Management of bleeding in acquired haemophilia A with recombinant activated factor VII: does one size fit all? A report of four cases

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Introduction

Acquired haemophilia A (AHA) is a rare but clinically relevant bleeding disorder due to autoantibodies (inhibitors) against coagulation factor VIII (FVIII)\(^1\)\(^-\)\(^3\). AHA is usually triggered by infections, malignancies, autoimmune diseases, or pregnancy. Some cases associated with drug intake have also been described, but about half of cases remain unexplained and are classified as "idiopathic". According to a 2-year prospective surveillance study from the UK, the incidence is approximately 1.5 cases per million persons per year\(^1\); the condition is most frequent in the elderly and the reported median age of affected individuals is above 70 years\(^1\)\(^-\)\(^3\). This acquired bleeding disorder should be suspected in subjects without a personal or family history of bleeding who have unexplained haemorrhages, prolonged activated partial thromboplastin time (APTT) and a normal prothrombin time. A mixing test which does not correct the APTT, in the absence of lupus anticoagulant and heparin administration, together with low FVIII levels and circulating FVIII inhibitor, confirm the diagnosis\(^1\). In the majority of cases bleeding is spontaneous and can range from mild to life-threatening\(^1\)\(^-\)\(^3\). Bleeding sites in patients with AHA differ from those associated with congenital haemophilia, traumatic muscle bleeds and haemarthroses being uncommon. Indeed, most events are spontaneous subcutaneous, deep muscle and retroperitoneal bleeds, although mucosal (gastrointestinal, lung, urogenital) and intracranial bleeds also occur. Bleeding is the main cause of death in the early phase of AHA and its severity does not correlate strictly with FVIII levels or inhibitor titre.

The management of AHA is directed at controlling the bleeding, eradicating inhibitors in order to prevent subsequent haemorrhagic complications, and treating any underlying associated disease\(^5\)\(^,\)\(^6\). Early treatment of bleeds is recommended. Available haemostatic agents do not have predictable efficacy; therefore, clinical review by physicians experienced in the management of inhibitors, supported by appropriate imaging and laboratory studies, is important\(^6\)\(^-\)\(^8\). Among the different approaches to control haemorrhages in AHA patients, the use of desmopressin and antifibrinolytics is mostly anecdotal and reserved only for minor bleeding. In selected cases FVIII concentrates, either recombinant or plasma-derived, could be appropriate\(^9\).

According to international recommendations, bypassing agents, i.e. recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC), are considered the first-line approach for the treatment of bleeding episodes\(^6\)\(^-\)\(^7\). The dosages and regimens of rFVIIa (Novoseven\(^\text{®}\)) that have been reportedly used in AHA are widely heterogeneous\(^3\)\(^,\)\(^10\)\(^-\)\(^13\), but current recommendations suggest bolus administrations of 90 µg/kg every 2-3 hours, until haemostasis is achieved\(^6\)\(^-\)\(^7\), similar to the treatment in patients with congenital haemophilia and inhibitors. The largest available collection of treatment records, the European Acquired Haemophilia (EACH2) registry, showed consistent concordance among physicians (rFVIIa dosage range 84.7-102.9 µg/kg every 2-6 hours)\(^13\). Unfortunately, due to the rarity of AHA, no methodologically rigorous study has been conducted to determine the most effective and safest dosage in this setting. Bypassing agents are generally well tolerated in AHA patients, although severe thrombotic complications may occur, such as myocardial infarction, disseminated intravascular coagulation, arterial and venous thrombosis, pulmonary embolism and stroke\(^11\)\(^,\)\(^13\). Although a causal relationship between bypassing agents and such thrombotic complications cannot be established in most cases, caution is required, in particular taking into account that the elderly age and frequent comorbidities of patients treated with these agents increase the risk of thromboembolism\(^3\)\(^,\)\(^9\)\(^,\)\(^14\).

Here we describe four patients with AHA whose bleeds were treated with lower dosages and/or longer intervals of bolus administrations of rFVIIa than those recommended. These regimens were chosen because of the high risk of thrombotic complications, given the patients' risk profile, concomitant with the need to treat severe, even life-threatening, haemorrhagic events.

Case reports

Case 1

A 79-year old male presented with recent-onset haematuria, easy bruising and muscle hematomas of the lower limbs. He had a history of moderate renal
insufficiency and thrombosis of the left iliac artery. On admission, his haemoglobin (Hb) was 8.6 g/dL, APTT-ratio 2.16 (normal values <1.2), FVIII coagulation activity (FVIII:C) 3% and FVIII-inhibitor 14.4 Bethesda Units (BU)/mL. Ultrasound examination revealed large haematomas of the thigh and calf and bleeding in the ankle joint. Treatment with rFVIIa was started at a dose of 67 µg/kg every 6 hours for 4 days, then every 8 hours for the following 3 days (Figure 1, panel a). In parallel, immunosuppressive therapy was given (prednisone 1 mg/kg daily). The patient had rapid relief from the lower limb pain and progressive resolution of haematomas. Searching for occult malignancy, a total body computed tomography (CT) scan did not reveal any relevant signs, whereas multiple polyps were found during colonoscopy. Endoscopic polypectomy was performed under the cover of prophylactic rFVIIa infusion (67 µg/kg) and a further three administrations were given at 8-hour intervals. No bleeding complications occurred. Dysplastic tubular adenomas were shown at histology. The inhibitor was eradicated after 30 days of immunosuppressive therapy.

Case 2

A 68-year old man was admitted because of a 30-day history of spontaneous cutaneous and retropharyngeal bleeding. The patient was a current smoker and had a history of arterial hypertension, diabetes mellitus and chronic obstructive pulmonary disease. On admission he presented with haematomas of the lower limbs, right gluteus and neck. As shown at CT scan, the haematoma in the neck displaced the tongue and pharynx, causing dyspnoea. Laboratory tests revealed anaemia (Hb 8.9 g/dL), APTT-ratio 1.45, FVIII:C 16.6% and inhibitor 2.3 BU/mL. The patient was promptly transfused with two units of packed red blood cells. Haemostatic treatment with rFVIIa was started at a dose of 80 µg/kg every 6 hours, but withdrawn after 24 hours because of the onset of chest pain, although electrocardiograms and cardiac markers of necrosis remained negative. However, the patient's dyspnoea improved and no further relevant bleeding episode occurred. After negative assessment for associated diseases, the AHA in this case was classified as idiopathic. In consideration of the labile control of the patient's diabetes, immunosuppressive therapy was given with a lower dose of prednisone (0.5 mg/kg daily). Ten days later, a trend to a reduction in the patient's Hb (Figure 1, panel b) was managed with an increase in the dose of prednisone (1 mg/kg daily) and the addition of cyclophosphamide (1 mg/kg daily),

Figure 1 - Trends in haemoglobin (Hb) levels (black lines) and relationships with rFVIIa treatment (grey lines) in the four reported patients.
Treatment with recombinant activated factor VII (rFVIIa) is expressed as mg/day. Scales for Hb and rFVIIa total dose are on the left y-axis and right y-axis, respectively. In case 2 (panel b) rFVIIa treatment is not shown because the patient received only two doses of rFVIIa (total 15 mg, see text for details).
in order to eradicate the FVIII inhibitor as soon as possible. This objective was achieved after 40 days of immunosuppressive therapy.

Case 3

A 74-year old woman was admitted because of recent appearance of multiple haematomas and bruising of the neck, tongue and left orbit. She had a history of rectal cancer and arterial hypertension. At laboratory assessment, an APTT-ratio of 2.62, FVIII:C of 1.5% and FVIII inhibitor of 7 BU/mL led to the diagnosis of AHA. The enlargement of the neck and the tongue hematomas causing airway obstruction necessitated tracheal intubation. Following haemostatic treatment with rFVIIa at a dose of 90 µg/kg every 6 hours for 24 hours, then prolonged to every 8 hours, the haematoma progressively reduced and spontaneous breathing was restored after 5 days. Maintenance with rFVIIa every 12 hours was given for a further 3 days (Figure 1, panel c). In parallel, immunosuppressive therapy (prednisone 1 mg/kg daily) was started. No relapse of cancer or other causes of secondary AHA were found during further investigations. Thus, idiopathic AHA was diagnosed, with inhibitor eradication after 28 days of immunosuppressive therapy.

Case 4

A 71-year old male presented with a 15-day history of left lower limb haematoma after physical effort. The patient had a history of ischaemic stroke on antiplatelet therapy, diabetes mellitus and dyslipidaemia. On admission he was asthenic and had severe backache, haematomas of lower limbs, and abdominal and thoracic bruising. Laboratory tests showing a Hb of 9.3 mg/dL, APTT-ratio of 2.58, FVIII:C of 0.2% and inhibitor titre of 14.6 BU/mL confirmed the suspicion of AHA. Total-body CT revealed a large haematoma of the left ilio psoas muscle (10 cm×25 cm) and of the abdominal wall. Antiplatelet therapy was promptly discontinued and the patient was given two units of packed red blood cells. Immunosuppressive therapy (prednisone 1 mg/kg daily) was started immediately, together with rFVIIa 70 µg/kg every 6 hours for the first day, then every 8 hours for 72 hours and every 12 hours for a further 3 days (Figure 1, panel d). After 7 days of treatment, a CT scan revealed a 30% reduction in the volume of the haematoma. Four weeks later, inhibitor was still detectable and, due to iatrogenic diabetes, prednisone was reduced to 0.5 mg/kg and combined with cyclophosphamide (2 mg/kg daily) for the following 6 weeks. The patient's clinical condition progressively improved and his bleeding tendency resolved. After 70 days of immunosuppressive therapy the inhibitor was eradicated.

Discussion

Our report on treatment of bleeding in AHA patients highlights the need for the most effective but safest haemostatic approach, a challenging and still open issue in the management of such a rare, but insidious disorder that can lead to death if not recognised and treated promptly and appropriately. International recommendations currently suggest administering bypassing agents to control bleeding, using the same doses and regimens reported for patients with congenital haemophilia with inhibitors. These regimens have been proven to be effective and safe in these latter patients; however, AHA patients show largely different clinical and laboratory features. As regards the sites of bleeding, mucous-cutaneous bleeding and muscle haematomas are prevalent in AHA, whereas haemarthroses represent the hallmark of congenital haemophilia, regardless of whether the patients do or do not have inhibitors. Virtually all available studies on treatment with bypassing agents refer to joint bleeding and so their findings cannot be translated automatically to other settings. Moreover, inhibitors show different kinetics in congenital and acquired haemophilia, so the efficacy and the dosage of bypassing agents may not necessarily be equivalent. However, the main clinical difference is that, at variance with younger patients with congenital haemophilia, physicians treating AHA patients have to face the challenge of severe bleeding episodes in a population of elderly patients at high risk of vascular and thromboembolic complications. Indeed, the median age of patients at diagnosis of AHA was 78 and 74 years in the two largest cohorts studied so far, the prospective UK study and the EACH2 registry, respectively, with more than 80% of patients older than 65 years. As shown in our series, this implies the coexistence of cardiovascular risk factors (diabetes mellitus, arterial hypertension, obesity, dyslipidaemia) or a previous history of arterial or venous thrombotic events in many AHA patients. Moreover, associated diseases responsible for secondary AHA, including solid or haematological malignancies in about one out of four patients and, less frequently, chronic inflammatory, infectious or immunological disorders, together with bed-rest (due to bleeding or underlying disorders), contribute significantly to the high thromboembolic risk in this setting. In the presence of bleeding, the withdrawal of previously administered antithrombotic treatments (as described in one patient in our series) may further increase vascular risk. Although rare, the risk of thrombotic events in patients treated with both bypassing agents, rFVIIa and aPCC, is well recognised.
Efficacy of low-dose rFVIIa in AHA-related bleeding

and such complications have been reported even in patients with AHA\textsuperscript{11,13}. In the EACH2 registry about 3% of patients experienced arterial or venous thrombosis, although the relationship with haemostatic treatment was not always shown or reported\textsuperscript{5,13}. Some authors have suggested that the use of FVIII concentrates as first-line haemostatic treatment could reduce the risk of thrombotic complications, because of more physiological activity and the feasibility of laboratory monitoring\textsuperscript{8,18}. However, treatment of bleeding with FVIII concentrates is usually taken into consideration only for patients with low-titre inhibitor levels (<5 BU/mL). The EACH2 registry showed that the majority of AHA patients have high-titre inhibitors\textsuperscript{5} and FVIII administration may result in an anamnestic increase of inhibitor titre.

In order to address the concomitant bleeding and thrombotic risk, the two faces of the coin in the four AHA cases reported here with different but severe bleeding episodes, we adopted individualised regimens of rFVIIa with lower bolus dosages (67-90 µg/kg) and/or longer intervals of administration (6-8 and up to 12 hours) than those usually recommended\textsuperscript{6,7}. In all cases bleeding was effectively controlled and none of the patients experienced thrombotic complications despite their high vascular risk. The literature shows a large heterogeneity of rFVIIa dose regimens used in AHA (Table I). With the exception of the study by Hay and colleagues\textsuperscript{10}, in which no correlation was found between clinical response and the dose of rFVIIa used, published studies do not enable a precise analysis of the relationships between doses administered and haemostatic efficacy or the occurrence of thromboembolic complications\textsuperscript{11,13,19,20}. Apart from the heterogeneity of the clinical conditions and bleeding sites in AHA, addressing this issue is made difficult by the lack of currently validated laboratory methods for monitoring treatment with bypassing agents. The possible role of thromboleastographic techniques or thrombin generation tests should be further, extensively investigated\textsuperscript{21}. Again, the different clinical pictures and inhibitor kinetics hamper the extrapolation of data from encouraging studies on inhibitors in congenital hemophilia\textsuperscript{22,23}.

In conclusion, our small case series shows that even lower-dose rFVIIa regimens, which could be considered suboptimal according to international recommendations, can be effective in the management of bleeding in AHA patients. Such regimens may be useful and safe in patients at high risk of thromboembolic complications. We are well aware that this report represents an anecdotal experience. However, in the setting of rare diseases, including AHA, in the absence of strong evidence to support clinical choices, personal experience and individualisation of treatment continue to play an important role. Methodologically rigorous studies are likely to be unfeasible; however, further multicentre and multi-national collection of prospective data remains a reasonable approach

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>Patients, n (bleeds)</th>
<th>Efficacy, %\textsuperscript{b}</th>
<th>rFVIIa treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hay, 1997</td>
<td>Retrospective</td>
<td>38 (74)</td>
<td>100</td>
<td>Median 28 doses (range, 1-541), initial dose 90 µg/kg (45-181), every 2-6 hours over a median of 3.9 days (0-43).</td>
</tr>
<tr>
<td>Baudo, 2004</td>
<td>Retrospective</td>
<td>15 (20)</td>
<td>87\textsuperscript{c}</td>
<td>Median 10 doses (range, 1-60), initial dose 90 µg/kg (46-118), every 2-6 hours over a median of 2.75 days (0-8). Seven patients treated by continuous infusion.</td>
</tr>
<tr>
<td>Sumner, 2008</td>
<td>Registries and literature review\textsuperscript{d}</td>
<td>139 (182\textsuperscript{e})</td>
<td>83</td>
<td>Partially effective in 14% of cases. Ranges of administered dose 60-160 µg/kg, number of boluses 1-33, duration 1-7 days (interval of administration not reported). Ten patients with 12 thrombotic events.</td>
</tr>
<tr>
<td>Ma, 2011</td>
<td>Retrospective, HTRS Registry</td>
<td>87 (193)</td>
<td>95</td>
<td>Partially effective in 12% of bleeds. Median 3 doses (range, 1-240), initial dose 90 µg/kg (22-270), over a median 1 day (1-60). Interval of administration not reported. One thromboembolic event.</td>
</tr>
<tr>
<td>Baudo, 2012</td>
<td>Prospective, EACH2 Registry</td>
<td>174 (NR)</td>
<td>91\textsuperscript{f}</td>
<td>Median 12 doses (range, 3-35), initial dose 90 µg/kg (85-103), median initial interval of administration 3 hours (2-6). Five patients (2.9%) had thrombotic complications</td>
</tr>
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</table>

\textsuperscript{a}Studies reporting at least 15 treated patients are considered; \textsuperscript{b}refers to the number of patients; \textsuperscript{c}very effective or effective in 18/20 bleeds. In 19/20 used as first-line treatment; \textsuperscript{d}combined data from the NovoSeven compassionate and emergency use programmes (1989-1999), the HTRS Registry, and published reports (1999-2005); \textsuperscript{e}bleeding episodes for which efficacy data were available (total reported, n=204). \textsuperscript{f}refers to 159 patients in whom rFVIIa was used as first-line treatment.
in order to clarify this and other unresolved issues regarding the management of AHA.

**Authorship contributions**

MDC designed the study. MDC and AN wrote the first draft of the paper. AC and AMC reviewed the paper for relevant contents. RM performed laboratory assessment.

All the Authors contributed to patients’ clinical follow up, data collection and approved the final version of the paper.

**Keywords:** acquired haemophilia, bleeding, rFVIIa.

**Conflict of interest**

AC received fees as a speaker in educational activities from Bayer Healthcare and Novo Nordisk and acted as a member of an advisory board of Bayer Healthcare.

GDM acted as a speaker or a member of a speaker bureau for Bayer, Biotest, Boehringer Ingelheim, Grifols, Novo Nordisk, Pfizer and Sanofi-Aventis and as a consultant or ad hoc speaker/consultant for Bayer, Biotest, Boehringer Ingelheim, CSL Behring, Eli-Lilly, Grifols, Novo Nordisk and Pfizer.

The remaining Authors state that they have no interests which might be perceived as posing a conflict or a bias.

**References**


