EXCEPTIONAL CASE REPORT

blood advances

Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies

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Key Points

- Type 3 von Willebrand disease with alloantibodies is a rare clinical entity with few treatment options.
- Emicizumab prophylaxis in such patients may result in improved hemarthrosis control, lower cost, and enhanced quality of life.

Introduction

Type 3 von Willebrand disease (VWD), an autosomal recessive condition characterized by undetectable levels of von Willebrand factor (VWF) in plasma, is rare, ranging from 0.1 to 5.3 cases per million, with considerable variability among countries.[1,2] The absence of VWF also results in low plasma levels of factor VIII (FVIII). The result is a severe bleeding tendency, manifesting as the mucocutaneous bleeding evident in VWD, as well as hemarthroses and hematomas, as observed in moderate to severe hemophilia A. Treatment typically involves prophylactic factor replacement, analogous to treatment of severe hemophilia but with plasma-derived VWF/FVIII concentrates or recombinant VWF. It is estimated that 5% to 10% of type 3 VWD patients develop alloantibodies to VWF after these infusions.[3] Patients with partial or complete gene deletions are at greatest risk, although nonsense mutations have also been implicated.[4,5] Patients with inhibitors present with symptoms ranging from bleeding unresponsive to VWF infusions to severe anaphylaxis. Patients with VWF alloantibodies are typically treated with recombinant activated factor VII (rFVIIa) and/or rFVIII that is devoid of VWF.[1] VWF inhibitor patients with bleeding symptomatology attributable to loss of FVIII (eg, hemarthrosis) are difficult to manage with FVIII concentrates because of the lack of FVIII stabilization by VWF, resulting in a very short half-life (<2 hours), similar to the limitations associated with rFVIIa infusions. Emicizumab, a humanized bispecific monoclonal antibody that is an FVIIIa mimetic and has a long half-life independent of VWF interaction, was recently developed and approved for prophylaxis of patients with hemophilia A with or without inhibitors.[6]

Case description

A 5-year-old boy with a diagnosis of severe type 3 VWD was initiated on prophylaxis with plasma-derived VWF concentrate (~45 units/kg per dose) 3 times per week because of hemarthrosis-induced left ankle synovitis that was a source of recurrent bleeding. At 7 years of age, after ~270 exposure days to VWF concentrate, he began to experience increased ecchymoses, hematomas, and joint swelling. Given these symptoms, pre- and postinfusion laboratory evaluations were performed and demonstrated a preinfusion FVIII level of 2%, ristocetin cofactor activity <10%, and VWF antigen <15%. Thirty minutes after infusion of VWF concentrate, activity and antigen remained below detectable limits, with FVIII activity at 0.64% and FVIII inhibitor positive at 17.5 Bethesda units (Table 1). Serial dilutions of the patient's plasma demonstrated an inhibitory effect against VWF activity within normal pooled plasma, consistent with an anti-VWF inhibitor. The impact on FVIII activity and positive FVIII inhibitor assay were thought to reflect steric hindrance from the anti-VWF antibody, as previously described.[7,8] Gene sequencing and comparative genomic hybridization[9] were performed and demonstrated a heterozygous partial deletion in the *VWF* gene encompassing exons 17 and 18, at least 8.7 kb in length, and a previously described coding mutation c.2435del, which results in absent protein expression.[10] Given the development of an inhibitor, his prophylaxis was changed to off-label use of rFVIIa (270 μg/kg per dose) 3 times per week. He continued to experience recurrent hemarthroses within his left ankle target joint, requiring admissions for alternating rFVIIa and activated prothrombin complex concentrates (aPCCs). Given his continued bleeding, he was transitioned to off-label use of daily aPCC prophylaxis

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Table 1. Laboratory evaluation

	2-y preinhibitor	2-y preinhibitor, 1 h post-VWF infusion	Postinhibitor day 0, 5 min post-VWF infusion	Postinhibitor day 7, preinfusion	Postinhibitor day 7, 30 min post-VWF infusion
FVIII activity, %	3	47	0.4	2	0.64
Ristocetin cofactor activity, %	<10	37	39	<10	<10
VWF antigen, %	<15	101	64	<15	<15
FVIII inhibitor, Bethesda units			13.3	17.8	17.5

(~100 units/kg per dose), with rFVIIa for breakthrough bleeding. He began to experience difficulty with venous access, so a port-a-catheter central venous access device was placed. He underwent radionuclide synoviorthesis, and subsequently, we were able to space his aPCC infusions to every other day, then 3 times per week. After the procedure, he had substantial improvement in overall bleeding. Although prophylaxis with aPCCs was quite effective, he continued to have rare spontaneous hemarthroses, as well as a significant treatment burden.

Methods

Given his substantial treatment burden and concerns regarding lack of steady-state hemostatic coverage with continued bleeding symptoms, he was transitioned to off-label use of emicizumab prophylaxis. After 4 weeks of a loading dose (3 mg/kg), he remained on once-per-week prophylaxis at standard dosing of 1.5 mg/kg without any bleeding symptomatology for approximately 9 months. At that time, given the lack of bleeding, he was transitioned to every-other-week dosing at 3 mg/kg per dose. For acute bleeds, he continues to use FVIIa (90-120 μg/kg per dose), but this has been only required for 1 trauma-induced soft tissue hematoma.

Results and discussion

To our knowledge, this is the first example of successful use of emicizumab in a patient with VWD with alloantibodies. Multiple reports of type 3 VWD patients with alloantibodies undergoing surgery using rFVIII products in the context of negligible VWF levels suggest that at least procedural hemostasis in these patients is primarily dependent on the coagulant activity of plasma FVIII.[11,12] Prophylaxis of these patients with FVIII is untenable, given the extremely short half-life in the absence of VWF stabilization. Although quite effective, bypassing agents did not eradicate all bleeding in our patient and imposed a significant treatment burden, considering the frequency of administration, large infusion volumes, economic cost, and difficulty with venous access. Given that this patient had achieved a degree of bleeding control with aPCC prophylaxis similar to that observed in hemophilia A with inhibitors, we hypothesized that emicizumab could also provide effective prophylaxis for severe VWD but with a reduced treatment burden. Concomitant use of emicizumab and rFVIIa has a theoretical risk of thrombosis and microangiopathy, although safety analysis of the HAVEN 1, 2, and 4 trials did not reveal any thrombotic microangiopathy or thromboembolic events.[13] Emicizumab prophylaxis resulted in improved bleed prevention in our patient and imposed a lower economic cost, decreased the frequency of administration, and provided ease of subcutaneous administration. The success of this approach provides further support that much of the bleeding symptomatology in type 3 VWD results from FVIII deficiency. This approach should be considered for type 3 VWD patients with alloantibodies requiring prophylaxis, especially when the primary bleeding symptoms can be attributed to the associated FVIII deficiency. Furthermore, this approach could be considered in patients with type 3 VWD without inhibitors, especially those with bleeding symptomatology similar to that of patients with hemophilia A, given the improved bleed prevention and substantially decreased burden of care.

Authorship

Contribution: All authors designed and performed research, analyzed the data, and wrote the paper.

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