Critical Bleeding in Acquired Hemophilia A: Bypassing Agents or Recombinant Porcine Factor VIII?

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Introduction

Patients with acquired hemophilia A (AHA) often present in an emergency setting to physicians not specialized in bleeding disorders.[1] If symptoms and laboratory signs are appropriately recognized, physicians will usually consult with experts, who will guide management of the initial bleed, either remotely or after patient referral. In patients with clearly acquired bleeding, isolated prolongation of the activated partial thromboplastin time, and low factor VIII (FVIII) activity, the suspicion of AHA is likely enough to warrant hemostatic treatment in the case of significant bleeding. If time permits, the FVIII inhibitor titer will be quantified by the Bethesda assay (in Bethesda units [BU]/mL), and differential diagnoses (like the acquired von Willebrand syndrome[2] or lupus anticoagulant) will be excluded by appropriate testing, before treatment is commenced.[3,4]

Although the diagnosis of AHA is usually clear-cut,[5] significant delays occur because of lack of awareness by nonexpert physicians. The European Acquired Hemophilia Registry (EACH2) documented a diagnostic delay of more than a week in 35% of patients, and the median time to start of hemostatic treatment was 20 days in these patients.[6] Delayed diagnosis and treatment may result in the accumulation of more severe tissue damage, in particular of large muscle hematomas, making hemostatic treatment more difficult and failure more likely. In EACH2, the only parameter that differed significantly between patients who responded to treatment and those who did not was a delay in time to treatment (median: 1 vs. 4 days).[7]

This narrative review article discusses the optimal use of existing hemostatic treatment options for patients with AHA, with emphasis on advantages and potential risks of particular agents in certain clinical situations.

The drugs discussed herein are summarized in ►Table 1. The inclusion of the bypassing agents (recombinant factor VIIa [rFVIIa] and activated prothrombin complex concentrate [APCC]) as well as recombinant porcine FVIII (rpFVIII) is based on their European Union (EU) licensing status for AHA and international treatment recommendations.[1] Plasma-derived and recombinant human FVIII concentrates are used only if other treatment options are not available and are therefore not discussed here.

Mode of Action

Under normal conditions, thrombin is first produced though the *initiation pathway* at the site of vascular injury by small amounts of factor Xa that are generated by tissue factor (TF) and factor VIIa (►Fig. 1). While this pathway is rapidly switched off by TF pathway inhibitor, initial amounts of thrombin will open the *amplification pathway* by activating factors V, VIII, and XI, resulting in several-fold higher factor Xa generation. Factor VIIIa is the limiting factor, and its inhibitors cause a severe impairment of Xa and thrombin generation.

rFVIIa can restore Xa production and consequently thrombin generation in the absence of FVIII. There is accumulating evidence that this occurs independent of TF through the interaction of rFVIIa with phospholipid surfaces and various receptors on vascular cells.[8]

APCC restores thrombin generation primarily by providing the factor Xa/prothrombin complex targeted to TF-bearing cells and activated platelets.[9] There is an ongoing debate about the risk of disseminated intravascular coagulation and thromboembolism with bypassing agents, because these contain activated coagulation factors (enzymes) rather than pro-factors (zymogens).

rpFVIII restores hemostasis by escaping the antihuman FVIII autoantibodies. As such, rpFVIII appears to replace FVIII in the human coagulation system, with its activation, cofactor activity, and inactivation being apparently very similar to those of human FVIII.[10] Although rpFVIII is a nonactivated cofactor, rather than an active enzyme, a dose-dependent risk of thromboembolism cannot be excluded, given the

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Table 1 Hemostatic agents to treat acute bleeds in AHA

Agent	Recommended starting dose and interval	Laboratory monitoring	Hemostatic effectiveness	Thromboembolic risk
Bypassing agents				
Recombinant factor VIIa (eptacog alfa activated, NovoSeven)	90 µg/kg q 2–3 h	None	Systematic review: 84–96%[12] Registries: EACH2 91%[7]	Systematic review: 0–5%[12] Registries: EACH2 2.9%[7]
Activated prothrombin complex concentrate (FEIBA)	50–100 U/kg q 8–12 h[a]	None	Systematic review: not available Registries: EACH2 93%,[7] US 76–100%[30]	Systematic review: not available Registries: EACH2 4.8%[7]
Recombinant porcine FVIII				
Susoctocog alfa (Obizur)	200 U/kg q 4–12 h	FVIII one-stage clot assay • 30 min and 3 h after first dose • Before and 30 min after subsequent doses	Systematic review: not available Clinical trial: 100% effective or partially effective at 24 h; 86% control of qualifying bleed[14]	Systematic review: not available Clinical trial: 0%[14]

Abbreviations: AHA, acquired hemophilia A; EACH2, The European Acquired Hemophilia Registry.
[a]Maximum daily dose of 200 U/kg body weight must not be exceeded.

compelling evidence for FVIII activity as a major risk factor for thrombosis in the general population.[11]

Data from Registries and Clinical Trials

►Table 1 contains a broad overview on efficacy and safety data.

Efficacy

For rFVIIa, a systematic literature review is available, collating information from >1,000 bleeds in 671 patients.[12] A narrative review, also including data on rFVIIa efficacy in surgery, is available.[13] For APCC, the EACH2 registry provides the most robust information.[7] Its efficacy was compared with rFVIIa by using propensity score matched samples ($n = 57$ per group) and found 93% hemostatic efficacy for both.[7]

rpFVIII efficacy data are available from the registration trial, comprising 29 patients,[14] and from a few case reports and series.[15–18] The trial excluded patients with a cross-reacting antiporcine inhibitor titer of >20 BU/mL. Of the qualifying bleeds reported in evaluable 28 patients, 100% showed an effective or partially effective hemostatic response after 24 hours. Definite bleed control was achieved in 24 of the 28 (86%). Of note, the starting dose of 200 U/kg administered in the trial, and recommended by the manufacturer, has not been used in the real-world reports after licensure.[15–18] The lower doses of 50 to 120 U/kg used in these cases were usually effective. In the Tarantino series,[16] 100 U/kg was used in six of seven patients, and resulted in FVIII peak levels >100 IU/dL in five of those.

Safety

In the aforementioned systematic review of rFVIIa, thromboembolic events have been reported in 0 to 5%.[12] Eight of the 10 studies included in that analysis had also assessed mortality. Fatal thromboembolic events were reported in a Japanese study (two deaths in 132 FVIIa-treated patients) and the Society for Thrombosis and Haemostasis Research (GTH) study (three deaths in 61 FVIIa-treated patients). The thromboembolic safety of rFVIIa was further addressed in a narrative review by Neufeld et al.[19] This collation of all available sources, including registries, postmarketing surveillance, and pharmacovigilance, updated in December 2013, listed a total of 54 thromboembolic events in 50 patients, including arterial (21 events), venous (12 events), and of mixed nature (21 events). Events were fatal in 19 out of 50 patients.

A safety review of APCC, mainly in patients with congenital hemophilia with inhibitors, has been published in 2004.[20] Comparing the number of thromboembolic events, including some events of disseminated intravascular coagulation, to the total numbers of infusions, the author concludes that APCC has a favorable safety profile. However, the data cannot be extrapolated to the population of patients with AHA because of obvious differences in age and cardiovascular risk factors. In the EACH2 registry, the number of patients with thromboembolic events was 3 in 63 treated with APCC (4.8%), 5 in 174 with rFVIIa (2.9%), and 0 of 70 (0%) with human FVIII or desmopressin.[7]

With rpFVIII, no thromboembolic events have been reported so far,[14–18] but the total number of patients (~40) is too low to allow for a good estimate.

Conclusions from Published Data

In summary, the data from registries and one clinical trial suggest an overall similar hemostatic efficacy of all three agents. Thromboembolic complications are a concern with bypassing agents, but the rate appears to be acceptably low considering the advanced age and risk profile of patients with AHA. The thromboembolic safety of rpFVIII needs to be studied in larger cohorts of patients before conclusions can be made.

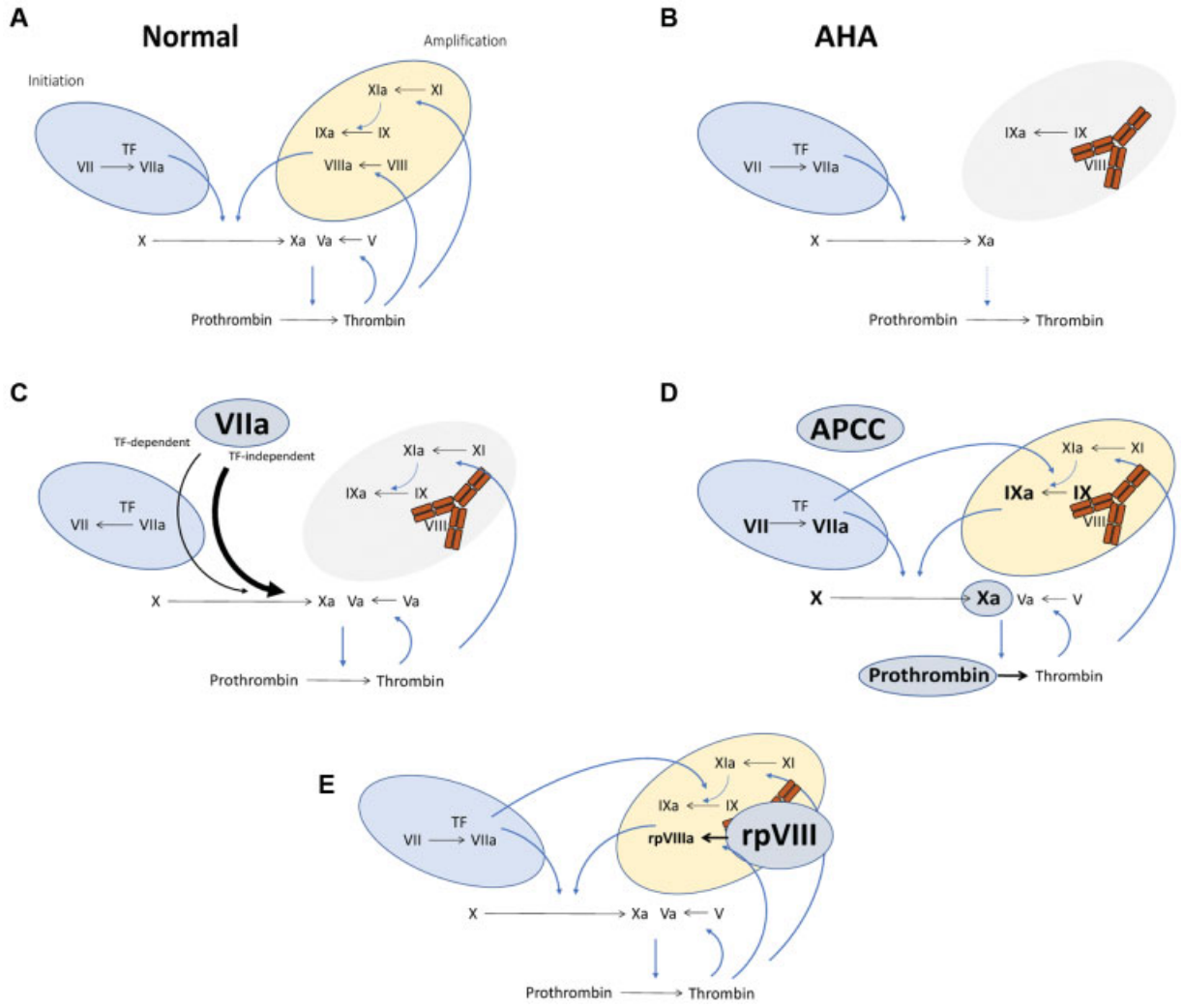

Fig. 1 **Simplified mechanisms of thrombin formation.** (**A**) Initiation and amplification pathways under normal conditions. (**B**) Impaired amplification in AHA due to anti-FVIII inhibitor. (**C**) rFVIIa restoration of Xa and thrombin formation. (**D**) APCC augmentation of thrombin generation (APCC components in bold). (**E**) rpFVIII restoration of amplification. AHA, acquired hemophilia A; APCC, activated prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; rpFVIII, recombinant porcine FVIII.

Other Considerations

Advantages and disadvantages of the bypassing agents and rpFVIII are listed in ►Table 2. In addition to clinical study data, however, some additional considerations may apply when choosing an agent as first-line treatment for real-world practice.

Licensing Status

In the European Union and the United States, both bypassing agents and rpFVIII are licensed for treatment of bleeds in AHA. rpFVIII is only distributed for in-house administration in hospitals, whereas bypassing agents could at least theoretically also be used in an outpatient or home care setting.

Uncertain Diagnosis

None of the agents are approved for acquired von Willebrand syndrome (AVWS), a disorder that could occasionally be confounded with AHA if just a low FVIII activity would be available in a bleeding patient in an emergency situation. It is not expected that rpFVIII would work in this situation, whereas rFVIIa has at least been suggested to be useful in AVWS.[21]

Availability of Agents

Given the potential harm from treatment delays, therapy should be started immediately in patients with AHA and clinically significant bleeding. Efficacy and safety data do not favor one drug over the others to an extend that would justify a delay because an agent is not immediately available or because additional laboratory tests or diagnostic procedures would be awaited to help guiding treatment. Therefore, physicians should use the drug that is immediately available.

AntiporcineCross-Reactivity

Patients with cross-reacting inhibitors >20 BU/mL were excluded from the registration trial of rpFVIII because testing of antiporcine cross-reactivity is not a requirement according to its current licensing status.

As shown recently in the GTH study, 44% of patients have at least some cross-reactivity of their anti-FVIII inhibitor

Table 2 Advantages and disadvantages of hemostatic agents to treat acute bleeds in AHA

Agent	Advantages	Disadvantages
Bypassing agents		
Recombinant factor VIIa (eptacog alfa activated, NovoSeven)	• Largest record of data including systematic reviews of registries • Consistent efficacy regardless of inhibitor titer • Long-term safety data available • Short duration of action in patients at risk of adverse events • Would probably also work in the case of acquired von Willebrand syndrome (AVWS) misdiagnosed as AHA in an emergency	• Frequent injections needed • Laboratory monitoring not available
Activated prothrombin complex concentrate (FEIBA)	• Consistent efficacy regardless of inhibitor titer • Efficacy similar torFVIIa • Long-term safety data available	• Risk of disseminated intravascular coagulation when exceeding maximum daily dose • Laboratory monitoring not available
Recombinant porcine FVIII		
Susoctocog alfa (Obizur)	• Can be monitored with standard FVIII assay • Efficacy and safety demonstrated in prospective, interventional clinical trial • Potentially low(er) risk of thromboembolic events compared with bypassing agents	• Risk of pre-existing or de novo cross-reacting inhibitors requires close monitoring of FVIII activity throughout treatment

Abbreviations: AHA, acquired hemophilia A; rFVIIa, recombinant factor VIIa.

with rpFVIII at baseline.[22] In patients with antihuman titers >100 BU/mL, the estimated likelihood of cross-reactivity was 97%. Cross-reactivity was usually of low titer (<5 BU/mL against porcine), which may not always preclude successful treatment. However, close monitoring of the FVIII activity is required. A review of data from the registration trial highlighted that patients with cross-reactivity needed much higher doses compared with patients without cross-reactivity (median 1,400 and 300 U/kg, respectively, in the first 24 hours).[23] Therefore, the use of rpFVIII in patients with known cross-reacting inhibitors (>0.6 BU/mL) or very high antihuman titers (>100 BU/mL) may not be cost effective.

In the Tarantino series,[16] treatment was clinically effective in five of the seven patients. Those who did not clinically respond to rpFVIII had very high antihuman FVIII titers (205 and 374 BU/mL), supporting the notion that cross-reactivity may be likely in patients with antihuman titers >100 BU/mL and may in fact jeopardize clinical efficacy. In one of the patients with treatment failure, the authors reported no meaningful increase in FVIII activity after dosing and a cross-reacting anti-rpFVIII inhibitor of 2 BU/mL detected retrospectively in a backup sample from day 1.

On these grounds, it appears currently not advisable to use rpFVIII if (1) cross-reacting antiporcine inhibitors are already known or (2) antihuman titers of >100 BU/mL exist. In all patients treated with rpFVIII, close monitoring of the FVIII activity is required 30 minutes after each dose (peak) and before each subsequent dose (trough), and cross-reactivity should be suspected if peak or trough levels are significantly lower than expected.

Safety Profile

Patients with AHA are usually of advanced age, and cardiovascular comorbidity was reported in approximately 30%.[6,24,25] Given an overall thromboembolic event rate of 0 to 5% for the bypassing agents, it is not justified withholding these drugs in patients with concomitant cardiovascular disorders or atrial fibrillation.

A preference for rpFVIII in such patients may be considered on theoretical grounds, but data from clinical trials and other sources are insufficient to demonstrate superiority over the bypassing agents. It should be noted that the recommended starting dose of rpFVIII 200 U/kg will result in supraphysiological FVIII activity in patients without cross-reacting inhibitors, and increased FVIII activity is a known risk factor for thromboembolic disorders in the general population. Therefore, the use of lower starting doses (50–100 U/kg) and close monitoring of peak and trough levels,[15] avoiding FVIII activity above the normal range, may provide the most appropriate management of AHA patients, in whom a particularly high cardiovascular risk is suspected.

Monitoring Requirements

Attempts to establish a relationship between laboratory assays and clinical efficacy of bypassing agents have not been successful.[26] Although it may be seen as a limitation not to have a monitoring test available, it is also an advantage to know that efficacy is consistent among different patient groups (e.g., high vs. low inhibitor titers) and that monitoring is not required.

With rpFVIII, monitoring of FVIII activity is possible and actually required to exclude that treatment is insufficient due to cross-reacting inhibitors. It may also help to avoid overshooting FVIII activity that may potentially increase the risk of thromboembolism.

Cost

Comparative pharmacoeconomic studies are currently not available. Comparing the cost of starting doses, rpFVIII appears to be more expensive than bypassing agents, but

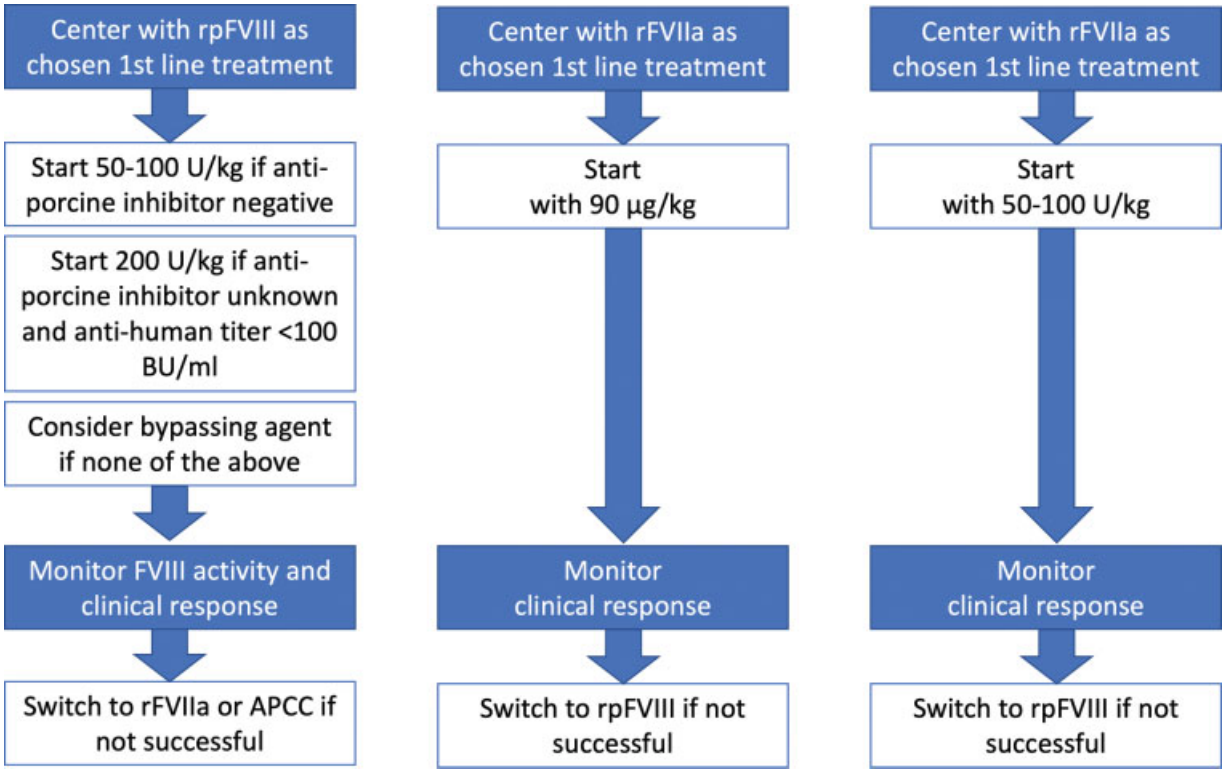

Fig. 2 Proposed algorithm for hemostatic agent selection in acquired hemophilia A (AHA).

dosing intervals and treatment duration determine the overall cost much more than the starting dose.

Personal Experience

Given the rarity of AHA, even experts usually treat just a few cases per year.[27] It may not be advisable, even for experts, to use different first-line therapies without reason in their routine practice. Professional experience can best be achieved by using an institutional treatment standard that specifies criteria for choosing a first-line treatment based on local availability, monitoring abilities, and cost considerations. Examples are shown in ►Fig. 2.

Switching an Ineffective Treatment

Although high efficacy rates have been documented for all treatment modalities discussed here, treatment is sometimes not entirely successful. This may include the development of de novo antiporcine inhibitors during the treatment with rpFVIII, or rebleeding after withdrawal or dose reduction of any agent. In this situation, switching to another treatment may be advisable.

Depending on the clinical circumstances, efficacy assessment and a decision to switch should made after 6 to >24 hours.[28] If time permits, longer time intervals may be justified before switching. In particular, when switching from a bypassing agent to rpFVIII, time may be well spent testing for antiporcine inhibitors to foresee if a switch will be likely successful.

Future Directions

Given that all AHA registries date back to the time before rpFVIII became available, it is important to collect more data allowing for a better comparison between rpFVIIIand the bypassing agents. It should also be noted that neither bypassing agents nor rpFVIIIis ideal for prophylactic use in AHA. Novel agents such as the nonfactor replacement therapies could possibly be useful to protect patients with AHA from bleeding until they achieve remission.[29] However, the safety and efficacy of such agents requires dedicated studies in AHA because data cannot be extrapolated from the usually younger and less ill population of patients with congenital hemophilia.

Conclusions

Both the bypassing agents and rpFVIII are established treatment modalities for acute bleeds in AHA. Institutional treatment standard should be in place, and treatment should be started with an agent that is immediately available. If rpFVIII is used, monitoring of FVIII activity is important and should be available around the clock. In the presence of cross-reacting antiporcine inhibitors, which is particularly likely in patients with antihuman titers >100 BU/mL, rpFVIII may be needed in very high doses, and bypassing agents may be more cost effective. If the cardiovascular risk is a particular concern, use of rpFVIII administered in low doses under close monitoring may be appropriate. Future registries should be set out to allow for a better comparison of bypassing agents and rpFVIII.

Conflict of Interest

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