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Lower doses of recombinant porcine factor VIII maintain excellent hemostatic efficacy

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Letter to the Editor

Acquired hemophilia A (AHA) is a rare disorder in which an acquired autoantibody inhibits the activity of coagulation factor VIII. It affects an estimated 1 per million population annually [1] and can cause bleeding that may be life-threatening. Mortality rates are estimated to be between 7% and 27% [1, 2], which may be influenced by the advanced age and co-morbidities of the typical patients with acquired hemophilia. The management of acquired factor VIII inhibitors is aimed at controlling active bleeding and eradicating the autoantibody. Traditionally, agents that bypass factor VIII – namely, anti-inhibitor coagulant complex (activated PCC, aPCC) and recombinant factor VIIa (rFVIIa) – have been used to manage bleeding complications. These agents, however, inconsistently achieve hemostasis in patients with inhibitors in AHA and congenital hemophilia A, [2–6] and cannot be monitored by standard coagulation assays, complicating management [7]. A plasma-derived porcine FVIII product (Hyate:C) was shown to be effective in treating patients with AHA, however, safety concerns over porcine parvovirus led to its withdrawal from the market in 2004. An advantage of porcine FVIII (pFVIII) is that the domains to which inhibitory antibodies to human FVIII (hFVIII) are most commonly made, A2 and C2, differ between hFVIII and pFVIII (84% and 76% homology, respectively), leading to less cross-reactivity between anti-hFVIII and anti-pFVIII inhibitors. Porcine FVIII is therefore used to avoid inhibition by anti-hFVIII antibodies, resulting in effective control of bleeding and the ability to monitor clinically using FVIII activity levels. In 2014, a recombinant porcine FVIII product – B-domain-deleted, antihemophilic factor (recombinant) porcine sequence (rpFVIII) – was approved by the FDA for the treatment of AHA[8]. A prospective phase II/III clinical trial of 28 patients with serious bleeding due to AHA demonstrated clinical efficacy of rpFVIII, with control of bleeding ultimately achieved in 24 of the 28 subjects [7]. The initial dose used in the prospective trial was 200 Units (U)/kg, followed by maintenance dosing titrated according to bleeding control and trough FVIII:c levels. The most common adverse event that occurred in the phase II/III trial was the development of inhibitors to porcine FVIII (anti-pFVIII), which occurred in 5/28 (17.9%) of patients who did not have

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detectable anti-pFVIII at baseline [7]. Data on rpFVIII use outside the setting of a clinical trial have not been reported.

Since its approval, we have treated 4 patients with AHA with rpFVIII for 13 bleeding episodes. Herein, we present this experience in which we used rpFVIII at lower than recommended doses with successful hemostatic outcomes.

Our management strategy for dosing rpFVIII in the setting of bleeding due to AHA is as follows. We administer an initial dose of 100U/kg, as opposed to the recommended loading dose of 200U/kg. We chose this initial dose because of the supraphysiologic FVIII:c levels that were reported in the pivotal trial [7]. We then aim to measure peak FVIII:c 30 minutes after dosing and trough FVIII:c after approximately 4 hours (immediately prior to the subsequent dose of rpFVIII). We target a peak FVIII:c of 80–100% and a trough of 30–50%. If either the preceding peak or trough level is below target, the ensuing dose of rpFVIII is again 100U/kg. If, however, both are within the target range, the ensuing dose of rpFVIII is 50U/kg. We continue to administer rpFVIII every four hours, and titrate the dose and interval based on peak and trough levels. Broadly, subsequent doses are reduced if peak FVIII:c level is above goal, and frequency of dosing is reduced if FVIII:c trough is above goal. We continue to titrate doses until clinical improvement in bleeding occurs. Figure 1 demonstrates our dosing strategy for a selected bleeding event.

Patients who received rpFVIII (Table 1) ranged in age from 54–78 years, with a median of 67.5 years. Half of the patients were men. Weight ranged from 76.2 to 133.9kg, with a median of 67.5kg. One patient received rpFVIII while on hemodialysis. Anti h-FVIII inhibitor titers at diagnosis ranged from 54–225 BU/ml. Three patients were treated with rFVIIa upon initial diagnosis of AHA, for between 3–9 days (median 7 days), but were switched to rpFVIII when acceptable hemostasis was not achieved. The fourth patient did not receive bypassing agents because of systemic arteriovascular disease. All patients were started on immunosuppressive therapy within four days of diagnosis; 3 patients received single agent Rituximab (4 doses of weekly 375 mg/m²) and the fourth patient was started on cyclophosphamide and prednisone.

To date, a total of 172 doses of rpFVIII have been given for 13 distinct bleeding episodes occurring at separate points in time. For several episodes, bleeding occurred at multiple sites simultaneously, as shown in Table 1. In total, each individual received between 7 and 90 doses (one dose was given prior to peripherally inserted central catheter). The mean peak plasma FVIII:c at 20 to 90 minutes after the initial dose of 100U/kg was 134% (SD 33%, range 94–183%). Doses were then titrated based on target peak and trough FVIII:c levels, with an overall mean dose of 51.2U/kg (SD 16.5, median 50U/kg). One patient's dose requirements were appreciably less than the others with a mean dose of 38.4U/kg (SD 16.9); after an initial dose of 100U/kg, his dose was sequentially reduced to 50U/kg, 33U/kg, and ultimately to 22U/kg to achieve factor VIII:c peak and trough activity within the target ranges. The number of doses needed to control a bleeding episode ranged from 2 to 34, with an average number of infusions of 13.2 (SD 10.5), over an average of 4 days (SD 2.1). For the majority of bleeding episodes (10/13), we were able to reduce the interval of dosing from every 4 hours to every 6–12 hours based on real-time FVIII level monitoring.

Three of four patients had detectable levels of anti-pFVIII antibody at diagnosis (range 0.6 BU/ml to 8 BU/ml). One patient (Patient 1, Table 1) had an elevation in anti-pFVIII that rendered further doses of rpFVIII ineffective, with lack of bleeding control and no rise in FVIII levels. Her baseline titer was 8.0 BU/ml, rising to 34 BU/ml (with continued efficacy of rpFVIII) with a subsequent nadir of 0.4 BU/ml during rpFVIII therapy, after which she received 12 additional doses of rpFVIII with resolution of bleeding; twelve days after the final dose, recurrent spontaneous bleeding occurred that did not respond clinically to rpFVIII and FVIII:c levels remained undetectable immediately after a loading dose of rpFVIII, when the anti-pFVIII titer was found to be 72 BU/ml. Two other patients had a rise in the anti-pFVIII antibody titer after initiation of therapy with continued efficacy of rpFVIII: Patient 3 (Table 1) rose from 1 BU/ml to a peak of 18 BU/ml, and Patient 2 (Table 1) developed a *de novo* inhibitor that rose to 5 BU/ml during rpFVIII treatment. Interestingly, Patient 2 was unexpectedly found to have a delayed rise in his anti-pFVIII titer to 34 BU/ml five months after receiving the last rpFVIII dose. Patient 4 (Table 1) did not have anti-pFVIII antibody levels checked after starting therapy. One patient developed a symptomatic distal lower extremity deep vein thrombosis (DVT) 10 days after the 45th dose of rpFVIII (FVIII:c <1% at the time of DVT diagnosis). Her FVIII:c had reached a peak of 193% 12 days prior to the onset symptoms. She had no prior history of VTE and the only identifiable risk factor for DVT was a month-long hospital admission for bleeding due to AHA, from which she was discharged five days prior to the onset of leg pain and swelling. No other adverse effects have occurred with rpFVIII. Thus far, 3 patients have entered remission with undetectable anti-hFVIII inhibitor levels a median of 4.5 months after diagnosis (range 3–7 months), and the fourth has an anti-hFVIII inhibitor titer that continues to decrease and is currently at 2 BU/ml.

Our experience supports the results from clinical trials regarding the clinical efficacy of rpFVIII in controlling bleeding in patients with AHA. Specifically, all 4 patients experienced clinical improvement within 12 to 24 hours of initiation of rpFVIII; 3 of these subjects had failed to respond adequately to bypassing agents. Our experience also demonstrates that rpFVIII is effective at much lower doses than those used in the clinical trial and recommended in the package insert. We achieved successful control of bleeding using an initial dose that was half of that used in the clinical trial (100U/kg compared to 200U/kg), with median maintenance doses after the first 24 hours of 50U/kg compared to 100U/kg in the trial. Furthermore, we were able to reduce the dosing interval for the majority of bleeding episodes based on trough levels. Notably, this approach requires round the clock access to real-time FVIII levels. By lowering the administered doses, we avoided supraphysiologic FVIII levels that may put the patient at risk for thrombosis [9, 10]. This approach also minimizes the high cost of rpFVIII therapy, without compromising efficacy.

As in the pivotal trial, rpFVIII was efficacious despite the presence of baseline anti-pFVIII antibodies, with continued efficacy despite subsequent rise in titers in the majority of patients. One patient did, however, develop a rise in inhibitor titer rendering further rpFVIII ineffective; this reinforces the need to promptly re-test anti-pFVIII levels when there is failure to control bleeding with appropriate doses of rpFVIII. While one patient also developed a DVT, our results are consistent with an otherwise favorable safety profile of rpFVIII.

Overall, our experience demonstrates clinical efficacy of rpFVIII in AHA-associated bleeding at much lower doses than are currently recommended. While our approach may not be generalizable to centers without constant and rapid access to FVIII:c levels for monitoring, our experience may support revised dosing strategies at institutions in which FVIII activity levels are available in real time.

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Figure 1. Sample dosing strategy for a selected bleeding event
FVIII:c, factor VIII activity level; q, every.

Table 1

Demographic and baseline characteristics, peak anti-pFVIII titers, and exposure to rpFVIII for individual patients.

Patient	Age/gender	Baseline FVIII activity (%)	Baseline anti-hFV III (BU/ml)	Baseline anti-pFVIII (BU/ml)	# of bleeding episodes	Primary bleed site for each bleeding episode	Total doses	# Days to control bleed (per episode)	# Doses to control bleed (per episode)	Peak anti-pFVIII (BU/ml)
1	68F	<1	54	8	3	1				
							Upper and lower extremity hematomas, hematuria			
						2	Thigh hematoma	7	32	72*
						3	Calf and thigh hematomas, scapular bleed	4	11	
								1	2	
2	54M	1	225	<0.4	3	1,2	Soft tissue hematomas			
								5	16	
						3	Posterior shoulder bleed	4	13	34
								1	2	
						1	Gluteal and arm hematoma			
						2	Retroperitoneal bleed			
3	67F	<1	140	1	6	3	Posterior thigh bleed	3	7	
								7	34	
						4	Thigh bleed	1	1	18
								3	12	
						5	Forearm hematoma	4	16	
						6	Knee hemarthrosis	6	19	
4	78M	<1	71	0.6	1					
								7	5	
						Soft tissue hematoma			7	--

* anti-pFVIII titer of 72 BU/ml rendered rpFVIII ineffective.

† one dose given prior to peripherally inserted central catheter (PICC).