

RECOMBINANT VON WILLEBRAND FACTOR: A FIRST-OF-ITS-KIND PRODUCT FOR VON WILLEBRAND DISEASE

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SUMMARY

von Willebrand disease (VWD) is caused by quantitative or qualitative defects in von Willebrand factor (VWF). The mainstay of therapy is desmopressin, which is, however, not useful in certain forms of VWD notwithstanding adverse events. For these patients, plasma-derived factor VIII (pdFVIII)/VWF concentrates have been available for close to three decades but have a theoretical risk of disease transmission, hypersensitivity/allergic reactions, inhibitors and thrombosis. A recombinant VWF (vonicog alfa,

VonvendiTM; manufactured by Baxalta, now part of Shire) was approved by the U.S. Food and Drug Administration (FDA) in December 2015. This review will survey the literature based on a MEDLINE review on the safety, efficacy and pharmacokinetics of Vonvendi. It will also summarize the ongoing studies on Vonvendi available in the public domain. Vonvendi may have an important role in the management of VWD. However, more studies are needed, especially in special populations such as surgical patients, patients with major gastrointestinal bleeding from arterio-venous malformations and pregnant women and children, who are most likely to benefit from it.

Key words: von Willebrand disease – von Willebrand factor – Recombinant von Willebrand factor – Vonicog alfa – Vonvendi – rVWF

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INTRODUCTION

First described by Erik von Willebrand in 1926 as hereditary pseudo-hemophilia, von Willebrand disease (VWD) is the most common inherited bleeding disorder with a prevalence of 1% in the population based on random population testing using lab criteria (1-4). However, only ~0.1 of individuals are symptomatic to the point of seeking medical attention and becoming diagnosed with VWD (3).

VWD is caused by defects in the synthesis, secretion, function or clearance of von Willebrand factor (VWF). VWF is a glycoprotein coded by the 178 kb VWF gene on the short arm of chromosome 12 (12p12) and synthesized in the endothelial cells and megakaryocytes. It circulates in the plasma as multimers of different sizes formed from a basic dimer subunit. The smaller multimers are secreted into the plasma, while the large multimers (ultra-large VWF multimers [ULM] and high molecular weight [HMW] multimers) remain in the platelets (alpha granules) and endothelium (Weibel Palade bodies) and are released at the time of endothelial injury or platelet activation (5).

VWF plays an essential role in primary hemostasis, which is defined as a process leading to the formation of the platelet plug at the initial site of the injured endothelium. VWF is a major adhesion molecule binding the platelets to the exposed subendothelium at sites of endothelial injury as well as binding platelets among themselves at sites of high shear stress/endothelial injury (6-9). A secondary role of VWF is to protect factor VIII (FVIII) from proteolytic cleavage, enhancing its plasma $t_{1/2}$ manifold (10, 11).

There are six different phenotypic variants of VWD, with Type 1 being the most common (~80%) with decreased VWF levels proportionately reduced in terms of function (as measured by the VWF ristocetin cofactor assay [VWF:RCo]) and amount of VWF antigen (VWF:Ag). Type 2 VWD is comprised of functional defects with the VWF:RCo activity disproportionately reduced relative to the VWF:Ag at a ratio < 0.6. Platelet binding and/or collagen binding is reduced in Type 2A and 2M while there is paradoxically increased platelet binding in Type 2B. Type 2N is characterized by the inability to bind to FVIII, resulting in FVIII deficiency. Type 3 has severe VWF deficiency with virtually no detectable VWF protein and resultant FVIII deficiency < 10% (5, 12, 13).

The symptoms of VWD are mucocutaneous as VWF is a "first" responder to injury to cutaneous and mucosal surfaces wherein a deficiency results in increased bruising, prolonged bleeding from cuts, dental-related bleeding,

epistaxis, heavy menses and childbirth-related bleeding. When the VWF deficiency is severe then binding to FVIII is markedly reduced resulting in symptoms similar to FVIII deficiency such as deep tissue bleeding including hemarthrosis. Most people, that is those with Type 1 VWD, have a mild reduction in the VWF levels, which is not readily recognized as VWD or may not have yet experienced a hemostatic challenge like menstruation, childbirth or surgery. This great variability in symptoms is one of the reasons patients are not diagnosed as commonly as expected per lab values.

DDAVP (desmopressin, 1-desamino-8-D-arginine vasopressin), which releases VWF and FVIII from endothelial stores, is the mainstay of treatment for Type 1 disease and for some of the patients with Type 2A and 2M disease (14-16). It can be administered intravenously, intranasally and subcutaneously, although the subcutaneous preparation is not available in the United States (17, 18). It is not useful in patients with severe VWF deficiency (Type 3 or severe Type 1 VWD and in most cases of Type 2 VWD) or patients with poor VWF stores in platelets (platelet low type VWD) (19, 20). Tachyphylaxis occurs after repeat DDAVP administration as cellular stores of VWF are depleted with successive administrations (14, 21). Vasodilatory side effects like headache, flushing, nausea and tingling can occur, which though often self-limiting, can lead to discontinuation of therapy (16, 22). Hyponatremia can occur and can be severe enough to cause seizures, especially in young children (23, 24).

Historically, plasma VWF-containing FVIII concentrates have been available and used for patients with Type 3 VWD, severe Type 1 disease and for many of the patients with Type 2A, 2B and 2M VWD. They are also used in Type 1 patients with serious bleeds when prolonged treatment is required (e.g., Type 1 patients undergoing major surgery or childbirth) or in young children, lest in all these situations tachyphylaxis and/or hyponatremia develop with successive doses. "Intermediate purity" plasma-derived FVIII (pdFVIII) concentrates (which also have VWF) as well as higher purity VWF concentrates have been available for some time. They are pasteurized or solvent detergent method-treated to reduce the risk of transmission of HIV, hepatitis and other viruses. Three of the intermediate purity VWF-containing FVIII concentrates (Humate-P, Alphanate and Wilate) are U.S. Food and Drug Administration (FDA) approved (Table I). Koate DVI and 8Y are two others which are not FDA approved. These concentrates have varying ratios of VWF:RCo activity relative to FVIII activity with Humate-P having the highest ratio. LFB-VWF (Wilfactin) is a high purity VWF-containing

Table 1. von Willebrand factor (VWF) products approved by the U.S. Food and Drug administration (FDA) (20, 36, 39).

Product	Humate	Alphanate	Wilate	Wilfactin	Vonvendi
Manufacturer	CSL Behring, USA	Grifols, USA	Octapharma, USA	LFB	Baxalta/Shire
Purification method	Multiple precipitation	Precipitation/heparin ligand CT	Precipitation/ion exchange and size exclusion CT	Ion exchange + affinity chromatography	Chinese hamster ovary cell line
Viral Inactivation	Pasteurization	S/D, dry heat	S/D, dry heat	S/D, dry heat/35 nm filtration	Not required
VWF:RCo/VWF:Ag	0.91	0.43	0.9-1.0	0.95	1.16
VWF:RCo/ FVIII:C ratio	2.88	0.82	1.0	50	No FVIII
ULM	Absent	Absent	Absent	Absent	Present
FDA approved	Yes	Yes	Yes	No	Yes

S/D, solvent detergent; CT, chromatography; FVIII, factor VIII; FVIII:C, factor VIII coagulation activity; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor; ULM, ultra-large multimers.

FVIII plasma-derived concentrate with approximately 10:1 VWF:FVIII activity, produced in France and used in several European countries but not available in the United States. In general, the plasma-derived VWF (pdVWF) concentrates have been shown to be quite safe and effective.

Humate-P (Haemate/Haemate P)

A retrospective study performed on 97 adult and pediatric patients for on-demand treatment, for prophylaxis or prior to surgery, found excellent/good treatment response in 97% of events (424/437). In the study, 97% of bleeding events (332/344), 100% of prophylactic cases (20/20) and 99% of surgeries (72/73) had an excellent or good response (25) on a 4-point scale of hemostatic efficacy. A prospective study to evaluate Humate-P in 35 patients undergoing minor, major or oral surgeries, found good to excellent hemostasis in 91.4% of patients immediately after surgery. Five serious bleeding events were however seen in 3 patients during the immediate postoperative period (26). Another prospective study in patients with VWD above 5 years of age undergoing major (n = 11) or minor surgery (n = 16) found excellent hemostasis in 81.5% of patients on the day of surgery, 92.6% on postoperative day 1 and 100% at final evaluation at postoperative day 14. One patient in the study had a pulmonary embolism 10 days after surgery in the setting of bilateral hip arthroplasty, advanced age > 80 years old and an FVIII level as high as 450 IU/dL the day before (27).

Alphanate (Fandhi)

A prospective study of Alphanate in the on-demand control of bleeding in 53 patients found 74.5% of bleeds to be controlled by a single infusion while an

additional 11.5% of bleeds were controlled with the second infusion (28). A subsequent retrospective study evaluating hemostatic efficacy of Alphanate/Fandhi found the response to be good or excellent in 97% of bleeds (111/114 bleeding episodes in 55 patients) and 99% of surgical procedures (130/131 procedures in 85 patients). Complete prevention of bleeding was achieved in 87% of patients (13/15) over a median period of 334 days (29). In another retrospective trial to evaluate prevention of perioperative bleeding in 39 patients, hemostatic efficacy was rated as good to excellent in 95.1% of cases on the day of surgery and 91.8% of cases on the day after surgery (30).

Wilate

A pooled analysis of clinical trial data from four prospective clinical trials evaluating hemostatic efficacy of Wilate for prophylaxis or treatment of spontaneous or traumatic bleeds in 44 patients rated the hemostatic efficacy as good or excellent in 96% of 1,095 spontaneous or traumatic bleeding episodes. The bleeding frequency was reduced from 4.5 per month to 1.4 per month in the 19 patients receiving Wilate for bleeding prophylaxis for a mean of 14.8 months (31). In another pooled analysis of four prospective trials to evaluate Wilate in 32 VWD patients undergoing surgery, hemostatic efficacy was judged as good or excellent in 51/53 (96%) procedures (32).

Wilfactin (Willfact)

One report combined two clinical trials and evaluated the pharmacokinetics (PK) of Wilfactin with concentrates containing both pdVWF and pdFVIII in 17 patients with severe VWD, as well as compared Wilfactin (which

undergoes three virus inactivation steps) with its earlier version, Facteur Willebrand-LFB (undergoing single virus inactivation method) in 8 patients with Type 3 VWD. Wilfactin was found to have a PK profile similar to that of pdVWF/pdFVIII, as well to Facteur Willebrand-LFB (33). Another prospective study combined the results of two comparable protocols. Fifty patients with clinically severe VWD were treated with Wilfactin alone, except when a dose of FVIII was required to correct an intrinsic coagulation defect. The efficacy of hemostasis was rated as excellent or good in 89% of the 139 spontaneous bleeds and FVIII administration was required only in 38% of the cases (53/139). Forty-four patients undergoing 108 surgical or invasive procedures were also studied. Efficacy was judged to be 100% in the 95 scheduled procedures (FVIII not infused) and 13 emergency procedures (FVIII administered with the first dose of VWF). No thrombotic complications or development of anti-VWF or anti FVIII antibodies were seen (34).

In summary, these pdVWF-containing FVIII concentrates have “set the bar high” for any future VWF product entering the marketplace given the > 95% good to excellent hemostatic response with a relatively low rate of adverse events (AEs) such as anaphylaxis and thrombotic events with risk of infection essentially nonexistent.

One new product now having entered the clinical arena is Vonvendi™ (vonico α , BAX-111), a recombinant VWF (rVWF) produced from Chinese hamster ovary cells, which was approved by the FDA in December 2015 and is the main focus of this article.

PRECLINICAL PHARMACOLOGY OF RECOMBINANT VWF

The preclinical pharmacology of rVWF was studied by Turecek et al., who compared it to an in-house pdVWF concentrate as well as with Humate-P (35). The ultra-structure of rVWF was studied by transmission electron microscopy and was found to be similar in morphology to VWF from human plasma seen in other studies. They

found rVWF contained higher concentrations of ultra-high molecular weight multimers as compared to the other two preparations. rVWF also lacked the proteolytic cleavage bands seen with the two plasma-derived preparations on electrophoresis, thought to be due to lack of exposure to plasma ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) (35).

The specific activity of VWF (VWF:RCo/VWF:Ag) was higher for rVWF than for the in-house pdVWF and Humate-P (Table II). Specific collagen binding capacity (VWF:CB/VWF:Ag) was also higher for rVWF as compared to the plasma-derived preparations. This was attributed to the high multimer content in the rVWF. The affinity to bind with FVIII was, however, similar between rVWF and pdVWF, as was the FVIII binding capacity (35).

Whole blood closure time was shortened by rVWF but not by the two plasma-derived preparations. A similar increase in platelet adhesion to collagen under shear stress as well as to immobilized fibrinogen was seen for all three preparations while neither of the three preparations induced spontaneous platelet aggregation. This was interpreted as large VWF multimers only augmenting the platelet aggregation process but not increasing the propensity to form platelet aggregates without activation by a normal trigger (35).

RECOMBINANT VWF PHARMACOKINETICS AND METABOLISM

Mannucci et al. published the first-in-human clinical trial to study the safety, tolerability and PK of rVWF in 2013 (36). It was a prospective, multicenter, randomized, blinded clinical trial comparing rVWF combined with recombinant FVIII (rFVIII) (Advate; Baxter) at a fixed ratio (VWF:RCo activity:FVIII coagulant activity = 1.3:1) versus Humate-P/Haemate P (VWF:RCo activity: FVIII coagulant activity ~2:1). The study enrolled 32 subjects with Type 3 or severe Type 1 VWD in a dual crossover design out of which 22 subjects eventually were considered for the PK studies while all 32 were considered for safety studies.

Table II. Comparison of specific collagen binding activity and von Willebrand factor (VWF)-specific activity between recombinant VWF (rVWF), Humate-P (Haemate) and a highly purified plasma-derived VWF (pdVWF) (35).

	Specific collagen binding activity = VWF:CB/VWF:Ag (IU/IU)	VWF specific activity = VWF:RCo/VWF: Ag (IU/IU)
rVWF	1.14 ± 0.16	1.16 ± 0.25
pdVWF	0.81 ± 0.06	0.5
Haemate (Humate-P)	0.84	0.51 ± 0.10

VWF:CB, VWF collagen binding; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor.

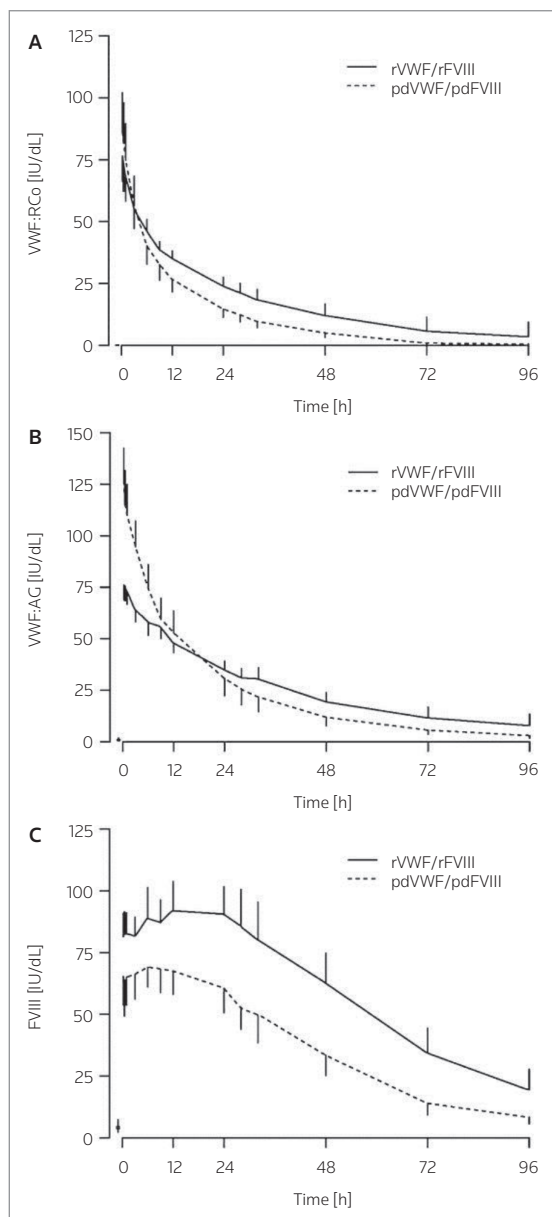


Figure 1. von Willebrand factor (VWF):ristocetin cofactor (VWF:RCo) (A), VWF:antigen (VWF:Ag) (B) and factor VIII coagulation (FVIII:C) activity (C) over time after administration of rVWF-rFVIII versus plasma-derived VWF-plasma derived FVIII (pdVWF-pdFVIII). (Republished with permission of the American Society of Hematology, from Mannucci, P.M., Kempton, C., Millar, C. et al. *Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial*. *Blood* 2013, 122(5): 648-57 (36). © 2013; permission conveyed through Copyright Clearance Center, Inc.)

Mannucci et al. found that the pdVWF-pdFVIII initially had higher VWF:Ag levels as compared to rVWF-rFVIII suggesting a higher specific activity since the dosing was at equivalent VWF:RCo activities. VWF:Ag levels then declined to a lower level between 12 and 24 hours post-transfusion (Fig. 1). VWF:Ag terminal $t_{1/2}$ was longer for rVWF-rFVIII as compared to pdVWF-pdFVIII (25.5 vs. 17.9 hours). The VWF collagen binding activity (VWF:CB) was higher with recombinant versus pdVWF. Specific collagen binding activity (VWF:CB/VWF:Ag) was 1.14 ± 0.16 for rVWF compared to 0.84 for Humate-P and 0.81 ± 0.06 for pdVWF (36).

rVWF-FVIII caused a greater rise in endogenous FVIII as compared to Humate-P with a significantly higher FVIII:C at 72 hours. The ultra-large VWF multimer proportion increased from 0% to 30% after 15 minutes post-infusion of rVWF, followed by a substantial decline between 12 and 24 hours (Fig. 2).

Two of the subjects had high titer of non-neutralizing anti-VWF-binding antibodies and were found to have lower VWF:Ag, VWF:RCo, VWF:CB and FVIII:C activities as well as faster degradation of HMW VWF.

In the subsequent FDA licensure trial, Gill et al. compared rVWF with rVWF:rFVIII at a VWF:RCo of 50 IU/Kg (Fig. 3) and found that plasma VWF:RCo consistently rose rapidly after a single infusion of rVWF without the addition of rFVIII. Mean VWF:RCo terminal $t_{1/2}$ was 19.6 hours for rVWF:rFVIII and 21.9 hours for rVWF alone (37). Endogenous FVIII levels reached hemostatic levels (> 40 IU/dL) within a median of 6 hours and were sustained there till 72 hours post-transfusion.

SAFETY AND DRUG INTERACTIONS OF RECOMBINANT VWF

No thrombotic episodes were encountered by either Mannucci et al. or Gill et al. It is hypothesized that the rapid proteolysis of ULMs in the rVWF by the endogenous ADAMTS13 precludes the development of thrombosis. No anaphylactic reactions occurred in the two trials, nor was rVWF associated with post-transfusion anti-VWF binding (neutralizing) antibodies or inhibitors to VWF or FVIII.

In the phase I trial, 8 transient nonserious AEs were seen in 4 patients after receiving rVWF (tremor, pruritus, psychomotor hyperactivity, hypertension, nausea, dizziness and variable soluble platelet selectin values) (36).

In the phase III trial, 8 AEs were considered to have a causal relation with VWF infusion. Six of these were considered nonserious (infusion-site paresthesia, moderate dysgeusia,

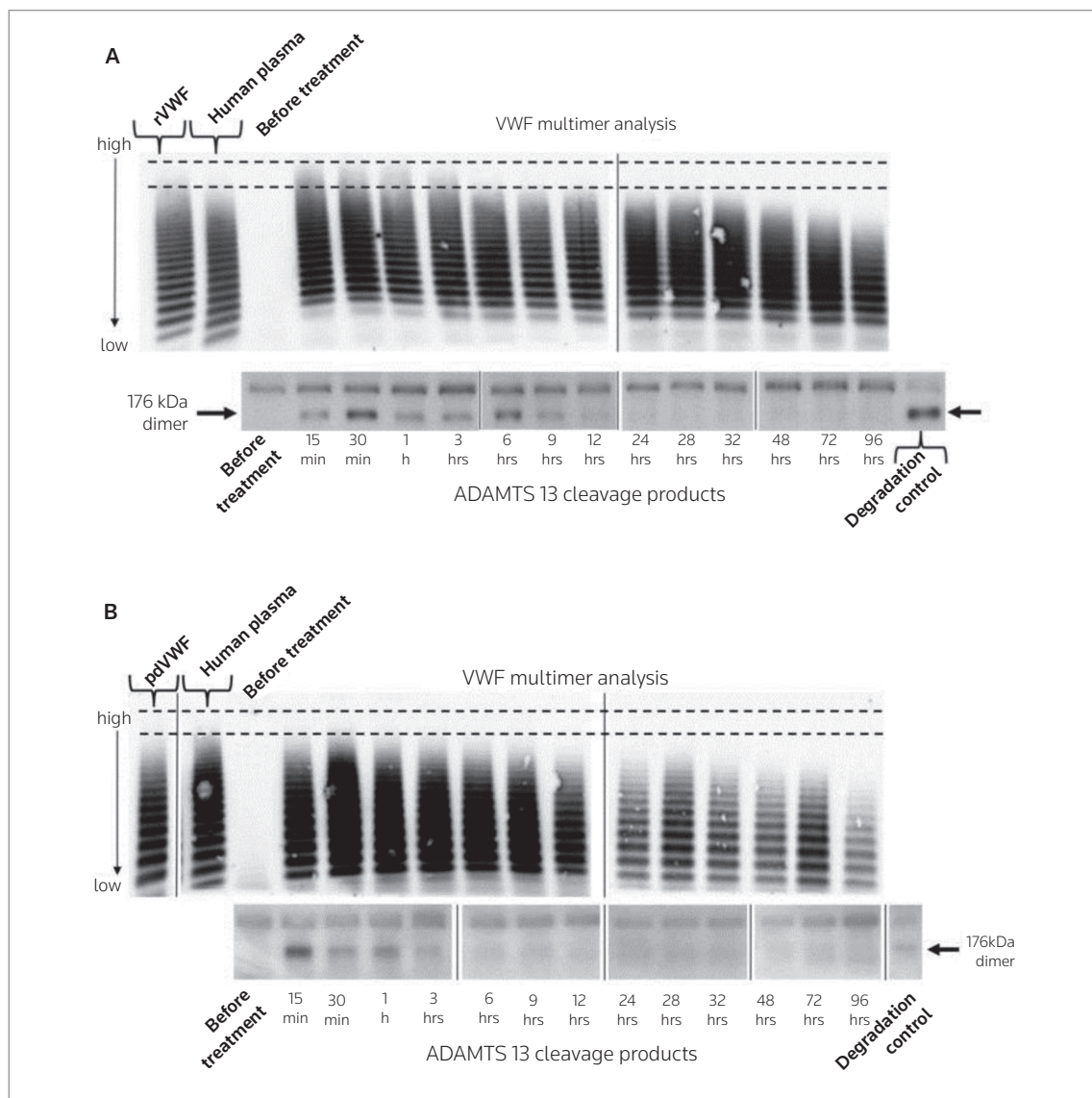


Figure 2. Increase in the proportion of ultra-large von Willebrand factor (VWF) multimers (ULM) after recombinant VWF (rVWF) infusion followed by rapid degradation (A) and lack of ULM after infusion of Humate-P (B). (Republished with permission of the American Society of Hematology, from Mannucci, P.M., Kempton, C., Millar, C. et al. *Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial*. Blood 2013, 122(5): 648-57 (36). © 2013; permission conveyed through Copyright Clearance Center, Inc.)

moderate tachycardia, mild ECG T-wave inversion, mild generalized pruritus and mild hot flush) and occurred in 4 subjects. One subject had 2 serious AEs of chest discomfort and tachycardia, which resolved in 10 minutes but required hospitalization for observation (Table III) (37).

Drug interactions for Vonvendi have not been well studied due to the paucity of trials and data. However, there may be theoretical interactions with oral contraceptives and antifibrinolytic agents, which could increase the risk of thrombosis.

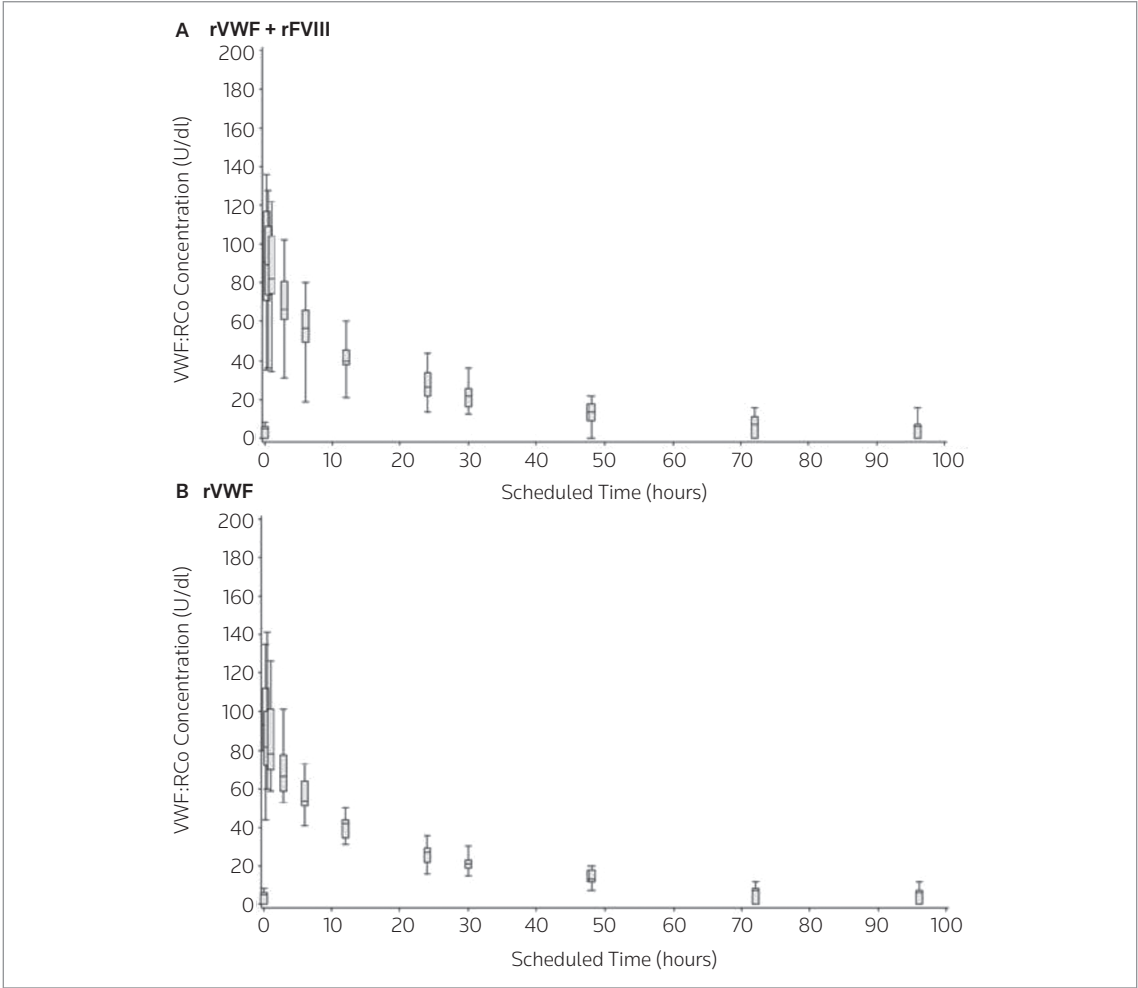


Figure 3. von Willebrand factor (VWF):ristocetin cofactor activity (VWF:RCo) of recombinant VWF (rVWF). Median, IQR and range of VWF:RCo after infusion of 50 IU VWF:RCo/kg rVWF alone or together with recombinant factor VIII (rFVIII). (Republished with permission of the American Society of Hematology, from Gill, J.C., Castaman, G., Windyga, J. et al. *Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease*. Blood 2015, 126(17): 2038-46 (37). © 2015; permission conveyed through Copyright Clearance Center, Inc.)

CLINICAL STUDIES

As previously noted, Gill et al. published a phase III trial in 2015 evaluating the PK, safety and hemostatic efficacy of rVWF in the treatment of bleeds in adults with severe VWD. This was a prospective, single-blinded, randomized crossover clinical study. They enrolled 49 subjects aged 18-65 years with Type 3, severe Type 1, Type 2A, Type 2B, Type 2N or Type 2M of which 37 were exposed to rVWF. They encountered 192 bleeds in 22 subjects (Fig. 4). A 4-point predefined scale (4 = none and 1 = excellent) was

used to grade the hemostasis. Bleeding episodes were treated with a dose of 40-60 IU/dL for minor to moderate bleeds and 80 IU/dL for major bleeds to maintain a trough VWF:RCo level of > 50 IU/dL. Most of the bleeds received rFVIII with the first infusion of rVWF but 10/192 were not administered concurrent FVIII. Among the second infusions, 21/35 were not administered concurrent rFVIII. The dose of rVWF (VWF:RCo of 50 vs. 80 IU/kg) did not make a difference nor did the use of rFVIII. Hemostatic control was found to be good or excellent

Table III. Adverse events of recombinant von Willebrand factor (Vonvendi) (36, 37).

Adverse event	Number of subjects (%) (n = 66)	Number of infusions (%) (n = 355)
Tachycardia	2 (3.03%)	2 (0.56%)
Nausea	1 (1.52%)	1 (0.28%)
Infusion-site paresthesia	1 (1.52%)	1 (0.28%)
Chest discomfort	1 (1.52%)	1 (0.28%)
Generalized pruritus	2 (3.03%)	2 (0.56%)
Hot flush	1 (1.52%)	1 (0.28%)
Hypertension	1 (1.52%)	2 (0.56%)
Dizziness	1 (1.52%)	1 (0.28%)
Dysgeusia	1 (1.52%)	1 (0.28%)
Tremor	1 (1.52%)	1 (0.28%)
Electrocardiogram T-wave inversions	1 (1.52%)	1 (0.28%)

in 119 of the 122 minor (97.5%), 59 of the 61 moderate (96.7%) and 6 of the 7 major bleeds (85.7%). Overall, 186 out of 192 bleeds were rated to have an excellent (96.9%) response while the remaining 6 (3.1%) had a good response. Table IV shows efficacy for treatment of mucosal bleeds. A single infusion was effective in 157 bleeds (81.8%) while the median of two infusions (range 1-3) was required for a major bleed. Tranexamic acid was given in approximately a quarter of the cases (37).

A phase III outpatient clinical trial is now planned to compare rVWF and tranexamic acid to minimize menorrhagia in female patients with Type 1 VWD based on a recent report based on surveyed hemophilia centers in the United States as well as a literature review to assess the use of VWF concentrate to treat menorrhagia in VWD patients wherein VWF infusions were found to safely reduce menorrhagia (38). The study will enroll 60 subjects and is estimated to be completed by June 2021 (ClinicalTrials.gov Identifier NCT02606045).

A phase III study evaluating the efficacy and safety of rVWF with or without Advate in 24 patients with severe VWD undergoing elective surgical procedures was completed in June 2016 but not yet published (ClinicalTrials.gov Identifier NCT02283268).

A phase III clinical trial to assess the efficacy, safety and tolerability of rVWF with or without Advate in the treatment of nonsurgical bleeds as well as during elective or emergency surgeries, in patients less than 18 years of age, is expected to start in November 2016 (ClinicalTrials.gov Identifier NCT02932618).

CONCLUSIONS

Vonvendi appears to be a safe and effective drug to treat severe bleeding in VWD patients who are not candidates for DDAVP therapy (Table V). Theoretically, it may prove to be superior to the pdVWF-containing FVIII concentrates. Vonvendi has a more uniform composition than pdVWF/ pdFVIII replacements, which have a variation in composition based on the source of plasma and the manufacturing process. The theoretical risk of virus transmission seen with plasma-derived products is also mitigated as it is a recombinant product. It is also not exposed to endogenous ADAMTS13 and thus is rich in ULM and HMW VWF multimers, conceivably increasing the hemostatic efficacy. This may be particularly of benefit in gastrointestinal (GI) bleeding from angiodysplasia where control of bleeding can be very difficult. There were only 6 patients treated with Vonvendi for GI bleed-ing so clearly more evaluation in this situation is needed

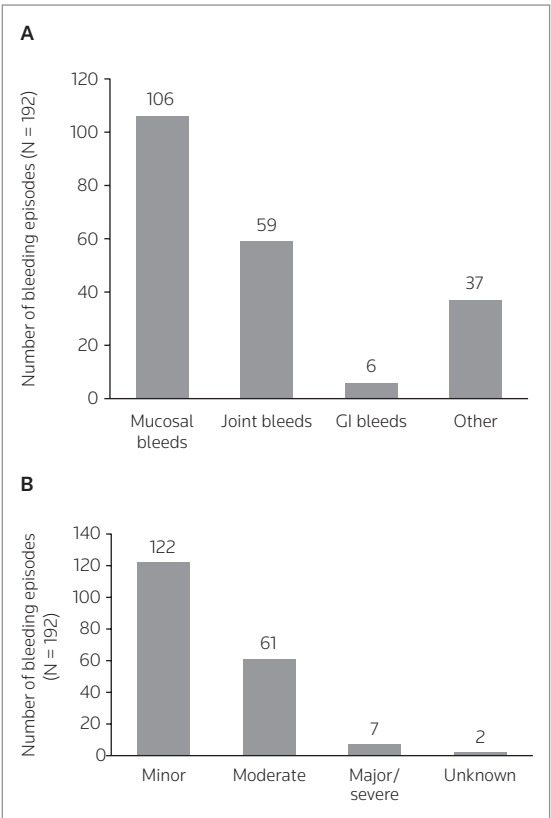


Figure 4. Bleed characteristics for the 192 bleeds in terms of (A) location (B) severity. Mucosal bleeds: epistaxis, menorrhagia, mouth/oral cavity.

Table IV. Efficacy of recombinant von Willebrand factor in mucosal bleeding episodes (37).

	Menorrhagia	Epistaxis	Oral cavity	GI bleed
Number of bleeding episodes	32	42	26	6
Total number of infusions administered	37	43	33	10
Median (range) number of infusions administered	1 (1-2)	1 (1-2)	1 (1-4)	1 (1-2)
Median VWF:RCo dose (IU/kg) per infusion (range)	43.3 (39.9-95.1)	40.4 (23.8-90.2)	50.2 (23.8-184.9)	60.0 (53.6-121.1)
Median (range) rFVIII dose (IU/kg) per infusion	30.6 (28.1-61.3)	28.7 (16.6-49.3)	36.9 (16.6-51.9)	33.2 (19.3-49.4)
% bleeds rated excellent or good ^a (excellent/good)	100 (31/1)	100 (41/1)	100 (26/0)	100 (5/1)

^aAs per predefined 4-point scale. GI, gastrointestinal; VWF:RCo, VWF ristocetin cofactor; rFVIII, recombinant factor VIII.

Table V. Pharmacological characteristics of recombinant von Willebrand factor (rVWF; as per Vonvendi package insert).

			Initial dose	Subsequent dose
Dosing: Adults	von Willebrand disease	Minor hemorrhage (e.g., readily managed epistaxis, oral bleeding, menorrhagia)	40-50 IU/kg	40-50 IU/kg every 8-24 hours as clinically required
		Major hemorrhage (e.g., severe or refractory epistaxis, menorrhagia, GI bleed, CNS trauma, hemarthrosis or traumatic hemorrhage).	50-80 IU/kg	40-60 units/kg every 8-24 hours for 2-3 days as clinically required
	Notes	*A bleed could be considered major if red blood cell transfusion is required or potentially required or if bleeding occurs in critical area. *If plasma VIII:C level is < 40% or unknown, recombinant factor VIII should be coadministered. (rVWF:rFVIII = 1.3:1). Initial dose of Vonvendi should achieve VWF:RCo > 0.6 and rFVIII should achieve FVIII:C > 0.4 IU/ mL in major bleeds, trough levels of VWF:RCo should be maintained > 50% for as long as considered necessary.		
Dosing: Geriatric		Not studied in patients aged > 65 years		
Dosing in pregnancy		Not studied in pregnant women. Not studied in lactating women.		
Dosing in pediatric population		Not studied in patients under the age of 18		
Dosing: Renal impairment		No dosage adjustment provided in manufacturer's labeling.		
Dosing: Hepatic impairment		No dosage adjustment provided in manufacturer's labeling.		
Indications		Treatment (on demand) and control of bleeding episodes in adults with von Willebrand disease.		
Contraindications		Patients with life-threatening hypersensitivity to Vonvendi or its constituents (trisodium citrate dihydrate, glycine, mannitol, trehalose dihydrate, polysorbate 80 or hamster or mouse protein)		
Adverse events		See Table II on adverse events		
Pharmacokinetics	t _½ elimination	19.1 to 21.9 hours		

wherein the high concentration of ULM and HMW may prove very effective in stopping the GI bleeding. However, the high concentration of ULM and HMW multimers theoretically places patients receiving Vonvendi for a prolonged duration for major bleeds at a risk for thrombosis, particularly in the postoperative setting. Yet, the lack of FVIII in the product may prevent accumulation of FVIII in cases of major surgeries and obstetrics, which could lower the risk of thrombosis. The impact of an rVWF product on the risk of clinically significant inhibitors will need further study also. The only two patients in the published studies, who had high-titer non-neutralizing anti-VWF antibodies, showed lower VWF:Ag and VWF:RCO levels on receiving Vonvendi and had faster degradation of HMW VWF. The risk of developing these antibodies and the subsequent effect these antibodies may have in response to rVWF is not completely clear. Further follow-up is in order.

Overall, Vonvendi's efficacy and safety, albeit based on only 22 patients who had received the product for bleeding and an additional 15 for safety and PK studies, seem on par with the presently available pdVWF concentrates although certainly further patients must be studied particularly in the surgical setting to confidently state that Vonvendi is interchangeable with the pdVWF-containing FVIII concentrates.

With further safety and efficacy data, Vonvendi may be preferable to the plasma-derived concentrates, particularly in terms of preventing viral transmission, which would be an attractive option to parents of newborns with Type 3 VWD alleviating their worry about exposing their child to lifelong plasma. Also, Vonvendi may be preferable in the obstetrics setting where the FVIII levels may be less likely to accumulate so decreasing the risk of postpartum thrombosis. The same benefit may extend in cases of major surgeries, where accumulation of endogenous and exogenous FVIII can potentially predispose to thrombosis. The apparent extended $t_{1/2}$ may also make its use attractive in the prophylaxis setting.

More studies are required before these questions can be answered satisfactorily. But still, it is fortunate, though, that the clinician now has an additional product to at least consider in individualizing the treatment of VWD necessitating VWF replacement coming close to the 21st century goal in medicine of individualized "precision" medicine.

DISCLOSURES

P. Kouides has received honoraria for consulting for Shire/Baxalta (who manufactures and markets Vonvendi), Octapharma (manufactures and markets Wilate) and CSL Behring (manufactures and markets Humate-P). M. Singal states no conflicts of interest.

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