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Activated prothrombin complex concentrate (FEIBA®) in acquired haemophilia A: a large multicentre Italian study – the FAIR Registry

Acquired haemophilia A (AHA) is a rare bleeding disorder caused by the spontaneous development of auto-antibodies against coagulation factor VIII (FVIII) in males and females with previously normal haemostasis (Kessler & Knobl, 2015).

This study aimed to assess dosage, duration of treatment, as well as the effectiveness and safety of activated prothrombin complex concentrate (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 (Zanon *et al*, 2015).

All the events occurring in the 4 weeks following resolution of the qualifying bleeding episode were recorded. Major bleeds and the resolution of acute bleeding were defined according to the International Society on Thrombosis and Haemostasis guidelines (Schulman *et al*, 2005). "Bleeding relapse" was defined as any bleeding event that occurred into the same 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 1 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, calculated on the inhibitor titre present at the onset of the therapy with aPCC, and assessed by the clinicians of each single centre. As FAIR is a registry, no special protocols were provided for patient management.

Statistical analysis included all 56 enrolled patients. Baseline characteristics and the treatment of the patients are summarised in Table I. 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 (interquartile range [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, and were more frequently used in the prospective group ($P = 0{\cdot}0339$). 57·1% of patients treated with antifibrinolytic drugs had serious co-morbidity. Among them, 40% presented severe cardiovascular diseases (myocardial infarction, ischaemic stroke and ischaemic 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 of the bleeds treated with double therapy required a 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, and 73·2% received no further treatment ($P = 0{\cdot}0048$). 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 a mean infusion frequency

Table I. Baseline characteristics and the treatment of patients enrolled in the FAIR study.

	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)

AHA, acquired haemophilia A; na, not available; SD, standard deviation.

*No patients used anti-fibrinolytics only.

†Some patients had more than one condition (Total >100%).

‡Assessment performed on 101 total bleeds.

of 24 h. Bleeding relapses were significantly higher in patients who received no prophylactic treatment with FEIBA®($P < 0·05$). An anamnestic response was reported in 6/101 (5·9%) bleeding treatments. The median inhibitor titre increase was 9·3 Bethesda units (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 (Knoebl *et al*, 2012), FAIR is the largest study on the use of FEIBA® in the treatment of AHA, but, unlike EACH2, almost half of the patients were studied prospectively. The FAIR registry included a population with a median age of 69·9 years, which was younger than in the FEIBHAC (Borg *et al*, 2015) and EACH2 registries (Knoebl *et al*, 2012), but older than in the American study (Sallah, 2004), and comparable with the French study (Goudemand, 2004).

The efficacy of aPCC as a first-line therapy in AHA is consistent with the data reported by Knoebl *et al* (2012). However, the FAIR registry is the first study to also highlight a positive clinical response to the combination of aPCC and antifibrinolytic agents, although 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 rate after the first episode, which is above 20% (Baudo *et al*, 2012). The FAIR registry showed that short-term prophylaxis prevented most bleeding relapses, 90·6% of which 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, confirming the data reported by Baudo *et al* (2012). In our study, the patients who presented an anamnestic response to aPCC were not treated for a longer period of time and did not need a higher amount of FEIBA® than those without an anamnestic response. Patients with an anamnestic response did not show more severe bleeding or worse outcomes than the remaining patients.

Differently from the EACH2 registry (Baudo *et al*, 2012), in which 4·8% of the patients treated with FEIBA® experienced a thrombotic event, none of the patients in the FAIR registry suffered this side effect. The overall mortality among the FAIR patients treated with aPCC was 14·3%, lower than in the other registries (Baudo *et al*, 2012; Borg *et al*, 2015).

The FAIR registry showed interesting results that may be useful in clinical practice, but controlled trials are needed to confirm the data obtained.

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New heterozygous variant in *GP1BB* gene is responsible for an inherited form of macrothrombocytopenia

Bernard-Soulier syndrome (BSS) is a hereditary bleeding disorder affecting the megakaryocytic/platelet lineage and characterized by large platelets, low platelet counts and defective glycoprotein (GP)Ib/IX/V complex, a platelet restricted multi-subunit receptor required for primary haemostasis. BSS is transmitted as an autosomal recessive trait (biallelic BSS), but a few reports have shown that it may occasionally be transmitted in an autosomal dominant fashion (monoallelic BSS) (Noris *et al*, 2012). BSS is caused by mutations in *GP1BA*, *GP1BB* and *GP9*, encoding the