

Recombinant von Willebrand factor for severe gastrointestinal bleeding unresponsive to other treatments in a patient with type 2A von Willebrand disease: a case report

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A recombinant von Willebrand factor (rVWF) was recently approved in the United States for on-demand treatment and control of bleeding episodes in adults with von Willebrand disease (VWD). In contrast to plasma-derived VWF products available in the United States, rVWF does not contain factor VIII (FVIII). To date, there is no published experience of rVWF in clinical practice. We report the acute and prophylactic use of rVWF in a patient with VWD type 2A and severe gastrointestinal bleeding. Dosing with plasma-derived VWF/FVIII concentrates was constrained by FVIII accumulation; the bleeding was unresponsive, and multiple red blood cell transfusions were required. After initiation of rVWF (4200 IU every other day), bleeding symptoms subsided, and no red blood cell transfusions were required during more than 3 months of prophylactic therapy (most recent dosage: 2800 IU every other day). rVWF may be effective in the prevention, as well as treatment, of severe

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Introduction

Von Willebrand disease (VWD), a common, inherited bleeding disorder in the United States, is caused by a deficiency or abnormality of von Willebrand factor (VWF) [1,2]. Gastrointestinal bleeding is a difficult-to-manage manifestation of VWD and tends to be highly recurrent [3,4]. Angiodysplastic lesions are the most common cause of recurrent gastrointestinal bleeding in VWD; they almost always occur in patients deficient in high-molecular-weight multimers (HMWM) of VWF, such as in VWD type 2A and 2B [5,6].

Acute episodes of gastrointestinal bleeding in VWD are typically treated with replacement plasma-derived (pd) VWF/factor VIII (FVIII) concentrates and tend to require higher doses of concentrate and longer treatment duration than other bleed types [7]. Prophylaxis with regular administration of replacement VWF may be the optimal approach for managing recurrent gastrointestinal bleeding [4,8] but, again, may be less effective than for other bleed sites [9–12].

A recombinant VWF (rVWF) [von Willebrand factor (Recombinant), VONVENDI, Baxalta US Inc, Westlake Village, CA, USA] was approved in 2015 in the United States for on-demand treatment and control of bleeding episodes in adults with VWD [13,14]. In contrast to replacement pdVWF/FVIII concentrates available in the United States, rVWF does not contain FVIII, enabling dosing of replacement VWF to be adjusted

independently from replacement FVIII, according to the patient's needs. In addition, rVWF contains ultra-large multimers (ULM) of VWF, as well as all the multimers found in natural plasma; large multimers may be important for restoring the full haemostatic function of VWF [15].

We report the prophylactic use of rVWF in a patient with VWD type 2A and severe gastrointestinal bleeding who was unresponsive to treatment with pdVWF/FVIII concentrates. This is, to our knowledge, the first published report of rVWF clinical use since its launch.

Case history

A timeline for case information and follow-up is shown in Fig. 1.

Presenting concerns

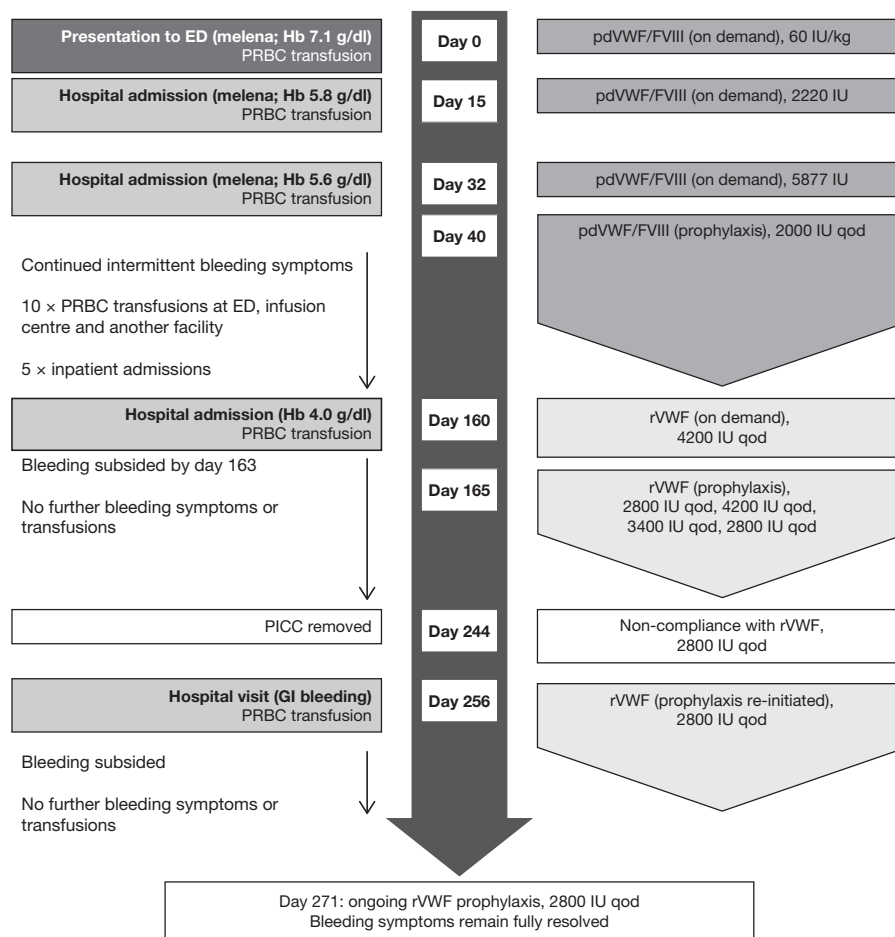
A 45-year-old woman with an existing diagnosis of VWD type 2A presented to the emergency department (ED) in 2016, reporting episodes of weakness and melena accompanied by chest pain and shortness of breath (day 0).

Assessment

Patient history

VWD type 2A was diagnosed 16 years previously following bleeding complications from a caesarean section. There was a history of heavy menstrual bleeding (HMB) with uterine fibroids and iron deficiency anaemia

Fig. 1



Timeline of interventions and outcomes. ED, emergency department; FVIII, factor VIII; Hb, haemoglobin; pd, plasma-derived; PICC, peripherally inserted central catheter; PRBC, packed red blood cells; qod, every other day; rVWF, recombinant von Willebrand factor; VWF, von Willebrand factor.

(with oral iron intolerance). The patient was not under regular care of a haemophilia treatment centre (HTC) until 2015; treatment had included intermittent use of pdVWF/FVIII products and desmopressin. A formal desmopressin challenge in late 2015 (with baseline

VWF:RCo < 20 U/dl, FVIII 170%) showed a poor VWF activity response, and on-demand pdVWF/FVIII was prescribed. HMB was managed by oral contraceptives and dilation and curettage with uterine ablation. Comorbidities and surgical history are shown in Table 1.

Table 1 Patient history and laboratory parameters upon presentation

Patient history	Symptoms and comorbidities	Laboratory parameters
<i>Bleeding-related history:</i> VWD type 2A diagnosed after caesarean section, heavy menstrual bleeding with uterine fibroids, and iron deficiency anaemia	<i>Symptoms:</i> weakness, melena, chest pain, and mild dyspnoea	<i>Complete blood count:</i> WBC 17.7 k/μl, platelets 221 k/μl, RBC 3.6 cells/μl, haemoglobin 7.1 g/dl, haematocrit 25.2%, MCH, 19.7 pg/cell, MCHC 28.2 g/dl, and RDW 25.4%
<i>Surgical history:</i> two caesarean sections, laparoscopic cholecystectomy, hysteroscopy, D&C with uterine ablation, and esophagogastroduodenoscopy	<i>Comorbidities:</i> hepatitis C (genotype 1b) infection, hypertension (controlled), osteoarthritis, gastroesophageal reflux disease, depression, and obesity	<i>CMP normal except for:</i> calcium 8.4 mg/dl, AST 61 IU/l, and ALT 47 IU/l
		<i>Clotting parameters:</i> prothrombin time 10.4 s, INR 1.0; partial thromboplastin time 28 s <i>Stool occult blood:</i> positive

ALT, alanine transaminase; AST, aspartate transaminase; CMP, comprehensive metabolic panel; D&C, dilation and curettage; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; RBC, red blood cells; RDW, red cell distribution width; VWD, von Willebrand disease; WBC, white blood cells.

The patient's father had a history of epistaxis, but no formal diagnosis of VWD, her sister had VWD, and one of her two children had a diagnosis of VWD.

Evaluation and treatment

Blood counts indicated severe anaemia, and stool testing showed positive for occult blood (Table 1); no use of NSAIDs, anticoagulants, or aspirin was reported. The patient had class 3 obesity (134 kg, BMI 52); weight loss and activity recommendations were hindered by anaemia symptoms.

A packed red blood cell (PRBC) transfusion (3 U) and proton pump inhibitor (PPI; Protonix, Wyeth Pharmaceuticals Inc, a subsidiary of Pfizer Inc, Philadelphia, PA, USA) drip were administered. Following admission, the patient received antihaemophilic factor/von Willebrand factor complex [Human (Humate-P, CSL Behring GmbH, Marburg, Germany), 60 IU/kg] based on ideal body weight (IBW). The colonoscopy was normal, and the computed tomography (CT) small bowel enterography and the video capsule endoscopy revealed no source of bleeding. An abdominal ultrasound was unremarkable. The patient was discharged (day 4) with a plan for haematology, gastrointestinal and hepatology outpatient follow-up, and prescriptions for PPI and pdVWF/FVIII concentrates to be used on demand. She was advised to monitor symptoms and seek evaluation if needed, to resume a regular diet and avoid aspirin or NSAIDs.

Follow-up during on-demand therapy with plasma-derived von Willebrand factor/factor VIII

The patient reported no symptoms on initial follow-up at the HTC and was 'feeling well' (day 6). One week later, the patient reported melena and weakness during an HTC telephone follow-up call but was unable to attend for blood tests and treatment. The patient presented to the ED 2 days later with melena and weakness and was admitted with haemoglobin (Hb) 5.8 g/dl and haematocrit (Hct) 20.3% (day 15). PRBC transfusion, PPI, and Humate-P 2220 IU were administered. Levels of VWF:RCo increased from less than 20 to 46 U/dl, and FVIII from 192 to more than 295%. Attempts to identify the source of bleeding using CT angiography of the thoracic aorta, colonoscopy, and esophagogastroduodenoscopy were unsuccessful. A chest radiograph showed pulmonary vascular congestion and no overt oedema. The patient was discharged with Hb 8.1 g/dl and Hct 26.7% (day 19).

Two weeks later, the patient reported to the ED with epigastric abdominal pain and melena, and was admitted with Hb 5.6 g/dl and Hct 20.3% (day 32). A PRBC transfusion, Humate-P 5877 IU and a combination of medications for gastrointestinal pain were administered, with postinfusion, 24-h levels of VWF:RCo and FVIII of less than 20 U/dl and 241%, respectively. The tagged red blood cell scan, capsule endoscopy, and the CT abdomen scan were unremarkable, and the differential diagnoses of

gastritis, pancreatitis, biliary colic, and sphincter of Oddi dysfunction were systematically excluded. The patient was discharged (day 34) with a plan for outpatient prophylactic dosing of Humate-P.

Follow-up during prophylactic therapy with plasma-derived von Willebrand factor/factor VIII

The plan was for Humate-P 3000 IU daily for 7 days, then 3000 IU every other day. This dosage was based on an IBW of 70 kg because of a raised FVIII level following previous Humate-P dosing. Peripheral infusion training [the patient had refused a peripherally inserted central catheter (PICC) placement], and the first prophylactic Humate-P 3000 IU infusion, were provided at the HTC (day 40). Peak postinfusion levels were VWF:RCo 52 U/dl, FVIII 266%, and VWF antigen 175%. Blood test results (Hb 6.7 g/dl and Hct 24.7%) received later that day indicated a need for a PRBC transfusion, but the patient was unable to return to the hospital.

The patient attended the ED the next day for a PRBC transfusion and Humate-P 2000 IU (day 41). Pre-Humate-P infusion levels (at ~24 h after the previous infusion) were VWF:RCo less than 20 U/dl, FVIII 215%, and VWF antigen 124%. Postinfusion levels at 24 h were VWF:RCo 21 U/dl, FVIII 232%, and VWF antigen 136%. The patient was discharged the same day with a plan for Humate-P 2000 IU every other day, instead of the desired 3000 IU, due to the high peak FVIII level observed with the 3000 IU dose.

The patient was compliant with Humate-P administration for the next week but thereafter reported difficulties with peripheral self-infusion, for which she received additional training (day 54). She subsequently failed to attend the clinic/ED for blood counts and lost contact with the provider for 1 week (days 56–62), during which time she attended another facility for a PRBC transfusion.

Over the next 3 months, with Humate-P 2000 IU administered every other day (days 63–159), the patient experienced intermittent weakness and melena, and an episode of HMB. Eight PRBC infusions were administered for low Hb/Hct at the ED and infusion centre (with a total of 54 PRBC units since initial presentation, excluding units received at other hospitals). Intravenous iron and oral folic acid were initiated, and progesterone (norethindrone 20 mg administered orally twice daily) to manage the HMB (day 81). The patient agreed to placement of a PICC because of poor venous access and difficulty with self-infusion (day 134). The gastrointestinal bleed location remained unidentified.

On-demand therapy with recombinant von Willebrand factor

rVWF became available for this patient 5 months after their initial presentation. When the patient was

hospitalized with a Hb of 4 g/dl (day 160), rVWF 4200 IU was administered (three vials of 1400 IU), based on a planned dose of 4000 IU (IBW of 70 kg \times 57 IU); 30-min peak levels were VWF:RCo more than 150 U/dl and FVIII 295%, and 24-h trough levels were VWF:RCo 45 U/dl and FVIII 286%. The patient was discharged and instructed to continue rVWF 4200 IU intravenous slow push every other day (day 161). Bleeding subsided within 3 days of the first infusion.

Prophylactic therapy with recombinant von Willebrand factor

rVWF prophylaxis was initiated at 2800 U every other day (day 165), rather than the planned dose of 3400 IU, as only 1400 IU vials were available; the dose was then increased to 4200 IU every other day following a VWF:RCo level at at least 24 h postinfusion of less than 20 U/dl (day 170). Subsequent dose reductions – to 3400 IU every other day (day 174) and 2800 IU every other day (day 225) – were implemented on the basis of the availability of 600 IU vials, progressive improvement in symptoms and Hb/Hct, and patient capability for self-administration. Intravenous iron infusion (Venofer, American Regent Inc, Shirley, NY, USA) was completed on day 198.

Bleeding symptoms remained fully controlled, and no PRBC transfusions were required for almost 3 months of rVWF prophylaxis (to day 244). FVIII levels at at least 24 h postinfusion generally decreased over time, falling to 103% (day 244), and Hb and Hct improved, to 10.7 g/dl and 36.5%, respectively. The patient reported improved subjective quality of life (feeling great) and physical well-being since initiating rVWF. No adverse events associated with rVWF were reported. The source of bleeding remained unidentified following a nuclear medicine scan for Meckel's diverticulum.

The PICC was removed on day 244, and the patient was instructed to infuse peripherally or contact the HTC for a PICC replacement. However, she was noncompliant and stopped infusing rVWF; 2 weeks after the PICC removal, the patient attended hospital with gastrointestinal bleeding requiring a PRBC transfusion (day 256). rVWF was resumed, and the PICC was replaced with no additional endoscopic procedures. Bleeding ceased and the patient became stable.

Outcome

At the time of writing (day 271), the patient remained stable with bleeding symptoms fully controlled by ongoing prophylaxis with rVWF 2800 IU every other day. She was considering placement of a PORT-A-CATH device (Smiths Medical, Minneapolis, MN, USA) for central venous access due to poor peripheral access and for long-term factor administration. The patient met with a gastroenterologist to discuss possible double balloon enteroscopy in the event of future bleeding episodes.

Discussion

We report the effective on-demand and prophylactic use of rVWF for the management of gastrointestinal bleeding and HMB in a patient with type 2A VWD and a 5-month history of inadequate response to pdVWF/FVIII. The patient's bleeding symptoms subsided promptly following rVWF initiation, and no PRBC transfusions were required during more than 3 months of prophylaxis. rVWF was well tolerated.

During the period of unsuccessful prophylaxis with pdVWF/FVIII, the dose could not be increased above 2000 IU every other day [equivalent to <30 IU/kg of IBW (70 kg)] due to sustained high levels of FVIII. Humate-P product recommendations for major haemorrhage in patients with type 2 and 3 VWD are a loading dose of 60–80 IU/kg, then 40–60 IU/kg every 8–12 h for 3 days, and then 40–60 IU/kg (equivalent to 2800–4200 IU for a 70 kg individual) for up to 7 days. There are no recommendations for prophylactic dosing [16].

FVIII accumulation from repeated infusions is of clinical concern because of potential increased risk of thrombosis [17]. Although thromboembolic events linked to treatment with factor concentrates are rare [18], it is recommended that FVIII levels are maintained at a maximum of 250–300 IU/dl during VWF concentrate replacement therapy [2]. Prophylaxis studies using pdVWF/FVIII concentrates have indicated that control of gastrointestinal bleeding requires more frequent infusions and higher doses of concentrate than for other bleed types [11], potentially increasing the likelihood of dose-limiting FVIII accumulation.

VWD type 2A is characterized by qualitative defects in VWF that result in relative loss of VWF activity and defective primary haemostasis. Endogenous FVIII biosynthesis is fully functional, and in many type 2A patients (including the patient in this case report), FVIII levels are normal, necessitating correction of functional VWF only [19]. The lack of FVIII in rVWF may be an advantage in such patients to reduce the risk of FVIII accumulation on repeated infusion.

The ongoing dose of rVWF 2800 IU every other day for this patient (adjusted for IBW) has been sufficient for sustained prevention of bleeding symptoms. A 12-day period of patient noncompliance with rVWF infusions resulted in a bleeding episode and a PRBC transfusion; on resuming prophylaxis, bleeding ceased and the patient stabilized. There are no published recommendations for prophylactic dosing, but VONVENDI package recommendations for treatment of major haemorrhage indicate an initial dose of 50–80 IU/kg, followed by 40–60 IU/kg every 8–24 h for approximately 2–3 days (as clinically required) [13]. Ideally, plasma levels of VWF:RCo and FVIII should be monitored during treatment with rVWF to avoid sustained, excessive VWF or FVIII activity [13]; however, in practice, it was sometimes difficult to obtain

levels, and dosing decisions were based on the patient's clinical response in addition to levels, when available.

The presence in rVWF of ULMs of VWF may have contributed to the successful outcome in this patient with type 2A VWD. HMWV of VWF that are deficient or lacking in VWD types 2A, 2B, and 3 are the most biologically active form of VWF; HMWV have a crucial role in primary haemostasis because of their binding capacity for collagen and platelet receptors, facilitating platelet aggregation under shear stress [15]. Loss of HMWV of VWF may play a further causative role in gastrointestinal bleeding in patients with VWD by contributing to the development of gastrointestinal angiodysplasia, as suggested by the strong association of angiodysplasia with VWD subtypes that lack HMWV [5,6]. Recent evidence supports a role of VWF in modulating the process of angiogenesis, and it is possible that HMWV of VWF are important for this function [20,21]. Angiodysplasia can be extremely difficult to identify, and affected patients may remain undiagnosed. Repeated investigation of the whole gastrointestinal tract is recommended for patients with type 2 (and type 3) VWD who present with clinical symptoms of gastrointestinal bleeding [3]. Although our patient underwent full exploration of the gastrointestinal tract without revealing a bleeding source, we hypothesize that angiodysplasia in the small bowel is the likely cause.

Recurrent angiodysplastic gastrointestinal bleeding in VWD is acknowledged to be particularly challenging. The results in this case are in line with previous reports suggesting that prophylactic VWF may be the most appropriate treatment [4,8]. Individual case reports have demonstrated the potential utility of antiangiogenic agents such as atorvastatin [22,23] and thalidomide [24,25], although thalidomide was unsuccessful in five cases included in a retrospective study of 48 patients [4]. Identification of patients with severe bleeding phenotypes using standardized bleeding assessment tools (BATs) such as the International Society on Thrombosis and Haemostasis (ISTH) BAT [5,26] may assist physicians to institute appropriate therapy.

Strengths of the management of this case included early identification of patient suitability for rVWF, and ease of transition from pd concentrate to rVWF without needing coadministration of recombinant FVIII (rFVIII). Limitations included inconsistent clinical and laboratory follow-up because of unforeseen hospitalizations and lack of patient transportation. The patient found home infusion difficult. Close communication between patient and clinic is important to foster patient motivation for home administration and prompt reporting of symptoms. Involvement of a social worker helped achieve a successful outcome in this patient who lacked socio-economic resources and had limited health literacy. A further challenge faced by the healthcare team was the lack of

published clinical experience with rVWF to guide treatment management and provide information about rVWF prophylactic use.

Prior to the introduction of rVWF, VWF replacement therapy for all VWD types was limited to the use of pdVWF/FVIII concentrates, which contain VWF and FVIII in variable proportions. rVWF may facilitate individualized treatment, with therapy tailored to VWD subtype and extent of the deficiency or defect in VWF, and to FVIII status. rVWF may be administered alone or in combination with rFVIII if needed (e.g., prior to stabilization of endogenous FVIII) [14,19]. The direct replacement of HMWV by rVWF in patients with VWD types characterized by their relative absence, such as type 2A, may also contribute to therapeutic efficacy.

rVWF may thus be considered for use in cases of gastrointestinal bleeding in VWD unresponsive to pd products. Baseline and recovery levels of VWF:RCO and FVIII should be obtained through periodic monitoring, to further inform dose adjustments based on clinical response. Our findings add to the currently limited available data to guide dosing of replacement VWF in gastrointestinal bleed prophylaxis. rVWF is not currently labelled for prophylactic use; an ongoing phase 3 study is evaluating the efficacy and safety of prophylactic treatment with rVWF in severe VWD [27].

Conclusion

In a patient with type 2A VWD, rVWF – a VWF replacement that does not contain FVIII – was effective in treating and subsequently preventing severe gastrointestinal bleeding that did not respond to 5 months' treatment with pdVWF/FVIII, the dosing of which was constrained by FVIII accumulation.

Consents

The patient has provided her informed consent for the publication of this case report.

No Institutional Review Board approval was required.

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Conflicts of interest

There are no conflicts of interest.

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