bjh review

How I manage patients with acquired haemophilia A

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Summary

Acquired haemophilia A (AHA) is a potentially life-threatening bleeding disorder occurring in patients without a previous personal or family history of bleeding. Development of immune-mediated autoantibodies against coagulation factor VIII is associated with a wide range of clinical disorders including pregnancy, autoimmune disorders, malignancy, or with no apparent disease. There exists great potential for morbidity and mortality related to acute and recurrent bleeding episodes, making prompt diagnosis and treatment necessary. The two primary goals of treatment focus on cessation of bleeding and eradication of the acquired factor VIII inhibitor. No randomized clinical trials have been conducted regarding treatment, so expert clinical opinion guides therapeutic intervention. This current report provides a profile of patient characteristics, an algorithm for diagnosis, and outlines treatment recommendations based upon current guidelines and clinical experience. As first-line interventions for acute bleeding and inhibitor eradication are generally accepted, we will emphasize discussion of second-line therapeutic options.

Keywords: acquired haemophilia, factor VIII inhibitor.

Patient characteristics

Acquired haemophilia A (AHA) or immune-mediated development of acquired factor VIII autoantibodies in non-haemophiliacs is an uncommon but clinically relevant entity that occurs most often in the elderly (Green & Lechner, 1981; Yee *et al*, 2000; Delgado *et al*, 2003; Collins *et al*, 2007; Knoebl *et al*, 2012). AHA has an incidence that ranges between 1·3 and 1·5/million/year and has a biphasic age distribution (Green & Lechner, 1981; Delgado *et al*, 2003; Collins *et al*, 2007; Knoebl *et al*, 2012). A small peak occurs in 20- to 40-year-old patients with a female predominance due to higher incidence in the postpartum period, and a larger peak is found in patients aged over 65 years with recent evidence suggesting slight male predominance (Green & Lechner, 1981; Delgado *et al*, 2003; Collins *et al*, 2007; Knoebl *et al*, 2012). Approximately half of all cases of AHA are idiopathic and it is commonly associated with pregnancy, autoimmune disorders, underlying malignancy, and various medications (Green & Lechner, 1981; Yee *et al*, 2000; Delgado *et al*, 2003; Collins *et al*, 2007; Knoebl *et al*, 2012). (Fig 1)

Bleeding episodes in AHA patients differ from those associated with congenital haemophilia, such that trauma-related muscle bleeds and haemarthroses are uncommon (Knoebl *et al*, 2012). Approximately 5% of patients present with isolated laboratory abnormalities and no bleeding (Knoebl *et al*, 2012), but severe bleeding occurs in the majority of patients and is associated with mortality rates ranging between 7% and 22% (Green & Lechner, 1981; Hay *et al*, 1997; Yee *et al*, 2000; Delgado *et al*, 2003; Collins *et al*, 2007; Bitting *et al*, 2009; Knoebl *et al*, 2012). Spontaneous subcutaneous, deep muscle and retroperitoneal bleeds represent the majority of events, but mucosal (gastrointestinal, lung and urogenital) and intracranial bleeds also occur (Knoebl *et al*, 2012). Death within the first week of diagnosis is associated with gastrointestinal or pulmonary bleeding, whereas later deaths commonly result from intracranial or retroperitoneal bleeds (Collins *et al*, 2007).

Diagnosis

Bleeding in the setting of an isolated prolonged activated partial thromboplastin time (aPTT) in a person without a personal or family history of bleeding should raise concern for AHA. An isolated prolonged aPTT may be seen with a lupus anticoagulant (LA), a specific coagulation factor inhibitor, factor deficiency, or in the setting of heparin therapy (Kershaw & Favaloro, 2012). A 1:1 mixing study will allow for differentiation between the presence of a factor inhibitor and deficiency. An uncorrected mixing study increases the likelihood of an inhibitor (factor VIII inhibitor being most common in patients that are bleeding) (Kershaw *et al*, 2009). Factor VIII inhibitors are autoantibodies that display second-

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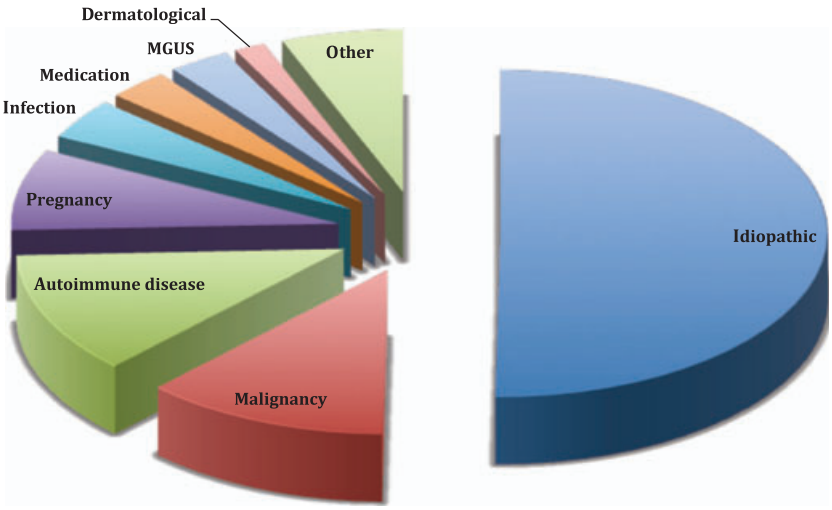

Fig 1. Documented associations with development of factor VIII autoantibodies and acquired haemophilia A, as adopted from data derived from the EACH2 registry (Knoebl *et al*, 2012). MGUS, monoclonal gammopathy of undetermined significance.

order kinetics and therefore result in non-linear inactivation of factor VIII. In the presence of weak autoantibodies, the aPTT may only be prolonged after decay of factor VIII from the normal plasma (Boggio & Green, 2001). For this reason, analysis of the mixing study should be completed at both 0 and 2 h (Verbruggen *et al*, 2009). After confirming the presence of a factor VIII inhibitor, the Bethesda assay (Nijmegen modification) is used to evaluate inhibitor titre levels (Bethesda Units, BU) (Kershaw *et al*, 2009; Verbruggen *et al*, 2009). Inhibitor titre levels do not consistently or directly correlate with disease severity and are not used to guide acute intervention (Collins *et al*, 2007; Baudo *et al*, 2012). However, they should be obtained at the time of diagnosis to monitor disease progression and assess for recurrent bleeding risk (Delgado *et al*, 2003; Collins, 2007; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). LA may mimic the laboratory findings seen in AHA (isolated prolonged aPTT and artifactually low factor VIII levels), so specific testing (dilute Russell's viper venom time or other phospholipid-dependent coagulation assays) is recommended to definitively exclude this diagnosis (Greaves *et al*, 2000). Significantly, LA patients generally will not present with bleeding and specific tests for LA will be normal in the presence of factor VIII inhibitors. If LA is present, enzyme-linked immunosorbent assay (ELISA) may be useful for diagnostic differentiation and for the direct quantification of factor VIII inhibitor (sensitivity 100%, specificity 97·8%) (Shetty *et al*, 2003; Sahud *et al*, 2007). Lastly, all recently hospitalized patients must have a heparin effect excluded with the thrombin time (or other) assay as this can also cause an isolated prolongation of the aPTT. Figure 2 summarizes a diagnostic algorithm for the diagnosis of AHA.

Acute treatment

Development of factor VIII inhibitor is accompanied by a wide range of clinical phenotypes, but in the majority of cases, spontaneous and severe bleeding is observed (Baudo *et al*, 2012). Following prompt diagnosis, consideration must be given for the severity of bleeding, patient co-morbidities, previous history of inhibitor development and accompanying treatment response, need for acute surgical intervention and primary underlying cause. If possible, a haematologist should be immediately consulted for initiation of appropriate therapy and monitoring of treatment response (Hay *et al*, 2000; Baudo & de Cataldo, 2004; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010).

Treatment for AHA is directed at bleeding control, inhibitor eradication to prevent subsequent bleeding episodes, and treatment of any underlying causative disease. No randomized control data is available to guide appropriate intervention, so selection of appropriate treatment has been based primarily on expert opinion. Recent observational data from the European Acquired Haemophilia (EACH2) Registry and proposed guidelines from several groups currently guide selection of initial therapeutic intervention (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010; Baudo *et al*, 2012) (Table I).

How to manage patients with major bleeding episodes

The International Guidelines presented by Hüth-Kuhne *et al* (2009) provide examples of clinical presentations that require acute anti-haemorrhagic treatment. Though this list is not exhaustive, patients should be started on bypass therapy (activated prothrombin complex concentrates (aPCC) or activated recombinant activated factor VII (rFVIIa)) and inhibitor eradication therapy with evidence of retroperitoneal or retropharyngeal haematomas, muscle bleeds, intracranial haemorrhage, gastrointestinal, pulmonary, post-operative bleeding, severe haematuria or bleeding from multiple sites (Hüth-Kuhne *et al*, 2009).

Recombinant FVIIa functions in part by initiating the formation of a complex between tissue factor and factor VIIa. This increases thrombin formation and activates a downstream cascade resulting in accelerated fibrin clot formation at sites of vascular injury (Croom & McCormack, 2008; Franchini & Lippi, 2010). Hay *et al* (1997) reported that treatment of 74 AHA bleeding episodes with rFVIIa was associated with a

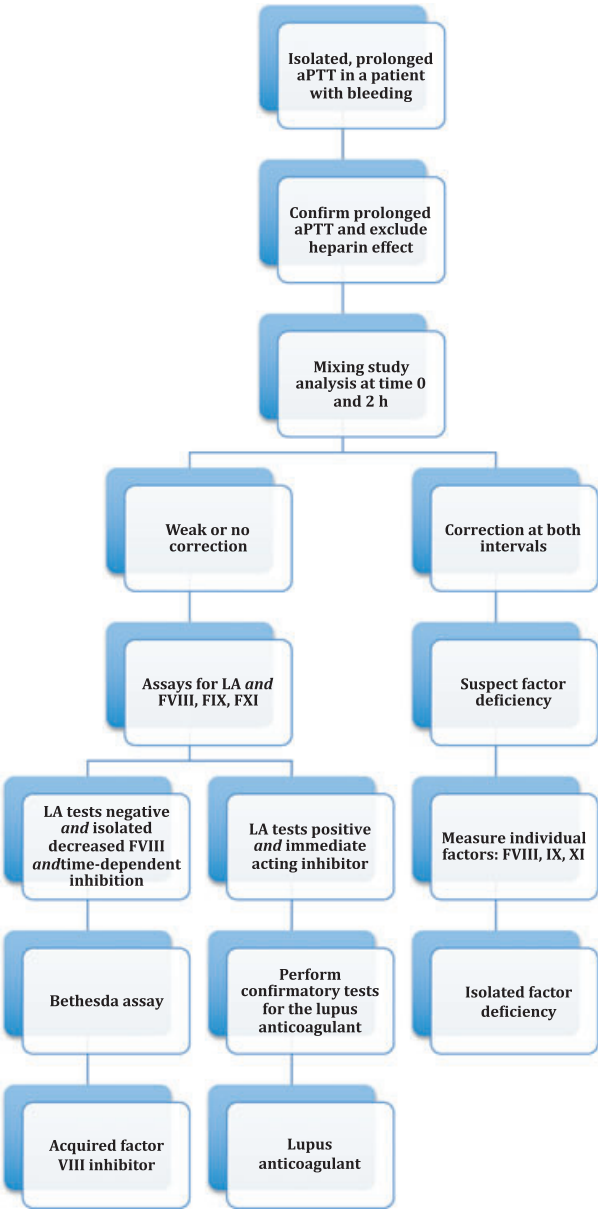

Fig 2. A diagnostic algorithm for the diagnosis of acquired haemophilia A. Patients with an isolated elevation of aPTT should be further evaluated with a mixing study to exclude factor deficiency. Testing to exclude heparin effect and a lupus anticoagulant should also be conducted. Inhibitor titre levels should be obtained with the Bethesda assay. aPTT = activated partial thromboplastin time, AHA = acquired haemophilia A, LA = lupus anticoagulant, FVIII = factor VIII, FIX = factor IX, FXI = factor XI. Adopted from Sborov & Rodgers, 2012 (Sborov & Rodgers, 2012), and reprinted with permission from *Clinical Advances in Hematology & Oncology*.

100% response rate when the drug was used as first-line therapy, 75% good or partial response when used as second-line therapy, and a 17% good or partial response when used as salvage therapy (17%). Importantly, it was noted that patients not responding to rFVIIa within 24 h were unlikely to respond to rFVIIa at any time. These successful results were confirmed by the Italian Registry, which reported an efficacy rate of 90% in a total of 20 bleeding episodes (Baudo *et al*, 2004). Sumner *et al* (2007) reported on data derived from the Hemophilia and Thrombosis Research Society Registry on a total of 182 bleeding episodes. In this report, rFVIIa had an overall response rate of 88% with 95% efficacy as the first-line agent and 80% efficacy when used as second-line or salvage therapy (Sumner *et al*, 2007). The optimal dosing of rFVIIa has yet to be defined, but current recommendations suggest use of 90 μg/kg every 2–3 h until effective haemostasis is achieved (Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010).

The most widely used aPCC is Factor VIII Inhibitor Bypassing Agent or FEIBA. Historically, aPCC safety and efficacy data was derived from congenital haemophilia patients with alloantibodies (Delgado *et al*, 2003), but numerous case reports and retrospective analysis indicate that FEIBA is both safe and effective in controlling acute bleeding episodes in AHA patients (Yee *et al*, 2000; Grunewald *et al*, 2001; Tjonnfjord, 2004). Prior to the EACH2 registry, Sallah (2004) had amassed the largest set of data on FEIBA use in AHA patients, and reported an overall response rate of 86% (100% haemostatic efficacy for moderate bleeds and 76% efficacy in severe bleeds). Additionally, Holme *et al* (2005) reported on 14 AHA patients that all achieved effective haemostasis with aPCC therapy. Recommended doses for FEIBA are 50–100 iu/kg every 8–12 h, with a maximum dose of 200 iu/kg per d (Baudo & de Cataldo, 2004; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010).

Current guidelines support that initial bypass agent selection is based solely upon drug availability and physician preference, as both agents show similar efficacy (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). This recommendation is based primarily on data derived from the FEIBA NovoSeven Comparative (FENOC) Study and the EACH2 registry (Astermark *et al*, 2007; Baudo *et al*, 2012). The FENOC Study was a crossover trial comparing FEIBA and rFVIIa in the treatment of acute bleeding episodes in haemophiliacs with inhibitors. The study failed to reach an equivalency goal, but both agents showed a high success rate (FEIBA 80% and rFVIIa 78%), suggesting that either agent could be used as a first-line agent without preference in this patient population (Astermark *et al*, 2007). The EACH2 registry was a pan-European, prospective database that amassed information on 501 patients and provides the largest set of data on AHA patients to date. With respect to use of either aPCC or rFVIIa as first-line therapy for acute bleeding episodes, it describes similar efficacy patterns for bleeding control as noted by the FENOC Study, but higher response rates in AHA patients (FEIBA 93·3% and rFVIIa 91·2%) (Baudo *et al*, 2012), thereby providing confirmatory evidence that these two agents should be considered first-line therapy.

Bypassing agents are undoubtedly effective and generally well tolerated haemostatic agents in AHA patients. However, these drugs are associated with potentially life-threatening side effects, such as myocardial infarction, disseminated intravascular coagulation, arterial and venous thrombosis, pulmonary embolism, and stroke (Ehrlich *et al*, 2002; Guillet

Table I. Treatment strategies for acquired haemophilia A.

	Bleeding control	Inhibitor eradication
First-line treatment	aPCC or rFVIIa	Steroid ± cyclophosphamide
Second-line strategies	Bypassing agent:	Rituximab ±
	Alternate	Steroid
	Sequential	Cyclophosphamide
	Parallel	Ciclosporin
	Immunoadsorption protocol	Azathioprine
		CVP

rFVIIa, recombinant factor VIIa; aPCC, activated prothrombin complex concentrates; CVP, cyclophosphamide, vincristine, prednisone.

et al, 2002; O'Connell *et al*, 2006; Aledort, 2008; Croom & McCormack, 2008; Katgi *et al*, 2012). Prior to the EACH2 Registry, estimates of adverse events ranged between approximately 2·5 (rFVIIa) and 8·0 (aPCC) per one hundred thousand infusions, with roughly double the risk with use of aPCC (Ehrlich *et al*, 2002; Abshire, 2008; Aledort, 2008). The EACH2 registry adverse event data roughly reflects these prior reports, such that adverse thrombotic events (myocardial infarction, stroke and venous thromboembolism) occurred more often with aPCC (4·8%) than rFVIIa (2·9%) (Baudo *et al*, 2012). Though clinically significant, adverse events with bypassing agents are relatively rare and in patients presenting with acute bleeding, the benefits probably outweigh any risk. As this risk may increase depending on patient co-morbidities, these agents should be used with caution in the elderly and those with underlying malignancy and cardiovascular disease. That being said, it is important to note that there are no absolute contraindications to bypass therapy, especially in the setting of limb or life-threatening bleeding episodes (Hüth-Kuhne *et al*, 2009).

How to manage patients with minimal or no bleeding

In patients presenting with minimal or no bleeding, selection of treatment can be quite difficult. Although a minority of patients (15–30%) with AHA receive no haemostatic therapy (Green & Lechner, 1981; Lottenberg *et al*, 1987; Knoebl *et al*, 2012), all patients with evidence of a factor VIII inhibitor are at risk for disease progression and therefore require intervention. Initiation of eradication therapy is indicated (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010), and clinical presentation and disease progression should dictate whether bypass therapy is initiated. At the very least, further intervention should include avoidance of all invasive procedures, use of routine local haemostatic techniques and potential discontinuation of anticoagulation or antiplatelet therapies (after considering co-morbidities such as coronary stent or valve replacement). In the case of mucosal haemorrhage, additional local therapy with an anti-fibrinolytic agent or topical thrombin may be considered (Sahu *et al*, 1996; Collins, 2011).

Traditionally, factor VIII concentrates and/or desmopressin (DDAVP) were used as first-line agents in patients with acute bleeding. Now, these are only considered in patients with low inhibitor levels (<5 BU) and evidence of insignificant bleeding, or if first-line agents are not readily available (Collins *et al*, 2010; Franchini & Lippi, 2011). This therapeutic strategy aims to attain effective haemostasis by neutralizing the inhibitor and increasing factor VIII levels utilizing bolus doses of plasma-derived or recombinant factor VIII concentrates. The plasma factor VIII level should be determined 10–15 min after the initial bolus and if there is not an appropriate response, a second bolus should be administered. There are no defined guidelines to direct adjustment of factor VIII dosing, but it would be reasonable to increase the dose by 25–50% and monitor for clinical effect. DDAVP (synthetic vasopressin analogue) stimulates the release of endogenous factor VIII and von Willebrand factor. A literature analysis presented by Franchini and Lippi (2011) reports on the use of DDAVP in minor surgical procedures and for treatment of non-life-threatening haemorrhage. A haemostatic effect was observed in 75·7% of patients reported, and the best responders were those with factor VIII coagulant activity (FVIII:C) >5% and inhibitor titre levels <5 BU (Franchini & Lippi, 2011). DDAVP can be used alone or in conjunction with factor VIII, and recommended dosing is 0·3 μg/kg IV or SC with a maximum dose of 24 μg (Collins *et al*, 2010).

How to define treatment failure and what is the next step in treatment?

Assessment of treatment response is based upon numerous clinical measures including stability of the haemogram, bleeding tendency, size of haematoma and degree of pain associated with bleeding. The International Guidelines suggest that treatment failure can be defined as no change in rate of blood loss, unchanged laboratory parameters despite red blood cell transfusions, progression of bleeding based on imaging studies, evidence of continued bleeding after 24–48 h (depending on bleeding severity), recognition of bleeding at a new site, or increasing pain associated with haematoma despite active anti-haemorrhagic treatment (Hüth-Kuhne *et al*, 2009).

Numerous strategies may be incorporated in the setting of initial treatment failure. As both aPCCs and rFVIIa have

shown similar efficacy, it is reasonable to switch to whichever agent has not yet been used. The decision to deem a particular treatment ineffective will be primarily dependent on the severity of bleeding. If bleeding is life threatening, we think it may be reasonable to decrease the threshold for changing therapy more quickly than the 24–48 h recommended by Hüth-Kuhne *et al* (2009). In those patients unresponsive to treatment with single agent bypass therapy, an alternative strategy utilizing sequential or combined use of aPCC and rFVIIa may be employed, understanding that this intervention is associated with increased risk of treatment complications (as reported in both AHA and congenital haemophilia patients) (Abshire & Kenet, 2004; Kraut *et al*, 2007; Miranda & Rodgers, 2009; Ingerslev & Sorensen, 2011). Ingerslev and Sorensen (2011) compiled data in a retrospective analysis on nine patients with AHA that received either sequential or combined treatment with bypassing agents. They found that among these nine patients, one patient developed deep vein thrombosis and pulmonary embolism, one developed fatal cerebral thrombosis and three patients developed disseminated intravascular coagulation (DIC). Treatment schedules and dosing regimens varied in these cases, so correlative data was not analysed. However, this report highlights the increased risk of thromboembolic events with use of combination therapy (Ingerslev & Sorensen, 2011). Conversely, in four congenital haemophilia patients with 48 bleeding episodes, use of alternating (sequential) dose therapy resulted in successful haemostasis without development of thrombosis or DIC (Schneiderman *et al*, 2007). Utilizing a regimen consisting of both bypass agents, either combined or used sequentially is probably an effective therapeutic strategy, but should only be used in life or limb-threatening situations in patients who failed both single agent therapies, considering the associated increased risk of thromboembolic events.

Patients with severe, high titre AHA refractory to conventional bypass interventions may benefit from other alternative strategies for bleeding control. Numerous case reports describe the successful use of immunoadsorption (Guillet *et al*, 2001; Freedman *et al*, 2003; Brzoska *et al*, 2007; Seibert *et al*, 2011), proposing that rapid elimination of acquired inhibitors may be an effective means of achieving control of acute bleeding. Zeitler *et al* (2012) built upon this concept and proposed that use of the modified Bonn Malmo protocol (MBMP) can achieve successful control of acute bleeding and maintain long-term inhibitor eradication in AHA patients (Zeitler *et al*, 2012). This therapeutic strategy theoretically eliminates factor VIII inhibitors, supplements functional factor for acute haemostasis, and utilizes immunosuppressive agents to attain a durable elimination of inhibitor. The protocol includes, (i) large-volume immunoadsorption (2·5–3 × total plasma volume) on days 1–5, (ii) intravenous immunoglobulin (IVIG) substitution (0·3 g/kg body weight/d) on days 5–7, (iii) immunosuppressive therapy with cyclophosphamide (1–2 mg/kg per d) and prednisolone (1 mg/kg per d) from day 1 until remission, and (iv) administration of factor VIII (100–200 u/kg) every 6 h with dose reduction throughout the treatment cycle. Complete remission (CR) was defined as normalization of factor VIII activity with undetectable inhibitor titre levels, and partial remission was defined as attainment of factor VIII levels up to 30% and/or reduction of the inhibitor titre to <5 BU (Zeitler *et al*, 2012). In their latest publication, 53 of 57 patients achieved a complete response at 1 year (93%) and 100% complete response was noted on long-term follow-up. Interestingly, relapses were only seen in those patients that received MBMP as second-line therapy. In patients achieving only partial remission, cancer was the suspected aetiology underlying inhibitor development (Zeitler *et al*, 2012). Overall, the available data on MBMP shows promise, but use of immunotolerance regimens utilizing immunoadsporption are only recommended in the context of life-threatening bleeding or clinical trial (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009).

What if the patient must undergo emergent surgical intervention?

Ideally, invasive or surgical interventions in any acute presentation of AHA should be deferred until there is evidence of inhibitor eradication, but if medically necessary, any procedure should be undertaken at an experienced centre under the guidance of a haematologist (Collins *et al*, 2010). Even in the setting of suspected AHA, extreme caution should be maintained against probable iatrogenic bleeding. As many of these patients may require central venous access, arterial puncture, lumbar puncture or surgery, we recommend initiating therapy with bypassing agents in the pre-procedure setting (Collins *et al*, 2010). Ideal dosing recommendations for AHA patients are not currently available, but treatment can be guided by experience gained with congenital haemophilia patients with inhibitors requiring surgery (Rodriguez-Merchan *et al*, 2004).

Inhibitor eradication therapy

What is first-line therapy for inhibitor eradication?

The control of acute active bleeding is a potentially life-preserving intervention, but the risk of recurrent bleeding events persists until acquired inhibitors to factor VIII are eradicated (Collins *et al*, 2007). Recommendations presented by Collins *et al* (2010) and others state that all AHA patients should receive immunosuppressive therapy upon initial diagnosis independent of bleeding severity (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). As AHA commonly occurs in an older population, patient age and co-morbidities must first be taken into account prior to initiation of eradiation therapy in order to decrease potential morbidity and mortality risk. The optimal therapeutic regimen has not been elucidated, but the current mainstay of inhibitor eradication includes immunosuppression with steroids and cytotoxic agents, alone or in combination. The most widely used agents include prednisone and cyclophosphamide.

As with all data in AHA, there are no randomized control trials to guide initial therapeutic decisions. However, important information is gained from meta-analysis, the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) surveillance study and the EACH2 registry in regards to inhibitor eradication therapy. Delgado *et al* (2003) amassed data on 249 patients and reported that treatment with prednisone alone resulted in a 30% CR, and that addition of cyclophosphamide increased overall response rates to 60–100%. The authors surmized that cyclophosphamide was a more effective agent than prednisone for inhibitor eradication, though at an increased cost of potentially life-threatening side effects (Delgado *et al*, 2003). The results of more recent data suggest a much smaller difference between responses to steroid *versus* steroid plus cyclophosphamide. The UKHCDO presented data from a non-randomized, consecutive cohort study (Hay *et al*, 2006). Response rates in patients treated with prednisone alone were higher (60–70%) than that reported by Delgado *et al* (2003), whereas similar rates were seen with combination therapy (70–80%) (Hay *et al*, 2006). Importantly, no difference in overall survival was noted, suggesting that although combination therapy may be more effective in inhibitor eradication, steroid therapy alone may be an acceptable alternative in patients unable to tolerate the potentially increased side effects from cytotoxic therapy. Aggregate data from 25 studies including data on 134 AHA patients presented by Collins (2011) found an even smaller difference in response rates (76% for steroids alone and 78% for steroid plus cytotoxic agents)(Collins, 2007). The EACH2 Registry, representing the largest available data set to date, argues for the use of combination therapy in the first-line setting. In 294 patients receiving either steroid alone or combination steroid and cyclophosphamide in the first-line setting, response rates similar to those previously reported were seen (80%) for patients receiving combination therapy (Collins *et al*, 2012). However, a lower rate of CR was reported with steroid alone (58%) (Collins *et al*, 2012). As was seen in the UKHCDO report, there was no difference in overall survival between the two regimens (Hay *et al*, 2006; Collins *et al*, 2012). The conclusions of these authors agree with recommendations made in recent guidelines, such that an initial inhibitor eradication regimen should include either prednisone (1 mg/kg per d) alone for 4–6 weeks, or combination of prednisone (1 mg/kg per d) and cyclophosphamide (1·0–2·0 mg/kg per d or 50–100 mg/d) for a maximum of 6 weeks (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). If cytotoxic therapy is used, strong consideration must be given to the possible development of cytopenias and potentially life-threatening infections. For this reason, we think that it is necessary to consider the patient's age and co-morbidities prior to initiating any eradication therapy.

What is second-line therapy for inhibitor eradication?

Alternative options for inhibitor eradication include the use of rituximab, immunoadsorption, or cytotoxic agents other than cyclophosphamide (calcineurin inhibitors, azathioprine, and vincristine) (Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). Importantly, IVIGs are no longer recommended by primary guidelines (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009). Alternate therapy may be considered after 3–6 weeks if there is no increase in FVIII:C or decrease in inhibitor titre observed (Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010).

Rituximab, a monoclonal chimeric antibody to the B-cell CD20 antigen has shown promise as a safe and effective eradication therapy when used alone or in combination with other immunosuppressive agents as second-line or salvage therapy. In 2001 and 2002, use of rituximab in AHA gained momentum. Small case series reported successful treatment of AHA with rituximab salvage therapy for patients not responding to combination cytotoxic therapy and steroid (Kain *et al*, 2002; Wiestner *et al*, 2002). Another study reported a cohort of 10 patients in an open-label trial in which eight patients achieved CR with rituximab (four patients had received prior cytotoxic agents or steroid) (Stasi *et al*, 2004). Three of these eight patients relapsed but subsequently achieved a sustained response after a second 4-week cycle of rituximab. Interestingly, these eight patients had inhibitor titres <100 BU. The remaining two patients that had higher titre inhibitors (>100 BU) showed only a partial response to rituximab, but had complete and sustained responses with addition of cyclophosphamide (Stasi *et al*, 2004). Aggarwal *et al* (2005) then presented a series of four patients that achieved CR with use of rituximab and prednisone as second-line therapy. Further, in a larger data set of 65 patients treated with a rituximab-containing regimen (rituximab with a cytotoxic agent or steroid) in both first or second-line settings, an overall response rate of 92%, and achievement of CR in 88% was observed, further confirming prior reports (Franchini, 2007). More recent data supports earlier studies and further justifies use of rituximab in the salvage setting. In this report of eight patients, a CR rate of 88% was reported when rituximab was used after other therapies (Singh *et al*, 2011). Interestingly, similar to the data presented by Stasi *et al* (2004), two patients with inhibitor titres <100 BU achieved CR with rituximab alone as first-line eradication therapy (Singh *et al*, 2011). Additionally, Boles *et al* (2011) reported similar findings in a retrospective analysis including 12 patients receiving rituximab as first-line eradication therapy (without previous treatment with steroid or immunosuppressive agents). Seven of 12 patients (median titre level of 22 BU) achieved a complete response while those patients with higher titres (834 BU) only achieved a complete response with addition of immunosuppressive agents (Boles *et al*, 2011). Collectively, these studies support the role of rituximab as a potential therapy for inhibitor eradication, but its place in the treatment algorithm remains unclear. In the EACH2 registry, 51 of 331 patients received rituximab in the first-line setting, either alone or in combination. Rituximab alone resulted in CR in 42% of patients, which was less than steroid alone (58%) and less than

combination steroid and cyclophosphamide (80%). Further, a higher CR was achieved with rituximab-containing regimens (64% with steroid + rituximab and 67% with cytotoxic agents + rituximab) than steroid alone, but less than combination steroid and cyclophosphamide (Collins *et al*, 2012). Therefore, we can surmize that combination rituximab + steroid remains a legitimate alternative (albeit less effective) in patients unable to tolerate cytotoxic therapy in the first-line setting. The conclusions of these data support recommendations made by the primary guidelines that rituximab, when used in conjunction with steroid or cytotoxic therapy provides a safe and effective alternative first or second-line inhibitor eradication therapy (Hay *et al*, 2006; Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). Further analysis of available data may be helpful in elucidating whether rituximab alone would be safe and effective in the first-line setting in those patients with lower initial inhibitor titre levels.

In addition to rituximab, examples of other potential second-line agents include immunoadsorption-containing protocols (as noted above) or use of calcineurin inhibitors. Numerous case studies suggest that ciclosporin may be an effective agent for inhibitor eradication (Au *et al*, 2004; Petrovic *et al*, 2000; Kam *et al*, 2011). In the majority of published case reports, calcineurin inhibitors were used as a second line agent after cyclophosphamide failed to induce an adequate response. In these relapsed patients, a high CR rate was achieved with ciclosporin (approximately 90%) (Pardos-Gea *et al*, 2012). Pardos-Gea *et al* (2012) presented 10-year follow-up data on 11 patients treated with calcineurin inhibitor (ciclosporin 5 mg/kg per d or tacrolimus 0·3 mg/kg per d) and steroid (methylprednisolone intravenous pulses at 1 g/d on days 1–3 and prednisone 1 mg/kg per d from day four onward) in combination as first-line inhibitor eradication therapy. Their results were promising, indicating a 91% response rate with achievement of normal factor VIII activity by an average of 6 weeks (Pardos-Gea *et al*, 2012). Though this study was small, at the very least, it provided long-term data on an additional potentially effective eradication agent. It is important to note that the side effect profile in these patients was minimal, although one patient did develop hypertensive posterior progressive encephalopathy.

Data concerning further treatment options is limited, but benefit has been reported utilizing alternate immunosuppressive regimens. In a report of 28 patients that received azathioprine (most commonly in combination with prednisone) at 100–200 mg daily for up to 6 weeks, 19 patients (11 of which received only azathroprine and prednisone) were noted to have either a partial or complete response (Green & Lechner, 1981). Two additional studies reported a total of 13 patients treated with combination azathioprine and prednisone. All patients showed either a partial or complete response except one patient who died (cause not known) (Söhngen *et al*, 1997; Tay *et al*, 2009). Azathioprine probably has a role in eradication therapy, but due to the limited amount of supportive data, its use should be considered only after failure of first- and second-line therapies. Söhngen *et al* (1997) suggested a regimen of azathioprine and prednisone for 6 weeks with discontinuation of immunosuppressive therapy with a factor VIII level >50% and a null inhibitor titre by Bethesda assay for more than 2 weeks.

Vincristine, in combination with cyclophosphamide and prednisone (CVP) is an additional regimen that has shown efficacy for inhibitor eradiation. Lian *et al* (2002) reported on six non-haemophiliac patients with AHA that received CVP (prednisone 100 mg daily on days 1–5, cyclophosphamide 7 mg/kg IV and vincristine 2 mg IV on day 1, followed by cyclophosphamide 3 mg/kg PO daily on days 2–5 repeated weekly for 3–4 weeks unless factor VIII levels normalized). Five of the six patients attained a CR after 1–7 courses (Lian *et al*, 2002). Further supporting the effectiveness of CVP, a meta-analysis of 359 total patients reported that of the patients receiving combination chemotherapy, 94% attained a CR (Bitting *et al*, 2009). The authors concluded from their study that combination chemotherapy (in comparison to combination immunosuppressive therapy or steroid alone) is the most efficacious regimen for decreasing the odds of persistent AHA and death (Bitting *et al*, 2009). Considering its chemotherapeutic element and increased potential for harmful side effects, this therapeutic regimen may only be suitable for younger patients or those with a better performance status.

Monitoring inhibitor eradication

AHA patients are at risk for disease recurrence and acute life-threatening bleeding episodes even after factor VIII autoantibodies are initially eliminated (Hüth-Kuhne *et al*, 2009). For this reason, long term monitoring of these patients is of utmost importance. Following stabilization and cessation of acute bleeding, patients may be monitored on an outpatient basis unless bleeding recurs or the patient requires an invasive procedure (Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010). Routine monitoring utilizing a haemogram, aPTT, inhibitor titre and factor VIII activity should be completed at least twice weekly for hospitalized patients and once weekly for outpatients (for at least 6 weeks). Once CR is achieved, patients can be followed with a haemogram, aPTT and physical examination monthly for 6 months, then every 2–3 months for 6 months, followed by every 6 months after the first year (Hüth-Kuhne *et al*, 2009). Considering a relapse rate of at least 20% and a median time to relapse of 7–9 months after stopping immunosuppressive therapy (Delgado *et al*, 2003; Hay *et al*, 2006; Collins *et al*, 2007, 2010) it is necessary to maintain this schedule to ensure maximum patient safety. If, at anytime, acute bleeding should recur, patients should be considered to have relapsed and will require a full evaluation as noted above. As elevated factor VIII levels are common in AHA patients in remission, it is reasonable to routinely monitor FVIII:C levels to assess for

increased risk of thromboembolism and provide prophylactic management during high-risk situations according to the American College of Chest Physicians Guidelines (Hüth-Kuhne *et al*, 2009; Collins *et al*, 2010; Guyatt *et al*, 2012).

In summary, the immune-mediated production of autoantibodies against factor VIII (factor VIII inhibitors) commonly results in a significant bleeding diathesis in patients without a personal or family history of bleeding. Because of the high morbidity and mortality related to AHA, prompt recognition, appropriate diagnosis and effective treatment is potentially lifesaving. Initiation of bypassing agent therapy and immunosuppression for inhibitor eradication represent the mainstays of acute therapy. Use of aPCC or rFVIIa is accepted as the primary intervention for initial bleeding control and is associated with risk of thromboembolism. Combination cyclophosphamide and steroid is recommended as the initial treatment of choice for inhibitor eradication, but numerous other modalities have shown effectiveness. Reports of successful utilization of immunoadsorption protocols and combination regimens incorporating rituximab, calcineurin inhibitors, azathioprine, and chemotherapy provide additional approaches that can be considered. As data continues to be gathered on different eradication regimens, use of potentially less toxic treatment strategies will provide the clinician with a greater armamentarium to combat this potentially life-threatening disease.

Authorship

DWS drafted the original manuscript and both authors participated in revision of the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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