

Acquired Hemophilia A: Diagnosis and Management of a Rare Condition associated with a Severe Bleeding Diathesis

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Acquired Hemophilia A (AHA) is a rare auto-immune disorder caused by an inhibitory antibody directed against circulating coagulation factor VIII. The incidence of AHA has been reported as 1.4 per million/year in general population, being similar in males and females (except in females aged between 15 and 40 years, who show an incidence peak of inhibitor due to pregnancy-related AHA) and increasing with age. It is uncommon in children, with an estimated incidence of 0.045 per million per year in those aged <16 years, rising to approximately 14.7 per million per year in the elderly (aged >85 years) [1].

In around half of subjects with AHA no underlying disorders that might be associated with the development of an autoimmune phenomenon are usually identified ("idiopathic-AHA"). In previous studies an association with other autoimmune diseases was reported in 11.6% of the cases, about one third of which were related to rheumatoid arthritis. There is a well-known association between malignant diseases (solid tumors and lymphoproliferative diseases in particular) and AHA as well as between AHA and pregnancy, with a median interval between delivery and diagnosis of 89 (IQR 21–120) days [2]. Other potentially causative risk factors, such as exposure to drugs, blood transfusions or infections, have rarely been reported, especially in elderly people, and their role remains uncertain. AHA patients often present with severe and massive bleeding. The most commonly affected organ is the skin, mucous membranes, soft tissue and muscles. Gastrointestinal/intra-abdominal bleedings, particularly retroperitoneal hematoma, are often involved. It is notable that hemarthroses most commonly appear in congenital hemophilia A but seldom occur or cause joint damage in AHA [2,3]. AHA is also associated with post-delivery or postoperative bleeding. Although relatively uncommon, intra-abdominal or intracerebral hemorrhage in AHA patients often leads to life-threatening bleeding. Persistent bleeding after surgical procedures, such as intramuscular injection, catheter insertion, and tracheotomy for treatment of underlying or incidentally coexisting diseases, may be the earliest symptom of AHA. This disease presents with a high rate of morbidity and mortality (14-44%, 8-22% respectively). Hemostatic control is therefore the first priority in AHA.

We suspect the presence of acquired hemophilia A when in a patient with no previous personal or family history of bleeding we find an isolated prolongation of activated partial thromboplastin time (APTT), which cannot be corrected by incubating equal volumes of patient plasma and normal plasma (mixing study) for 2 hours at 37°C. A reduced FVIII level with evidence of FVIII inhibitor activity (titrated using the Bethesda assay or its Nijmegen modification) confirms the diagnosis of AHA [4-6]. Even though inhibitor level does not correlate with the severity of bleeding symptoms, patients could be distinguished between those with a low titer inhibitor (<5 Bethesda Unit/ml) and those with a higher one (\geq 5

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5 BU/ml). Such differentiation could be useful for tailoring haemostatic management to the needs of each patient. Treatment of AHA is based on two main aspects: 1) bleeding control and 2) inhibitor eradication.

Bleeding Control

In the EACH2 registry-the main European retrospective registry on AHA subjects over 96% of patients presented with any bleeding event, and severe in over 69%. Of the 482 patients with at least one bleeding episode reported, 144 (30%) received no hemostatic treatment [7]. Treated and untreated patients differed only in Hb level (8.6 vs 10.9 g/dL), site, and severity of bleeding (all $P < .0001$). Consensus recommendations for treatment of bleeding events in AHA [8] suggest the use of bypassing agents (BAs) recombinant activated FVII-rFVIIa, Novoseven[®], Novo Nordisk, or activated prothrombin complex concentrate-aPCC, FEIBA[®], Baxalta) as first-line treatment of bleeds.

In subjects with high titer of inhibitor (\geq 5 BU/ml) the use of by-passing agents is mandatory. rFVIIa is a product of recombinant technology; when administered in pharmacological doses, it activates factor X (FX) on the surface of activated platelets [9,10]; FXa then forms a complex with FVa so as to generate a large thrombin 'burst' [11]. The thrombin burst produces a stable hemostatic plug at the site of vascular injury [9], resulting in bleeding control. In order to manage the bleed, rFVIIa should be used at a dosage of 90 μ g/kg intravenously as soon as possible and should be repeated every 2-3 hours during the first hours of therapy; later, when hemostasis has been obtained, it will be administered as 4-6-8-12 hours for the time required according to the clinician's decision and severity of the bleeding. Alternative activated prothrombin complex concentrate (APCC) could be used to manage bleeding in AHA; it is a plasma-derived product containing mainly factors II, IX, X and FVII both in the activated and non-activated forms. It is capable of inducing thrombin generation by direct activation of FX without needing the participation of factor VIII [12]. In the literature, it is suggested to start with a dosage between 60-100 IU/kg every 8-12 hours up to a maximum of 200 IU/kg daily. When using bypassing agents (rFVII or APCC), the duration of therapy is left to the clinician's decision according to bleeding severity and clinical response. 25% of patients relapse into bleeding with a mean period of recurrence of 14 days (3-45 IQR) [7]. Some authors have shown that maintaining lower doses of aPCC as a "short-term prophylaxis" may be effective in preventing bleeding relapses [13]. Though hemostatically effective, the parallel use of rFVIIa and aPCC is generally not recommended in AHA as a very high incidence of thromboses has been reported. BAs may be associated with thrombotic complications, especially in the elderly with cardiovascular co-morbidity, and should be carried out cautiously, since a literature review reported that 7% of patients treated with rFVIIa

experienced thrombotic events. Another limitation of BAs is the lack of a specific laboratory test to detect the efficacy of both of the products.

In subjects with low inhibitor titer (<5-BU/ml) the use of FVIII concentrates instead of BA should be considered. The efficacy of FVIII in AHA has been reported since the early 1990s. Two protocols of treatment with FVIII concentrates are available from the literature: the first one proposed by Blatt et al. [14] suggests the use of a bolus dose of 200-300 IU/kg body weight (b.w.) followed by continuous infusion of FVIII (4-14 IU/kg/h based on FVIII *in vivo* levels, which have to be monitored and maintained higher than 60% at least in the first hours of treatment); the second protocol suggests a bolus neutralized dose calculated according to inhibitor titer and body weight (20 IU/kg for each BU of inhibitor) plus an additional bolus of 40 IU/kg b.w./daily [15]. The first option allows clinician to adjust the dose in relation to each patient's response and to FVIII activity obtained *in vivo*. In our experience FVIII-VWF concentrates could be safely used in the management of bleeding events in AHA patients with low titer inhibitor, especially in those in whom cardiovascular risk is very high and BA could lead to an increased risk of thrombotic events [16].

DDAVP can be considered in patients with measurable level of FVIII. A literature review of 22 cases showed a good response to DDAVP in patients with low inhibitor titer (<5BU) and a residual FVIII:C level greater than 5% [17]. The response to DDAVP is not predictable then we suggest to use it for minor bleeding episode.

Inhibitor Eradication

In order to avoid bleeding risk in AHA patient inhibitor eradication should be obtained as soon as possible. Different protocols of immunosuppression are used: steroids alone, steroids with cytotoxic agents, rituximab, cyclosporin A, plasmapheresis or immunoabsorption and FVIII immunotolerance. These protocols have been used in different combinations by different groups with varied success rates. The most common treatment options: steroids with or without cyclophosphamide as a first line and rituximab as a second-line therapy will be briefly discussed [18,19].

A retrospective analysis of patients treated with steroids alone showed 76% remission rate versus patients treated with steroids and cytotoxic drugs with 78% RR [20]. This observation has also been confirmed in a meta-analysis from 20 published articles on comparison of the remission rates between steroid treated and combined steroid/cyclophosphamide treated patients [5]. The EACH2 Registry data show a remission rate of 82% in the combination therapy of steroids and cytotoxic agents as compared with 60% in steroid treated patients [21]. The time needed to obtain inhibitor eradication also proved to be significantly shorter using the combined therapy in comparison to steroids alone.

Rituximab has been used in AHA patients with different degrees of success. There are no clear indications in the reported literature that rituximab is superior to other treatment protocols. Most of the reports show that rituximab is more effective when combined with immunosuppressants than when being used alone [22]. The latest EACH2 Registry data show that 59% of the patients treated with rituximab as first-line treatment along with other treatment products achieved remission; however the remission rate was only 42% when patients were treated with only rituximab as first-line therapy [23]. Thus the available evidence shows better efficacy of rituximab as a second-line therapy or when the patient is refractory to other modes of treatment protocols.

Risk of Relapse

Acquired hemophilia is a rare disorder and very little is known about long-term follow-up and the risk of relapse. According to EACH2, which

is the most complete registry available nowadays, relapse was reported in 18% of patients who achieved a complete response (negative inhibitor and normal FVIII activity) with steroids alone. This means that a stable CR after first-line treatment with steroids alone was reported in 68 of 142 (48%) patients. There were 8 (12%) relapses in the steroid and cyclophosphamide group, resulting in a stable CR in 58 of 83 (70%) patients. One patient relapsed after a rituximab-based regimen (3%), resulting in a stable CR in 30 of 51 (59%) patients. Relapse time in the steroid-alone group was a median 134 days (IQR, 36-317 days) after the immunosuppression had been stopped. The steroid and cyclophosphamide group had a relapse after 139 days (IQR, 14-135 days), while relapse after a rituximab based regimen occurred 44 days after CR. The median follow-up of the patients who achieved CR was 149 days (IQR, 30-603 days) after immunosuppression had been stopped [7,13].

Future Perspective

Recently a recombinant porcine FVIII (rpFVIII, Obizur[®], Baxalta) was approved for the treatment of bleeding in AHA. At initial dose of 200 IU/kg and subsequent adjustments to maintain FVIII target levels was effective in the control of bleeding episodes in 86% of cases Clinical studies in which the product was tested showed as the presence of cross reactive antibody against pFVIII before the exposition to the drug as the development subsequently to the treatment. These antibodies appeared to be not related to a reduced clinical efficacy of the therapy [24]. The use of rpFVIII would have the following advantages: 1) to evaluate the clinical efficacy of rpFVIII infused correlating it to the levels of FVIII obtained "*in vivo*". 2) to choice of a dose irrespective of the inhibitor titer 3) to reduce the risk of thromboembolic events. Further studies are needed to confirm these findings.

Conclusion

This disease presents a complex clinical challenge to the treating Internists and Hematologists. As the disease is associated with high mortality, prompt management is necessary. Early recognition, quick diagnosis and timely referral to a specialized center are important for better management of these patients.

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