Acquired hemophilia A: a review of recent data and new therapeutic options

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ABSTRACT

Objectives: Acquired hemophilia A (AHA) is a rare, but potentially life-threatening, bleeding disorder caused by an autoantibody against factor VIII that interferes with its coagulant function.

Methods: We performed a narrative review focusing on the diagnostic aspects of AHA and on the current treatment strategies with particular regard to new data and therapeutic developments.

Results: The management of this severe hemorrhagic disorder is based on the control of bleeding with the use of bypassing agents and on the utilization of a variety of immunosuppressant agents with the goal of eliminating the autoantibody permanently.

Conclusion: The optimal management of AHA should be multidisciplinary and requires a close collaboration between physicians from various specialties.

KEYWORDS

Acquired hemophilia A; factor VIII; bleeding; eradication therapy

Introduction

Acquired hemophilia (AH) is a rare bleeding disorder, with an estimated incidence in the general population of about 1.5 case per million persons/year, caused by circulating autoantibodies directed against a specific clotting factor [1–3]. As factor VIII (FVIII) inhibitors are the most commonly reported autoantibodies, AH is, in the majority of cases, an acquired FVIII deficiency (acquired hemophilia A, AHA) [4–6]. This phenomenon is similar to what happens in congenital severe hemophilia A and B, where alloantibodies against infused FVIII occur about 10 times more frequently than those against exogenous factor IX [7,8].

The incidence of AHA increases with age, being a very uncommon condition in children [9]. The median age of patients at diagnosis was 78 and 74 years in the two largest available cohorts, a prospective study carried out in the United Kingdom [10] and the European Acquired Hemophilia (EACH2) registry [11], respectively, with more than 80% of reported patients being 65 years or older. The age distribution of FVIII autoantibodies is, thus, typically biphasic with a small peak between 20 and 30 years, due to post-partum inhibitors, and a major peak in elderly patients. The incidence in males and females is similar, with an exception in the age group from 20 to 40 years, due to pregnancy-related cases [12–14]. In about half of the cases, FVIII autoantibodies occur in patients lacking any relevant concomitant disease, while the remaining cases may be associated with post-partum period, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders), underlying hematologic or solid cancers, infections, or use of medications (see Table 1 for a detailed list) [15–20].

The bleeding pattern of AHA is quite different from that of congenital hemophilia A. Thus, most patients with FVIII autoantibodies have hemorrhages into the skin, muscles or soft tissues, and mucous membranes (e.g. epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas, post-partum bleeding), whereas hemarthroses, a typical feature of congenital FVIII deficiency, are uncommon [21]. The hemorrhages are often serious or life-threatening and the disease may manifest more dramatically by excessive bleeding following trauma or surgery or by cerebral hemorrhage [21]. AHA is, therefore, considered a severe bleeding disorder, being associated with high morbidity and mortality rates. Severe or life-threatening bleeds, requiring hemostatic and transfusion treatment, occur in 70–90% of patients, being fatal in 5–10% of cases [5]. The clinical impact of AHA is also higher because severity of bleeding is affected by diagnostic delays, inadequate treatment, and bleeding complications during invasive procedures for controlling hemorrhages. These factors may also contribute to the overall mortality rate (between 15 and 42% according to the literature data) [5], which is significantly increased by the underlying diseases and adverse events of treatment (infections or sepsis on immunosuppressive treatment), particularly in elderly patients [11].
In this narrative review, we summarize the main laboratory and therapeutic aspects of this acquired hemorrhagic disorder.

**Laboratory diagnosis**

An anti-FVIII inhibitor should be suspected in the presence of bleeding with sudden onset, often severe, which occurs spontaneously or after minor trauma, following invasive procedures or surgical interventions in patients without a personal or family history of bleeding [22].

The laboratory hallmark for the diagnosis of AHA is a prolonged activated partial thromboplastin time (APTT), not corrected by normal plasma (mixing test), with a normal prothrombin time (PT) [23]. This type of test allows to distinguish between factor deficiency and the presence of an inhibitor. The APTT of mixtures of the patient’s plasma and normal plasma must be determined before and after incubation at 37°C for at least 2 hours, because the inactivation of FVIII is time- and temperature-dependent. An abnormal prolongation of the APTT of the mixture after incubation compared with an immediate correction after mixing is typical of FVIII autoantibodies.

Besides coagulation factor deficiencies, a prolonged APTT may be attributable to the presence of lupus anticoagulant and heparin [23]. Prolonged APTT values of the 1:1 mixture of patient’s plasma with normal plasma which are similar at time 0 and after incubation are indicative of the presence of lupus anticoagulant. The presence of lupus anticoagulant can then be confirmed by specific tests, such as the diluted Russell viper venom time (dRVVT) and tests at low phospholipid concentrations, e.g. the kaolin clotting time and silica clotting time [24]. In addition, the clinical presentation helps the differential diagnosis, as patient with AHA tend to bleed, while patients with lupus anticoagulant tend to have a hypercoagulable state [24]. Both unfractionated heparin and low-molecular weight heparin (LMWH) (at therapeutic doses) may prolong APTT [25]. The presence of unfractionated heparin is suggested by a prolonged thrombin time (TT) with a normal reptilase time [25], while the demonstration of the presence of LMWH requires an anti-activated factor X (FXa) assay [25,26]. In addition, direct FXa and thrombin inhibitors may prolong APTT and their presence is confirmed by anti-FXa (for direct FXa inhibitors) and TT (for direct thrombin inhibitors) assays [25]. In all cases in which an anticoagulant drug action is suspected, the withdrawal of the drug and repeat APTT testing is mandatory. Also vitamin K antagonists usually prolong APTT, but their presence/absence can be easily verified by a prolonged/normal PT [25]. The diagnosis of AHA is, then, confirmed by the reduction of FVIII coagulant (FVIII:C) activity and by the specific inhibitor quantification by the Bethesda assay (or, better, by the Nijmegen modification which has increased sensitivity), in which residual FVIII:C activity is measured after dilution of inhibitor plasma with pooled normal plasma [27,28]. According to the Bethesda unit (BU) measurement, AHA patients are classified as having low (<5 BU/ml) or high (>5 BU/ml) inhibitor titer. Figure 1 shows the algorithm for the diagnosis of AHA.

Similar to the alloantibodies occurring in congenital hemophilia A [29], FVIII autoantibodies are reported as being polyclonal and belonging predominantly to IgG1 and IgG4 subclasses. Moreover, both auto- and alloantibodies appear to react with the same regions on the FVIII molecule (i.e. A2, A3, and C2 domains), thus interfering with its interaction with activated factor IX, phospholipids, and von Willebrand factor [5]. Autoantibodies are thought to arise from the breakdown of peripheral immune tolerance mechanisms which regulate a normal immune response to FVIII [30]. In this context, FVIII-specific CD4+ T cells play a central role, as documented by the observation that inhibitors in severe congenital hemophilia A may spontaneously disappear in conjunction with an HIV-associate decline in CD4+ counts [31]. In particular, a complex interaction between different CD4+ subsets, i.e. Th1 (stimulating B cells to produce IgG1 antibodies) and Th2 (stimulating B cells to produce IgG4 antibodies) cells, is implicated in the synthesis of anti-FVIII antibodies [32]. The breakdown of immune tolerance is thought to be the result of a combination of environmental and genetic factors. Among the latter, some human leukocyte...
antigen class II alleles and a polymorphism of cytotoxic T lymphocyte antigen 4 (CTLA-4) gene have been recently surmised to play an important role [33].

The most striking difference between auto- and alloantibodies consists in their inactivation patterns. Most inhibitors in congenital hemophilia are ‘type 1’, in that there is linear inactivation when the logarithm of the residual FVIII:C activity is plotted against the plasma concentration of the inhibitor. These antibodies completely neutralize FVIII when present in high concentrations. By contrast, most autoantibodies in AHA have a non-linear complex inactivation pattern, which may lead to an underestimation of the inhibitor potency. Notably, in the EACH-2 registry [11], the severity of bleeding at presentation correlated positively with inhibitor titer but not with residual FVIII:C activity, as evidenced by severe hemorrhages in some cases even in the presence of relatively high levels of FVIII:C. Finally, the detection of anti-FVIII IgG autoantibodies by a commercially available ELISA was recently validated as a diagnostic tool for AHA in a prospective multicenter observational study [34]. This assay was found to be similarly sensitive and specific as the Nijmegen Bethesda assay, being probably easier to perform, less difficult to interpret, and less expensive.

Management of acquired hemophilia A

Besides the elimination of the underlying condition, if present and curable, that triggered the FVIII autoantibody, the fundamental aspects of therapeutic strategy in patients with AHA include the treatment of acute bleeding episodes and the long-term eradication of the autoantibody [35] (see Table 2).

Hemostatic therapy

Pertaining to the hemostatic therapy, bypassing agents (recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrates (APCC) are considered the first-line treatment option of bleeding episodes in AHA patients [36–41]. Both types of bypassing agents have been demonstrated to be effective, although there are no comparative trials to demonstrate superior efficacy for either product [42–46]. The efficacy of the plasma-derived product APCC (FEIBA,
Baxalta, Bannockburn, IL, USA) in AHA has been documented by various reports in the literature and by a retrospective review of 34 patients, which showed an overall efficacy of 86% when the treatment was used as the first-line option at a typical dose of 75 U/kg every 8–12 hours [43]. The median number of infusions necessary to control a severe bleeding episode was ten, while six infusions were sufficient in the case of moderate bleeding. The efficacy of rFVIIa (NovoSeven, Novo Nordisk, Bagsvaerd, Denmark), which does not carry the risk of transmission of blood-borne pathogens being a recombinant product, in cases of AHA is documented by the experience in 139 patients in whom it was used as the first-line treatment and was effective in controlling bleeding in 95% [45]. The median dose administered was 90 µg/kg, although there was considerable variability in the dose (60–160 µg/kg), number of infusions (1–33), and duration of treatment (1–7 days). In the EACH2 Registry, rFVIIa was the most frequently used hemostatic agent, with a success rate of controlling bleeding (92%) similar to that of APCC (93%) [47]. The main safety concern remains the thromboembolic risk, reported for both agents [48–50]. Eleven thrombotic events (seven arterial and four venous) were reported in the EACH2, with a similar incidence between rFVIIa (2.9%) and APCC (4.8%) [47]. However, this incidence appears to be higher than that reported in congenital hemophilia and it is probably due to the fact that the older age and additional age-related cardiovascular risk factors in AHA patients enhance the thrombotic risk of bypassing agents.

Alternative treatments, aimed at increasing the levels of circulating FVIII, include FVIII concentrates and desmopressin. Data from the EACH2 registry confirm a significant higher rate of bleeding control in patients treated with bypassing agents than in those receiving FVIII concentrates or desmopressin (93.3 vs. 68.3%, p = 0.003) [47]. Indeed, human FVIII is usually inadequate as hemostatic treatment, unless the inhibitor titer is low (<5 BU/ml) and is administered at doses able to overwhelm the inhibitor, so that hemostatic levels of FVIII can be achieved. Similarly, desmopressin alone or in association with FVIII concentrates may be useful in treating minor bleeds in patients with a low inhibitor titer and measurable FVIII levels [51,52].

Owing to the low cross-reactivity with human FVIII inhibitors, a plasma-derived porcine FVIII concentrate (Hyate-C, Speywood/Ipsen, Wrexham, UK), fractionated from pig plasma, was successfully used for over two decades in AHA [53], but it is currently no longer available. Very recently, however, the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the marketing of a recombinant B-domain deleted factor VIII of porcine origin (susoctocog alfa, Obizur, Baxalta, Bannockburn, IL, USA) with the indication for use in patients with AHA [54,55]. This recombinant product was developed with the aim of eliminating the main limitations of the previous plasma-derived preparation, i.e. the allergic reaction to porcine plasma protein and the risk of viral contamination (in particular parvovirus) [55]. The registration study, evaluating Obizur in 28 AHA patients, was published in 2015 by Kruse-Jarres and colleagues [56]. At the initial dose of 200 U/kg and subsequent adjustments to maintain FVIII target levels, irrespective of inhibitor levels and anti-porcine FVIII cross-reactivity, recombinant porcine FVIII was effective in the control of bleeding episodes in 86% of cases without serious adverse reactions [56]. The safety and the good hemostatic efficacy profile of Obizur in AHA has been confirmed in a case series published very recently by Tarantino and colleagues [57], in which, however, lower loading doses (100 U/kg) were used than those reported in the registration trial.

In patients with a high titer of inhibitor and severe hemorrhages, the extracorporeal removal of the auto-antibody by therapeutic plasmapheresis, or its immunoadsorption to staphylococcal protein A or to polyclonal sheep antibodies against human immunoglobulins, can be used for achieving a prompt, although transient, inhibitor removal and enabling treatment with FVIII concentrates [58–60].

Finally, the hemostatic efficacy of the recombinant humanized anti-factor IXa/X bispecific antibody ACE910 has been recently documented in a primate model of severe AHA, thus making this experimental agent a very promising therapeutic tool for preventing hemorrhages in both acquired and congenital hemophilia A patients [61].

**Inhibitor eradication**

Pertaining to the inhibitor eradication, it is based on immunosuppressive therapy, aimed at inhibiting or eliminating the cellular clone responsible for the synthesis of autoantibodies [35]. A variety of immunosuppressive regimens have been reported, including the use of corticosteroids alone or in combination with cytotoxic agents (cyclophosphamide, azathioprine, 6-mercaptopurine, and vincristine), rituximab,

| Table 2. Therapeutic options for AHA. |
|-------------------------------|------------------------------|
| Treatment | Acute bleeding episodes | Inhibitor eradication |
| Bypassing agents | FVIII concentrates | Prednisone (1 mg/kg/day, 4–6 weeks) alone or with cyclophosphamide (1.5–2 mg/kg/day, maximum 5 weeks) |
| - APCC (50–100 IU/kg, every 8–12 hours, maximum 200 IU/kg/day) | Desmopressin | Azathioprine | Mycophenolate | Vincristine |
| - rFVIIa (90–120 µg/kg, every 2–3 hours) | Recombinant porcine FVIII | Cyclophosphamide | |

APCC: activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII; FVIII, factor VIII.
cyclosporin A, and FVIII immune tolerance [5]. In 30% of cases, however, the autoantibody may disappear spontaneously, a phenomenon that is more commonly observed in pregnancy- or drug-related AHA cases [62]. Different strategies can, therefore, be adopted in different types and subgroups of patients [21]. Thus, while a ‘watch and wait’ approach may be indicated in children, in cases associated with pregnancy and the use of drugs, a combined immunosuppressive therapy may be indicated in AHA cases associated with cancer or autoimmune diseases [21].

The most commonly used therapeutic strategy, which achieves complete remission (CR) in approximately 70–80% of patients, utilizes steroids alone (prednisone 1–2 mg/kg/day for 4–6 weeks) or in combination with cyclophosphamide (1–2 mg/kg per day for a maximum of 5 weeks) [21]. In the EACH2 registry, which included data on the first-line immunosuppression for 276 patients, those given steroids were compared with patients receiving steroids plus cyclophosphamide [63]. Significantly higher stable CR rates with combination therapy versus steroids alone were reported (70% vs. 48%, median time to CR for both regimens: approximately 5 weeks) and this difference remained significant even after adjustment for age, weight, gender, FVIII level, inhibitor titer, and underlying conditions (odds ratio [OR] 3.25; 95% CI, 1.51–6.96; \( p < 0.001 \)) [63]. These findings are in agreement with several other previous reports showing that the first-line treatment with steroids plus cyclophosphamide is more likely to achieve a CR than steroids alone [1,10,64,65]. Nonetheless, the final outcome of treatment, measured as overall survival, was the same for both regimens in all large studies, probably reflecting increased toxicity (in particular infection-related mortality) of the more intensive regimens. Interestingly, in the GTH study enrolling prospectively 102 AHA patients, FVIII \( \geq 1 \) IU/dl and inhibitor concentration <20 BU/ml were independent predictors of overall survival and identified a subgroup of patients with better prognosis who may benefit from less aggressive treatment (i.e. steroids alone) with a lower rate of treatment-related adverse events [66].

Among alternatives to immunosuppressive treatment, cyclosporine, usually in combination with steroids, has been successfully used as a second-line treatment in AHA patients [67–69].

There is increasing experience with the use of the anti-CD20 monoclonal antibody in patients with AHA [70–72]. A systematic literature review of 65 AHA patients treated with rituximab alone or in combination with other immunosuppressive agents reported a complete or partial response in more than 90% (57/65 cases), being the presence of high inhibitor titers (>100 BU/ml) a negative prognostic factor for response to rituximab [71]. In the EACH2 registry, 30 of 51 (59%) patients treated with a first-line immunosuppressive regimen that included rituximab achieved a stable CR, a success rate that was halfway between that achieved with steroids alone (48%) and steroids plus cyclophosphamide (70%) [63]. Furthermore, seven of 14 patients (50%) achieved a stable CR with rituximab-based regimens used after the failure of the first-line drugs or relapse [63]. By contrast, the time to remission with rituximab alone was longer compared with other regimens [63]. Thus, the current evidence supports that AHA patients resistant to the standard first-line immunosuppression respond to the second-line rituximab [21].

Immune tolerance induction protocols, like the ones used for the treatment of alloantibodies in congenital hemophilia, have been proposed also for the eradication of FVIII autoantibodies. The Budapest protocol [73], consisting of 3 weeks of treatment with a combination of FVIII concentrates, intravenous cyclophosphamide and methylprednisolone, resulted in inhibitor eradication in more than 90% of treated cases. Similarly, the modified Bonn-Malmö protocol [74], including a combination of oral cyclophosphamide, prednisolone, large-volume immunoadsorption, high-dose intravenous immunoglobulin, and FVIII concentrates, obtained a rapid (median 14 days) CR in 90% of patients [75].

**Conclusions**

AHA is a rare but often life-threatening condition, the management of which represents a great challenge to physicians. A prompt recognition of this severe bleeding disorder and an early and aggressive treatment are mandatory, as diagnostic delays or inadequate treatments are still associated with high mortality rates. Thus, the optimal management of AHA is multidisciplinary and requires a close collaboration between hematologists operating at specialized hemophilia treatment centers (HTCs) and physicians of many other specialties (laboratory, internal medicine, oncology, rheumatology, geriatric, obstetrics, etc.). In particular, laboratorists play an important role in supporting HTCs as they are involved not only in the diagnostic process, but also in the choice of the therapeutic armamentarium (such as the choice of hemostatic treatment according to the inhibitor titer) and in monitoring of its effects on inhibitor eradication.

For hemostatic treatment, the bypassing agents rFVIIa or FEIBA should be used as the first-line therapy, while the recent marketing of recombinant porcine FVIII represents an interesting, emerging, alternative therapeutic option. Available data suggest that a combination of steroids and cyclophosphamide should be considered as the most-effective approach to eradicate FVIII autoantibody, while regimens including rituximab did not have any advantage in terms of remission rate over other immunosuppressive regimens and thus should be used only as a second-line approach.
Future studies should help us to better identify prognostic factors for remission and survival in AHA patients in order to develop more targeted immunosuppressive regimens able to achieve faster and more durable responses with less toxic effects.

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