

CASE REPORT

Recombinant porcine factor VIII in acquired hemophilia A: Experience from two patients and literature review

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Abstract

Background: Acquired hemophilia A (AHA) is a disease caused by antibody formation inhibiting the function of factor VIII, causing bleeding. Recombinant porcine factor VIII (rpFVIII) escapes human FVIII antibody recognition and can provide life-saving hemostasis. However, the development of antibodies against pFVIII can limit its use. We report two cases in which loss of response to rpFVIII occurred, likely because of inhibiting antibodies. In case 1, the patient achieved hemostasis but lost response to rpFVIII within a few days. In the second case, rpFVIII controlled bleeding but the patient experienced diminishing half-life of rpFVIII infusions over time, necessitating a switch to emicizumab which provided lasting hemostasis.

Key Clinical Question: Based on our experience with these cases, we reviewed the available literature regarding the use of rpFVIII in AHA. The Key Clinical Question was to determine how often inhibitors were associated with rpFVIII treatment failure.

Clinical approach and conclusions: We identified 43 AHA patients across five studies who were treated with rpFVIII. Twenty-two patients (51%) developed pFVIII inhibitors and seven cases (16%) reported loss of efficacy associated with an inhibitor. In conclusion, rpFVIII can be a life-saving therapy in AHA. However, clinicians should be aware that pFVIII antibody development can reduce the efficacy and duration of response. Recombinant pFVIII's limitations support the utility of further investigation of alternative therapies such as emicizumab in early AHA management.

Essentials

- Recombinant Porcine Factor VIII (rpFVIII) is designed to stop bleeding in Acquired Hemophilia A.
- We report two cases of AHA in which loss of response to rpFVIII occurred.
- We review the literature showing 21% of patients with AHA failed treatment with rpFVIII.
- Alternative hemostatic therapies for AHA like emicizumab show promise and deserve further study.

This work was carried out at the University of Colorado Anschutz Medical Campus.

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1 | INTRODUCTION

Acquired hemophilia A (AHA) is a disease affecting 1.48 persons per million per year with a mortality rate as high as 20%.¹ It is characterized by the development of antibodies that target and inhibit factor VIII (FVIII) of the coagulation cascade, leading to abnormal, sometimes catastrophic bleeding.^{1,2} AHA manifests as spontaneous bleeding in the form of soft-tissue hematomas, mucosal bleeding, or prolonged postpartum and procedural bleeding.³ It is associated with a prolonged and abnormal mixing study wherein the activated partial thromboplastin time (aPTT) does not correct or will correct only transiently.⁴ A FVIII activity level and Bethesda inhibitor assay can confirm the diagnosis.

Treatment for AHA involves control of bleeding in conjunction with suppression of the FVIII inhibiting antibody. The latter is accomplished through the use of high-dose steroids along with either rituximab, cyclophosphamide, or IVIG, which are successful in inducing remission in 59%–89% of patients. However, prolonged therapy sometimes lasting for months could be required.^{1,5} Remission is durable in most patients, with 80% of patients never experiencing relapse.²

Several agents are available to control abnormal bleeding in patients with AHA. Bypass agents such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates are 75%–93% efficacious in controlling bleeding in AHA.^{2,5,6} In addition to a lack of efficacy for some patients, bypass agents are limited by their risk of thrombosis and lack of reliable laboratory-based monitoring tools (2.9% and 4.8%, respectively).^{2,7}

An alternative to bypass agents in the treatment of AHA is recombinant porcine factor VIII (rpFVIII). As a result of differences in the A2 and C2 domains between human and porcine FVIII (pFVIII), rpFVIII can often escape recognition by human FVIII (hFVIII) antibodies.⁸ Compared with bypass agents, rpFVIII is possibly less thrombogenic and can be monitored with aPTT and FVIII activity levels. As a result of low-level cross-reactivity between human and pFVIII, up to 35.7% of patients will have pFVIII antibodies before receiving rpFVIII.⁷ Porcine antibodies can also develop during administration of rpFVIII and lead to an increase in hFVIII antibodies.

We describe two cases of AHA bleeding in which patients lost response to rpFVIII, probably because of pFVIII antibodies. A literature review of prior publications relating to pFVIII antibody development and efficacy in this population is also included.

2 | CASE 1

A woman in her early 70s presented to an emergency room with nausea, vomiting, and bruising and was found to be in hemorrhagic shock with a hemoglobin level of 5.7 g/dl and severe coagulopathy, including an aPTT of 88.1 s. She had been admitted 1 month prior for hematemesis attributed to esophagitis. During that hospitalization, she was also found to have a spontaneous rectus sheath hematoma. A computed tomography angiogram of the chest/abdomen/

pelvis showed the previously reported rectus sheath hematoma had increased in size and was accompanied by a new, large, left chest wall hematoma. Hematology was consulted and a diagnosis of AHA was confirmed with a FVIII activity level of <1% and a Bethesda titer of 180.8 BU.

She was treated with rFVIIa infusions every 2 h at a dose of 100 mcg/kg and tranexamic acid 1 g IV every 8 h. She was given prednisone 1 mg/kg daily, IVIG 500 mg/kg, and rituximab 1 g. She continued to require packed red blood cell transfusions, and a repeat chest imaging suggested ongoing active arterial extravasation into the thoracic wall hematoma. Arterial embolization was attempted and ineffective. The patient was then switched from rFVIIa to a loading dose of rpFVIII at 200 units/kg.

After the first dose of rpFVIII, her bleeding resolved. Her aPTT normalized and her FVIII activity level was 128%. She was continued on rpFVIII targeting FVIII troughs of > 60%. Three days later, the patient's FVIII activity troughs, peaks, and half-life began markedly decreasing. A pFVIII Bethesda titer was not collected. Upon the loss of response to rpFVIII, the development of an inhibitor was suspected. Figure 1 illustrates the time course of her FVIII activity in relation to rpFVIII administration.

Despite an increased dose and frequency of rpFVIII infusions, she exhibited recurrent chest wall bleeding and new bleeding from her left inguinal vascular access site. On hospital day 6, she was switched back to rFVIIa. Her bleeding remained uncontrolled and, as a result of other complications related to her critical illness, family members decided to transition her to comfort care and she died on day 7 of her hospitalization.

3 | CASE 2

A man in his 90s presented to the emergency room with diffuse bruising and right hip pain. He was found to have a hemoglobin of 8.7 g/dl, and a magnetic resonance imaging scan of his right hip revealed a gluteal hematoma. His aPTT was prolonged at 117.1 s and did not correct with mixing. His chromogenic assay FVIII activity level was <1% and his Bethesda assay was 331.5 BU/ml, consistent with a diagnosis of AHA.

Recombinant FVIIa infusions were started every 2 h at a dose of 90 mcg/kg along with prednisone 1 mg/kg daily and rituximab 375 mg/m² weekly. The patient experienced adequate hemostasis with these interventions and rFVIIa was slowly tapered off. However, 1 week after being discharged, he returned with hypotension and worsening anemia (Hb 7.8 g/dl) secondary to a new right iliopsoas hematoma. His FVIII activity level remained undetectable, and his Bethesda titer remained elevated at 89.8 BU. He was restarted on rFVIIa but after 48 h was still requiring packed red blood cell transfusions. He was therefore switched to rpFVIII, which was titrated to a FVIII activity level trough of 40%–60%. His pFVIII Bethesda titer was 0.4 BU before initiation of rpFVIII and, although he required increasing amounts of rpFVIII over time and his hFVIII Bethesda titer increased to 104 BU, his pFVIII inhibitor remained stable.

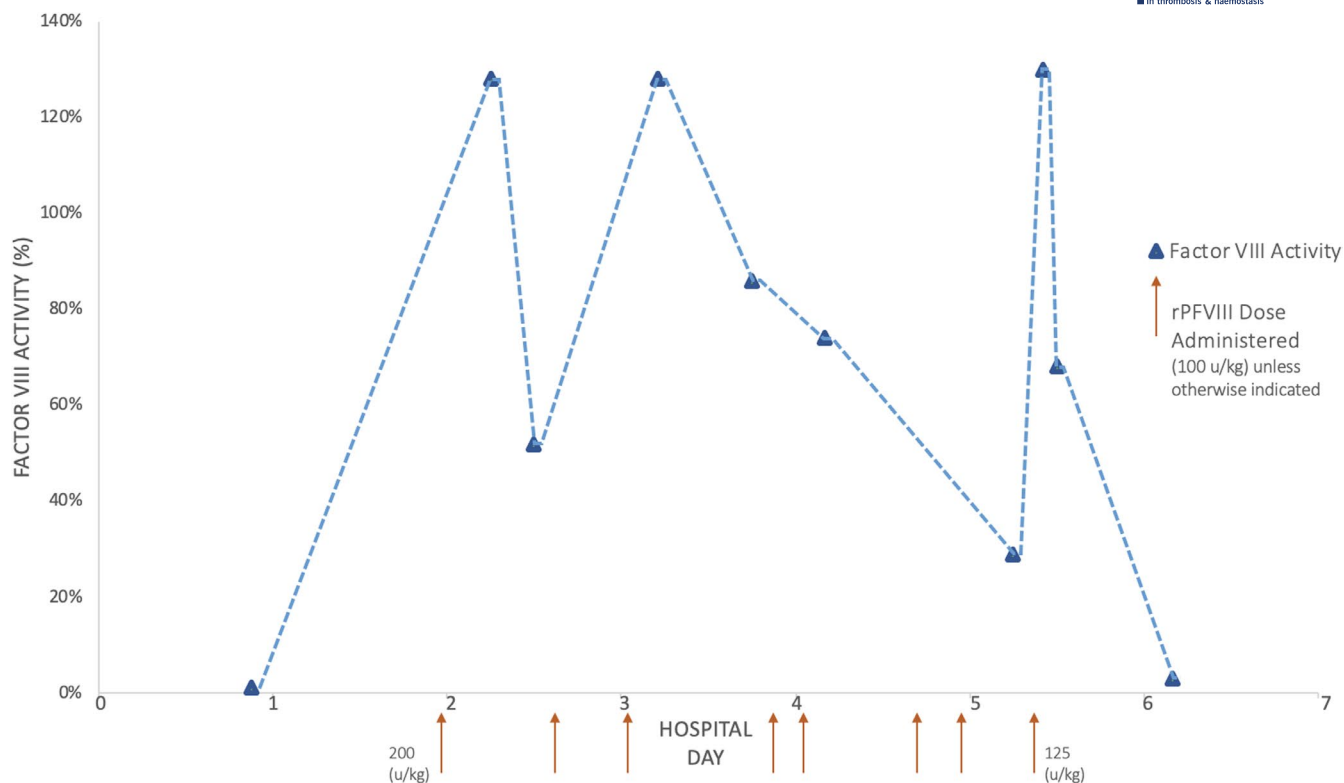


FIGURE 1 Factor VIII activity over hospital course in days along with timing of rPFVIII doses. Abbreviations: FVIII, factor VIII activity; rPFVIII, recombinant porcine factor VIII

TABLE 1 Literature review summary

Author (N = number of subjects)	Primary bleed hemostatic control with rpFVIII	Median days of rpFVIII use	Patients with pFVIII ab during treatment	Time to discontinuation because of lack/loss of response
Kruse-Jarres et al. ⁹ (N = 28)	24/28	7	15/28	Subject 7: 1 day (inh) Subject 8: 1 day Subject 18: day 8 (inh) Subject 15: day 85 (inh)
Khan et al. ¹⁰ (N = 5)	5/5	5	2/5	None
Tarantino et al. ⁸ (N = 7)	5/7	14	3/7	Subject 1: day 26 (inh) Subject 2: day 8 (inh) Subject 3: day 17 (not reported) Subject 4: day 3 (inh)
Owen et al. ¹¹ (N = 1)	0/1 ^a 1/1 ^a	12	1/1 0/1	Day 1 (inh)
Stemberger et al. ¹² (N = 2)	2/2	12	2/2	

Abbreviations: ab, antibody; inh, porcine inhibitor present; pFVIII, porcine factor VIII; rpFVIII, recombinant porcine factor VIII.

^aOne patient was exposed to rpFVIII on two separate occasions separated by 28 days. This patient had a pFVIII Bethesda titer of 5.4 BU at baseline and had no initial response to rpFVIII. A Bethesda titer against pFVIII was reassessed and found to be 0 BU, at which point patient was rechallenged and had a good clinical and FVIII response to rpFVIII.

The patient achieved hemostasis after being on rpFVIII for 2 weeks. However, because of the slow improvement in the hFVIII inhibitor and a diminishing half-life of the rpFVIII infusions, he was started on emicizumab and rpFVIII was stopped 3 days after the first dose of emicizumab. In total, more than 30 doses of rpFVIII were administered to

the patient before its discontinuation. Emicizumab was given at 3 mg/kg weekly for a total of 3 weeks and then every 3 weeks at 1.5 mg/kg. His hemoglobin remained stable and he was able to be discharged back to a rehabilitation center with a FVIII activity of 2%. He received a total of six doses of emicizumab, which was discontinued after his factor VIII

activity level reached 29%. Shortly after this, he was discharged to the care of family members and was subsequently lost to follow up.

4 | LITERATURE REVIEW

Using the MeSH feature on PubMed to initiate our search, we searched the terms “acquired hemophilia” and “porcine.” Articles that included patients with congenital hemophilia A were excluded. Studies in which nonrecombinant porcine FVIII was used were also excluded. A total of 35 total articles were generated. Twenty-five of the 35 titles appeared relevant to our investigation. Of those 25 titles, nine abstracts addressed the topic of rpFVIII’s use in AHA and five presented primary data on the efficacy of rpFVIII in controlling AHA-related bleeding. Table 1 summarizes the information presented in those five articles.

Across the five identified studies, a total of 43 patients with AHA were treated with rpFVIII. Thirty-seven patients (86%) achieved primary bleed hemostasis during treatment. Twenty-two patients (51%) were found to have inhibitors to pFVIII, either from inherent cross reactivity with the hFVIII or from *de novo* inhibitor formation after receiving rpFVIII. Nine patients (21%) experienced a lack or loss of efficacy with rpFVIII, seven of whom had pFVIII inhibitors.

5 | DISCUSSION

Recombinant porcine factor VIII is an effective up-front therapy for acute bleeding resulting from AHA. Both patients in our case series and 37/43 (86%) patients in the literature review attained hemostasis with its use. However, >20% of patients in prior studies and both patients described here experienced a diminished response to rpFVIII over time, most of which were associated with a pFVIII inhibitor. Patients who attained a good clinical response and FVIII activity level in the presence of a pFVIII inhibitor often did so through administration of higher rpFVIII doses and more intense monitoring.⁷

Several of the patients in the review and both patients in our case series experienced or developed inadequate hemostasis with bypass agents and rpFVIII, underscoring how difficult it can be to control bleeding in AHA. The clinical limitations of bypass agents and rpFVIII present a need for broader hemostatic options in the management of AHA.

Emicizumab has been proposed as a novel agent for treating patients with AHA. Emicizumab is a recombinant, bispecific, FVIII monoclonal antibody that mimics the role of FVIII in the coagulation cascade by approximating factor IX and factor X. It is effective at preventing bleeding in individuals with congenital hemophilia both with and without inhibitors.^{13,14} A few small studies have investigated the use of emicizumab for the treatment of AHA. In the largest study by Knoebl et al., 12 patients with bleeding from AHA received emicizumab until endogenous FVIII

activity rose to >30%. One to 3 days after the initial injection, patients experienced normalization of their aPTT and hemostasis was achieved with cessation of bypassing agents after an average of 1.5 days. No rebleeding occurred in any of these 12 patients. Two patients experienced arterial thrombotic events associated with concomitant use of bypass agents and emicizumab.¹⁵ Four additional published reports demonstrating successful use of emicizumab in AHA have been published.¹⁶⁻¹⁹ Emicizumab was also effective in treating case 2 in our series after bypassing agents and rpFVIII had failed. Based on results from these cases, emicizumab appears to be a promising potential therapy in AHA and may limit the need for prolonged use of rpFVIII and other bypass agents, shorten the duration of hospitalizations, and reduce morbidity and mortality caused with bleeding.

Despite these encouraging results, the underlying pathophysiology and hemostatic milieu of AHA is distinct from that of congenital hemophilia, and larger studies are needed to determine if emicizumab is safe and efficacious for the management of AHA. Because the onset of action of emicizumab is slow, an examination of how to safely administer this medication together with rpFVIII and bypass agents (in particular, activated prothrombin complex concentrates) during active bleeding is greatly needed. If ongoing studies support a role for emicizumab in AHA, its subcutaneous route of administration may allow for earlier outpatient management, which has the potential to offset its cost, especially if it leads to a reduction in bleeding events.

6 | CONCLUSION

Although rpFVIII is efficacious in controlling acute bleeding in most patients with AHA, inhibitor development presents a limitation to its use in a disease where other alternatives are lacking. There is a need to find alternatives that offset the bleeding risk in individuals with AHA until inhibitor eradication and, in most cases, curative outcomes can be achieved. Early studies of emicizumab in this population support its use early in the course of AHA management, which may limit the need for prolonged administration of rpFVIII and other bypass agents. Further investigation of emicizumab in AHA is awaited.

RELATIONSHIP DISCLOSURE

All authors declare that there are no conflicts of interest or funding sources to disclose.

AUTHOR CONTRIBUTIONS

Alexander Hayden designed the methods for and performed the literature review, created the figures for the report, and wrote the manuscript with the exception of the second case report. Nelloe Candelario wrote the second case report and revised the manuscript. Genevieve Moyer wrote and provided critical revision to the manuscript.

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