Can the plasmaderived factor VIII still play a role in the treatment of acquired hemophilia A at the time of new drugs?

Samantha Pasca[a], Vincenzo De Angelis[b], Marta Milan[a] and Ezio Zanon[a]

Bypassing 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 of this study was to evaluate whether the pdFVIII can still play a role in the treatment of AHA, and which patients could benefit from this therapy. All patients with AHA, presenting severe cardiovascular comorbidities, and treated with pdFVIII with or without von Willebrand factor (vWF), referred to two different hospitals, were initially considered. Eight patients were studied and divided into two groups: first, patients treated with daily infusion of pdFVIII; second, patients treated with pdFVIII continuous infusion. After 6 months of follow-up, all patients reached complete response. Mean consumption of clotting factor (219 000 vs. 142 000 IU), mean duration of therapy (61.5 vs. 10.5 days), and mean time necessary to disappearance of the inhibitors (INHs) (64 vs. 9 days) were higher in group 1, and the differences between the two groups were statistically significant ($P<0.05$). Patients in group 1 also had a mean INH titer of 20.4 BU, higher than that of group 2 patients (8.4 BU), with a lower detectable FVIII level. Our study showed that pdFVIII can be an effective option for patients at high thromboembolic risk, even for those with high-titer INHs, especially if combined with vWF. The immunomodulatory role of vWF should, however, be better investigated in wider trials. The days of treatment with pdFVIII continuous infusion was proven to be similar to those reported with other drugs. *Blood Coagul Fibrinolysis* 29:000–000

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[a]Hemophilia Center, University Hospital of Padua, Padua and [b]Transfusion Medicine Department, University Hospital of Udine, Udine, Italy

Correspondence to Samantha Pasca, Hemophilia Center, University Hospital of Padua, Via Giustiniani, 35128 Padua, Italy.
Tel: +39 049 8212175; e-mail: sampasca27@gmail.com

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Background

Acquired hemophilia A (AHA) is a rare bleeding disorder that affects equally men and women. This disease is characterized by a development of autoantibodies against the factor VIII (FVIII); often its cause is unknown, but in almost 50% of cases, it is secondary to cancer, autoimmune diseases, or infections. AHA is more frequent in elderly people, whereas a peak of events was found in young women 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 (INHs), and, if possible, in treating the concomitant disease that caused AHA [4].

Hemostatic 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 bypassing 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 FVIII (pdFVIII) can be an alternative to bypassing agents, but the published guidelines recommend this treatment only in case of a low-titer INHs (<5.0 BU) [5,6]. In the last years, a new recombinant porcine FVIII (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 INHs, whereas the use of rituximab is suggested only in cases of a contraindication to immunosuppressive therapy (IST) [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 INHs, and

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Table 1 Baseline characteristics of patients and comorbidities

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

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CHD, coronary heart disease; DM2, diabetes mellitus type 2.

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 ITI and continuous infusion of pdFVIII in terms of concentrate consumption, therapy duration, and clinical response.

Methods

This is a retrospective study that 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 is defined according to the International Society on Thrombosis and Haemostasis guidelines [10].

According to AICE (Italian Association of Hemophilia Centers) guidelines [6], complete response (CR) 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 Emoclot, Kedrion, Italy; Fanhdi, Grifols, Barcelona, Spain; Haemoctin, Biotest, Dreieich, Germany.

Emoclot and Haemoctin: as the vWF factor is present in minimal nonstandardized 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 INH titer and disappearance. Baseline characteristics of patients and significant cardiovascular comorbidities are shown in Table 1.

Eight patients were studied, divided into two groups: first, patients with confirmed AHA, treated with daily administrations of pdFVIII (ITI); second, patients with confirmed AHA, treated with continuous infusion of pdFVIII.

An IST was prescribed to all patients. All of them were treated with corticosteroids for a mean of 75 days (tapering dose); seven out of eight patients received cyclophosphamide for a mean of 30 days (tapering dose). Only one patient with concomitant pulmonary infection (patient 01) received only prednisone, whereas 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. Of all, 75% were men; three patients were treated with pdFVIII alone, whereas one, a 71-year-old man, was treated with a concentrate of pdFVIII/vWF. All these patients had an INH titer more than 5 BU (refer to Table 2).

Patient 01

A 70-year-old man, with previous atrial fibrillation, aneurysm to middle cerebral artery, renal failure, chronic obstructive pulmonary disease was admitted to hospital with ileopsoas hematoma revealed by CT-scan and initially attributed to oral anticoagulants. The anticoagulation was interrupted, but the hemorrhagic 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/

Table 2 Synthesis of laboratory data, plasmaderived consumption, duration of treatment, and time to inhibitor disappearance

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[a]	0.3	4.36		164 000	13	6
06[a]	10.4	1.0		84 000	14	14
07[a]	15.3	3.48		159 000	8	7
08[a]	2.4	10.5	162 000		7	8

INH, inhibitors. [a] Treatment with continuous infusion.

day for 21 days. Subsequently, the concentrate was reduced to 3000 IU/three times a week (3 weeks), followed by pdFVIII 2000 IU/three times a week (2 weeks), by pdFVIII 2000 IU/ two times week (1 week) and finally by pdFVIII 2000 IU/day for 15 days. Three months later, the INH disappeared.

Patient 02

A 71-year-old man admitted to hospital with anemia [hemoglobin (Hb) 10.3 g/dl] and a serious hemorrhagic mucocutaneous 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 comorbidities as thromboendoaterectomy to the left carothid artery, aortoiliac bypass, acute myocardial infarction (AMI) with consequent coronary artery bypass graft. 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 INHs 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 3 days associated with rFVIIa 8 mg/day), by pdFVIII 2000 IU/bid for 8 day, by pdFVIII 4000 IU/day for 3 days, and finally by pdFVIII 3000 IU/three times a week (3 weeks). The INHs 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 mucocutaneous 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/ three times a week (3 weeks), and finally by pdFVIII 3000 IU/two times a week (2 weeks). The INHs disappeared after 2.5 months.

Group 2 (continuous infusion)

Four patients with confirmed AHA, mean age 72 years (range 65–78 years), were included in this second group. Of all men, three were treated with plasmaderived FVIII/vWF, whereas one only with pdFVIII. All patients had concomitant severe cardiovascular diseases. One patient included in this group had a high-titer INH at the onset of the treatment (refer to 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 presented also a history of AMI treated with percutaneous transluminal coronary angioplasty 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 INHs 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 treated with bilateral endarterectomy, and pancreatic jejunal anastomosis for chronic pancreatitis. No family or personal coagulation disease was 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 INHs 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 was reported, and 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 9 days. FVIII INH 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 15 IU/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 INHs 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 INH disappearance was shown in Table 2.

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

In the case of the only patient included in group 1 and 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 INH 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 INH 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 6 days in association to pdFVIII, but the concentrate consumption, the treatment duration, and the time to INH disappearance remained similar to other patients of the group 1, never treated with bypassing agents.

At the beginning of the pdFVIII treatment, the mean of INH 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%, whereas in the group 2, it was 7.1%; even in this case, no differences statistically significant were found ($P = 0.84$).

At 6 months of follow-up, all patients had reached a 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 8 months after discharge (patient 06), but the death was related to a cancer progression.

Discussion

Bypassing 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 comorbidities.

In the EACH2 Registry [11], thromboembolic events occurred in the 3.6% of patients treated with bypassing 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 [1,12], AHA is usually considered a bleeding disorder that affects equally men and women, but in our little experience 87.5% were

men. Only one of our patients suffered from cancer; in the other cases, the AHA was considered idiopathic.

International guidelines recommend use of plasmaderived products only in case of low-titer INHs [5,6], but our study has clearly shown that also in case of patients with high-titer INHs 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 [13] and an INH eradication with combined use of IST, whereas ITI 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 with continuous infusion, in which the days of exposure to pdFVII were similar to those reported in the large trials with bypassing agents [11,12] or with rpFVIII [7]. Based on our experience and published data [9,14,15], 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 ITI in patients with congenital hemophilia A and INHs. 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 [16–19]. An immunomodulatory role of vWF has been hypothesized, but not completely confirmed. In a recent 'in-vitro' study, Chen *et al.* [20] have shown the role of VWF in attenuating FVIII memory immune responses in hemophilia A mice, but a confirm in the volunteer subjects subjects is needed.

Plasmaderived concentrates are often used in the ITI rescues in patients with inherited hemophilia A and INHs [21,22], but their use in patients with AHA is very rare, and only few cases are published in literature [14,15]. As AHA often occurs with severe bleeding in the presence of high-titer INHs and very low level of FVIII, pdFVIII are not considered the first-line therapy, but also the severe comorbidities 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 INHs, especially if combined with the vWF, that seems to be actively involved in reaching a CR. The immunomodulatory role of vWF should, however, be 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 are treated with plasmaderived FVIII. A larger study would be needed to confirm our data.

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Conflicts of interest

There are no conflicts of interest.

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