possible adverse events of therapy; they were also asked to accept such prolongation of therapy.

We collected baseline patients' demographic characteristics, coagulation parameters, FVIII activity and FVIII inhibitor levels and clinical features of the bleeding event in all recruited patients. We recorded all events occurring in the 4 weeks following resolution of the qualifying bleeding episode, including bleeding relapses and thromboembolic or cardiovascular events. A "bleeding relapse" was defined as any bleeding event occurred into the previous site or into a different one within a month after the resolution of the first episode.

At diagnosis, as well as during treatment and follow-up, activated partial thromboplastin time (aPTT, sec, Actin®, Siemens), prothrombin time (PT, %, Thromborel S®, Siemens), International Normalized Ratio (INR), and FVIII activity (% one stage assay, Coagulation Factor VIII Deficient Plasma®, Siemens and Actin®FS, Siemens), were assessed through a BCS XP-Analyser (Siemens Healthcare diagnostic Coagulometric Method, Marburg Germany); platelets count ($x10^9$/L) was determined by automatic methods (Counter Sysmex XE-2100 Dasit Spa, Milan Italy) as previously described [14] and FVIII inhibitor activity (BU/ml, Coagulation Factor VIII Deficient Plasma®, Siemens and Actin®FS, Siemens) was measured with the Bethesda Assay [15].

According to the ISTH guidelines [16] (Schulman et al., 2005), major bleeding episodes were defined as symptomatic bleeding in an organ or a critical area, that is intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin levels of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells. Outcome assessors (a group of clinicians) were unblinded.

2.1. Statistical analysis

For comparison of baseline characteristics between patients with and without treatment prolongation, the Fisher test was used for the categorical parameters, while Student's t-test was used for the continuous parameters. All tests for statistical significance were two-tailed and p values lower than 0.05 were considered statistically significant. Statistical analyses were performed by means of a commercially available statistics software package - SPSS 17.0 (SPSS Inc., Chicago, Il, USA).

3. Results

3.1. Patients

The main demographic, clinical and laboratory features of the recruited patients are shown in Table 1, separately for patients who had (Group A) or did not have (Group B) the treatment prolongation beyond the bleeding resolution. As shown in the table, no significant differences between the two study groups were seen for age, gender, PT or aPTT values, platelets count, FVIII:C and FVIII inhibitor titre.

AHA was apparently unexplained in 7 patients of group A, and in 7 of Group B, while it was associated with rheumatologic disorder in one patient, was post-partum related in another two and correlated with cancer in one patient of Group A. Four patients received concomitant steroids alone (Group A), while in the remaining 11 they were associated with cyclophosphamide (then replaced by azathioprine or rituximab in 2 patients of Group A and with rituximab in 1 patient of Group B). No statistically significant differences in time to obtain inhibitor eradication were found betweenthe patients treated only with steroids and those treated with steroids and cyclophosphamide (median, 50 days $\pm$17.3 vs 34.2 $\pm$ 23.0, p = 0.21); hence, more prolonged inhibitor exposure in Group A is unlikely to have occurred. Similarly, in the EACH2 registry no differences in time to obtain inhibitor eradication were found between the subjects treated with steroid alone or steroid and cyclophosphamide [17].

We recorded a median time of inhibitor clearance of 60 days (min 21, max 390 days) and a median time of 44 days to obtain a FVIII:C level higher than 50% (min 22-max 279). At the end of prophylaxis for Group B the FVIII:C levels were 28.4% (median value, min 4%, max 55.3%)".

Table 2 shows also the type and severity of the index bleeding event in each of the two groups. Bleeding qualified as major in 6 of the 11 patients of Group A, and in 3 of the 7 additional patients of Group B.

3.2. Management of the acute bleeding episode.

Data on bleeding management according to treatment strategy are shown in Table 2. While no difference was seen between the two groups in terms of treatment doses of FEIBA, the duration of the acute bleeding

Table 1
Clinical characteristics according to the two treatment strategies.

	Acute phase-only *Group A* **n = 11**	**Acute phase plus short-term prophylaxis** *Group B* **n = 7**	P
Male Sex (%)	7 (63.6)	4 (57.1)	0.8
Age (years)*	62 (46–78)	71 (60–82)	0.1
Type of AHA (%)			
Idiopathic	7 (63.6)	7 (100)	0.1
Post-partum	2 (18.1)	-	
Rheumatologic disorder	1 (9)	-	
Neoplastic	1 (9)	-	
Immunosuppressive treatment (%)			0.23
Steroids	4 (36.4)	-	
Steroids + cyclophosphamide	5 (45.5)	6 (85.7)	
First line + azathioprine	1 (9)	-	
First line + Rituximab	1 (9)	1 (14.3)	
PT (%)°	85 $\pm$ 7	79 $\pm$ 5	0.67
aPTT (sec.)°	65.2 $\pm$ 15.7	71.2 $\pm$ 14.9	0.78
Platelets Count ($x10^9$/L)°	325 $\pm$ 123	289 $\pm$ 92	0.82
FVIII:C (%)°	3.1 $\pm$ 6.2	11.8 $\pm$ 8.1	0.07
FVIII-inhibitor (BU/ml)°	7.8 $\pm$ 5.8	5.5 $\pm$ 5.6	0.3

* expressed as median $\pm$ IQR.
° at time of diagnosis expressed as mean $\pm$.

Table 2
Bleeding management according to the two treatment strategies.

	Acute phase-only *Group A* n = 11	Acute phase plus short-term prophylaxis *Group B* n = 7	P
Type of Bleeding			
Major (%)	6 (54.5)	3 (42.9)	0.4
Minor (%)	5 (45.5)	4 (57.1)	0.6
Cause of Bleeding			
Idiopathic (%)	6 (54.5)	6 (85.7)	
Post-traumatic	4 (36.4)	1 (14.3)	0.49
Post-partum	1 (9)	-	
aPCC loading dose (U kg-1 day)*			
Major bleeding	205.0 ± 7.1	162.2 ± 33.3	0.137
Minor bleeding	64.0 ± 40.4	85.0 ± 10.0	0.380
Treatment duration* (days)			
Major bleeding	4.2 ± 1.9	8.5 ± 0.7	0.004
Minor bleeding	2.0 ± 1.2	11.8 ± 11.2	0.178
*aPCC prophylaxis dose** (U kg-1 day)			
Major bleeding	-	77.3 ± 33.7	
Minor bleeding	-	28.5 ± 9.3	
Prophylaxis duration (days)*			
Major bleeding	-	12.7 ± 5.7	
Minor bleeding	-	12.25 ± 10.7	
*Total amount of aPCC** (U kg-1)	479.4 ± 335.1	1246.8 ± 952.1	0.05
Number of relapses	6	0	0.02

* expressed as median ± IQR.

phase of major bleeding was significantly longer in Group B than in Group A (8.5 ± 0.7 vs 4.2 ± 1.9 days; p = 0.004).

In patients belonging to Group B, prolonged treatment was maintained with a mean dose of 77.3 ± 33.7.0 U/kg-1/day for a mean period of 12.7 ± 5.7 days in patients with major bleeds, and 28.5 ± 9.3 U/kg-1/day for a mean period of 12.3 ± 10.7 days in those with minor bleeding. The prophylactic dose was decided upon according to the dose used during the acute bleeding phase; specifically,the dosage was decreased by about 75% of the therapeutic dose.

3.3. Bleeding relapses and thromboembolic events.

Six relapses of bleeding occurred after interruption of FEIBA, all of them occurring in the 11 patients of Group A in whom the aPCC was discontinued after resolution of the qualifying haemorrhagic episode, while no events were observed in the patients belonging to Group B. Four relapses occurred into a different site (dental bleed post extraction, spontaneous shoulder haemarthrosis, post-traumatic below-knee muscle haematoma, spontaneousright hand haematoma that required surgical drainage, respectively), and two into the same site (post-traumatic above-knee muscle haematoma and spontaneous calf haematoma, respectively). Three were major and three minor bleeding episodes. Considering the traumatic bleeds, in one case the traumatic event was very mild and caused a large haematoma. For the dental extraction, the patient was covered with tranexamic acid during procedure and despite that she started to bleed. At the moment of the procedure FVIII was almost 25% with an inhibitor titre of 1.54BU/ml. She did not inform the centre of the procedure planned, which the dentist considered at low risk of bleeding.

Even though our planned time of follow-up was of four weeks, we collected information for the long term follow-up and one patient of Group A with a persistent inhibitor titre presented a new spontaneous haematoma in the right arm more than four weeks after diagnosis; a new treatment with FEIBA was necessary for the acute phase and then a prophylaxis with 30UI/kg daily of FEIBA was started until inhibitor reduced by more than 50% of the baseline level without any other relapses.

No other events were reported, but more than one year from the first diagnosis two relapses of AHA occurred after two major bleeding events (spontaneous retroperitoneal haematoma and haemoperitoneum due to ovarian bleeding).

No thromboembolic complications or unexplained deaths were reported in either of the treatments.

4. Discussion

Our results suggest that extending the administration of aPCC treatment in lower doses beyond the resolution of the acute bleeding episode until the titre of FVIII inhibitor has reduced by more than 50% of the baseline level has the potential to safely decrease the risk of bleeding relapses in patients with AHA. It should be specified that our decision was arbitrary, and based on the perception that a substantial decline in the titre of factor VIII inhibitor may be regarded as an indicator of the response to immunosuppressive drugs; thus it is likely to anticipate the reduction in the risk of bleeding relapse. As a matter of fact, none of the patients whose treatment was prolonged beyond the acute phase experienced bleeding recurrences, as compared to 6 of the 11 in whom the treatment was discontinued. Of interest, neither thrombotic complications nor other adverse events were observed during the period of additional lower-dose aPCC treatment. Obviously, the arbitrary choice of continuing prophylaxis until the inhibitor titre has reduced by more than 50% is a limitation of our work and would need further confirmation.

Our results are consistent with those occasionally reported by others. In one of the 10 patients with AHA described by Grünewald et al. in 2001 [8], the initial high dose of aPCC (150 U/kg-1 day), administered for severe anaemia due to cutaneous and muscular haematomas was followed by reduced dosage (dosage not specified in paper) for 45 days, with inhibitor disappearance 100 days after diagnosis. In 2012, Kang et al. [18]published a case report on a 26-year-old female with AHA and severe anaemia due to intramuscular femurs haematoma. She was treated with aPCC in a dose of 100 IU/kg-1 twice a day for 9 days followed by 5 IU/kg-1 every 12 h for 13 additional days, achieving successful haemostatic control. FVIII inhibitor titre dropped from 110 BU/ml to 13.2 BU/ml. The prevention of bleeding events through prophylaxis with FEIBA also appeared to be effective [19–20] in patients with congenital haemophilia and inhibitor.

Our results confirm that confining the initial treatment to the acute phase may be unsuccessful in many patients with AHA. Indeed, our strategy has the potential to provide further protection against bleeding without leading to thrombotic complications. Given the high costs of FEIBA, however, the cost-to-benefit ratio of this procedure should be carefully evaluated. Recently, data from a prospective registry of French AHA patients treated with FEIBA were published; in that study median duration of treatment was 4.0 days with interquartile range (IQR) 2.2–8.0 days, but no information was reported on bleeding relapses [21].

A potential limitation of our findings is the remarkable difference in the duration of the treatment of acute bleeding between the two study groups. Indeed, during the acute bleeding phase patients of Group A received a much shorter duration of aPCC treatment. However, it should be considered that the first 11 patients were managed according to current guidelines [3], and that four of the six relapses occurred into different sites, suggesting that the duration of treatment may have been adequate.

The sequential study design, small number of patients evaluated and unblinded outcome assessment prevent us from drawing firm conclusions. There is a need for randomized clinical trial, in which a higher number of consecutive patients with AHA are allocated to either the conventional short-term treatment or a longer one where the use of lower doses is guided by the FVIII inhibitor titration. Our findings

should, therefore, be regarded as hypothesis-generating. They have the potential to help define standard protocols in the treatment of bleeding in acquired haemophilia.

Disclosures

Dr. Ezio Zanon has received fees as speaker or for occasional consulting from Bayer, Baxalta, CSL-Behring, Grifols, Novonordisk. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

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E.Z. designed the research study, wrote the paper.
M.M. analysed the data, wrote the paper.
C.A. analysed the data, performed the research.
L.S. analysed the data, wrote the paper.
N.M. analysed the data, performed the research.
G.G. designed the research study, analysed the data.
GS performed lab tests.
PP analysed the data, wrote the paper.

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