Bioequivalence of von Willebrand factor-containing concentrates: implications for the choice in patients with von Willebrand disease. A position paper from the Italian Association of Hemophilia Centers

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ABSTRACT

Von Willebrand disease (VWD) is a bleeding disorder caused by quantitative and/or qualitative defects of von Willebrand factor (VWF), a multimeric glycoprotein synthesized by endothelial cells and megakaryocytes. VWF plays a crucial role in hemostasis by mediating platelet adhesion to the sub-endothelium, platelet-platelet aggregation, and by acting as the carrier protein for circulating factor VIII (FVIII) in plasma, protecting it from early proteolytic degradation. The treatment and prevention of bleeding episodes in VWD patients requires the administration of either VWF/FVIII or purified VWF-containing concentrates when desmopressin (DDAVP) is contraindicated or ineffective. Many VWF/FVIII-containing concentrates, one purified plasma-derived VWF (pd-VWF) and one recombinant VWF (rVWF) product are available. These products are characterized by different manufacturing methods, variable VWF/FVIII ratio and multimers composition and content, which could influence their hemostatic efficacy. With this as background, the Italian Association of Hemophilia Centers (AICE) established a multidisciplinary expert panel to analyze the available literature evidence about the bioequivalence of the different licensed VWF-containing products. The data retrieved and their implications for therapeutic choices are discussed in this manuscript, which AICE endorsed as a position paper.

Key words: von Willebrand factor; von Willebrand disease; bioequivalence; factor VIII.

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Introduction

This review presents a comprehensive analysis of the bioequivalence of various licensed von Willebrand factor (VWF)-containing concentrates, a relevant issue to consider with an aim to optimize treatment strategies in von Willebrand disease (VWD), an inherited bleeding disorder due to quantitative or qualitative defects of VWF. VWF is a complex multimeric glycoprotein produced by endothelial cells and megakaryocytes, which is essential for primary hemostasis through interaction with platelets and contributes to secondary hemostasis by carrying factor VIII (FVIII) in plasma.[1-3] Management and prevention of bleeding episodes in VWD patients often necessitate the administration of VWF-containing concentrates, particularly when desmopressin (DDAVP) is contraindicated or proves ineffective. Currently, plasma-derived (pd)-VWF/FVIII concentrates, one purified pd-VWF concentrate and one rVWF product are commercially available. These therapeutic products differ significantly in the manufacturing process, their content of FVIII and VWF and VWF multimeric pattern. These differences raise important questions about their choice in the management of VWD. Recognizing the clinical significance of this issue, the Italian Association of Hemophilia Centers (AICE) established a multidisciplinary panel of experts with the primary objective to review and analyze the existing literature concerning the bioe-

quivalence of the various licensed VWF-containing concentrates. The evidence gathered from this analysis is reported in this review, also discussing the potential implications for therapeutic choices in the clinical management of VWD.

Von Willebrand factor and pathophysiology of von Willebrand disease

Structure of von Willebrand factor

VWF is a complex multimeric glycoprotein consisting of repeated monomers , each with a molecular weight of approximately 250 kD that are encoded by the *VWF* gene, located on chromosome 12.[1] Each monomer consists of multiple domains with distinct functions: i) D1 and D2, pro-peptide regions are involved in multimer formation and processing; ii) D3, is important for binding to FVIII; iii) A1, binds to platelet receptor GPIb; iv) A2, contains a cleavage site for the ADAMTS13 protease, which degrades VWF; v) A3, contains the binding site for collagen; vi) C1, is involved in platelet aggregation through binding to integrin αIIbβ3; vii) C2, is involved in collagen binding.

Synthesis, storage, and regulation of VWF

VWF is synthesized by endothelial cells and megakaryocytes.[1-3] It is stored in Weibel-Palade bodies of endothelial cells and in α-granules of platelets. VWF undergoes extensive glycosylation, which influences its stability, multimerization, and interactions with other proteins.[4,5] Dimers of VWF subunits, formed in the endoplasmic reticulum, further multimerize into large, functionally active multimers in the Golgi apparatus and are continuously secreted in blood circulation, accumulating in the subendothelial matrix. Multimers size range from 500-2500 kDa (1-5 dimers, low molecular weight multimers, LMWM), to intermediate molecular weight multimers (IMWM) of 3000-5000 kDa (8-10 dimers), high molecular weight multimers (HMWM) of 5500-1000 kDa (11-20 dimers), and ultra-large multimers (ULMWM) of >10000 kDa consisting of >20 dimers.[4] The concentration of HMWM may increase in plasma, upon vascular injury or stimulation by agents such as thrombin. The size and activity of circulating VWF multimers are tightly regulated by ADAMTS13, a metalloprotease, which cleaves VWF at the A2 domain under conditions of high shear stress, thus reducing their size and preventing excessive platelet aggregation with the possible related thrombotic complications.[6] However, the presence of intact HMWM is essential for efficient VWF-platelet interactions, as they bind with higher affinity to both platelet receptors, namely the glycoproteins Ib and the IIb/IIIa complex.[7] After administration of DDAVP, a synthetic analogue of vasopressin, which stimulates endothelial VWF release, the transient normalization of VWF multimer pattern in plasma shortens the bleeding time in some VWD patients.[8,9] Cattaneo *et al*. showed that in type 3 VWD patients the PFA-100 closure time, a surrogate of bleeding time, was not corrected with pd-VWF/FVIII concentrates alone, since these products do not contain HMWM.[10] This observation underscores the importance of considering VWF multimer composition when selecting appropriate replacement products.

Von Willebrand disease classification

VWD is classified into three major types based on the nature of VWF deficiency:

- Type 1: characterized by a partial quantitative deficiency of VWF.
- Type 2: characterized by qualitative defects of VWF molecule; further categorized into four variant types (2A, 2B, 2M, and 2N) based on specific functional abnormalities. At variance with type 2A, 2B and 2M, 2N VWD is characterized by normal or slight reduced VWF levels and reduced FVIII levels due to the impaired binding between the two molecules therefore resembling mild hemophilia A.
- Type 3: characterized by a near-total absence of VWF, leading to the most severe bleeding phenotype.

To note, VWF defects usually cause a secondary deficiency of FVIII which may impinge upon the bleeding phenotype. On the same note, the administration of VWF alone is able to induce an increase of endogenous FVIII levels which occurs after approximately 6-8 h from VWF administration.

Replacement treatment options for VWD

For patients with VWD in whom DDAVP is ineffective or contraindicated, replacement therapy with pd-VWF/FVIII concentrate, purified pd-VWF or rVWF is considered the treatment of choice. Based on the manufacturing process, pd-VWF/FVIII products display different VWF/FVIII ratios as well as different multimer pattern (Table 1). Although clinical studies have shown comparable hemostatic efficacy and pharmacokinetic (PK) among different pd-VWF/FVIII products, understanding their differences is crucial for optimal patient management, briefly:

- FVIII content: FVIII is essential for coagulation, especially during surgery and to control soft tissue bleeding; however, the use of concentrates with a low VWF ristocetin cofactor (RCo) activity/FVIII ratio can lead to supraphysiologic FVIII levels due to the addition of endogenous to exogenous FVIII, potentially increasing thrombotic risk.
- HMWM content: since HMWM are the most effective in supporting interaction with collagen and platelet receptors, their specific content in different concentrates can influence therapeutic outcomes mostly with respect of mucosal bleeding.[11].

Product selection should be tailored to the patient's laboratory profile and bleeding tendency. In patients with normal or near-normal FVIII levels, pd-VWF/FVIII concentrates with low FVIII content, purified pd-VWF or rVWF may be preferable, as they help to avoid excessive FVIII level fluctuations with accumulation over time.

Pharmacokinetics and clinical efficacy of VWF concentrates in VWD

In 2002, the PK and clinical efficacy of two different preparations of Alphanate® (Alpha Therapeutic, Los Angeles, CA, USA) -one virally inactivated with solvent/detergent and the other with an additional heat treatment- were prospectively evaluated in 81 patients with VWD.[12] In 11 subjects with type 3 VWD, using the double viral inactivated preparation, the mean

half-life of FVIII (23.8 h) was approximately double than that of VWF:Ag (12.9 h), likely due to the normal endogenous FVIII synthesis. Similar findings were later reported in a smaller study evaluating Fanhdi® (Grifols, Barcelona, Spain), a product with a superimposable manufacturing process of Alphanate®.[13]

A prospective PK analysis of Humate-P® (CSL Behring, Marburg, Germany) in 29 VWD patients undergoing elective surgery a median terminal half-life of 15.6 h for VWF:RCo and 20.6 h for VWF:Ag was reported with variations depending on VWD type (22.1 h in type 1 and 14.6 h in type 3 patients) (Table 2).[14] Additional retrospective studies on Haemate-P®/Humate-P®, Alphanate®/ Fanhdi® confirmed these findings.[15-20]

In a head-to-head, randomized crossover study, the PK profile of Wilate® (Octapharma, Vienna, Austria), a high-purity concentrate, possessing a 1:1 VWF:RCo/FVIII ratio and the PK profile of Humate-P® were compared in 20 subjects with inherited VWD type 1, 2A, 2B, 2M, or 3. Patients were randomized to a single intravenous dose of either 40 VWF:RCo U/kg of Wilate® or Humate-P® in Period 1, and then switched to the other study drug in Period 2, after a washout period of at least 7 days. PK profiles showed no statistically significant differences. The mean terminal half-lives of VWF:RCo and VWF:Ag were 10.4 and 15.8 h for Wilate® and 9.3 and 12.8 h for Humate-P®, respectively.[21]

Wilfactin® (LFB, Les Ulis, France) is a plasma derived, highly purified VWF concentrate with minimal FVIII content. Unlike other plasma-derived products it allows for independent dosing of VWF and FVIII based on the patient's specific needs. Indeed, while some patients may require both VWF and FVIII replacement, others may need VWF replacement only. Wilfactin® offers clinicians the flexibility to administer VWF alone, avoiding FVIII overdosing. In type 3 VWD patients treated with such product, VWF:RCo and VWF:Ag half-life was 12.4±1.8 h and 15.9±1.5 h, respectively, with an *in vivo* mean recovery of 2.1±0.3 and 1.8±0.3 IU/kg, respectively.[22] FVIII levels increased progressively after Wilfactin® administration with peak levels reached between 12 and 24 h post infusion.[22]

Vonicog alfa (Veyvondi®/Vonvendi®, Takeda, Lexington, MA, USA) is the only human rVWF available. It is synthesized in Chinese Hamster Ovary (CHO) cell line co-expressing *VWF* and *F8*. It is free of animal and human plasma proteins and purified through immune-affinity chromatography. [23,24] It is produced in the absence of the VWF-cleaving protease ADAMTS13, implying that it retains an intact multimeric pattern, including ULMWM which are physiologically present in endothelial cells and platelets but not in normal plasma. The presence of ULMs in the final formulation of this product raised concerns about the potential thrombotic risk *in vivo*, swept away thanks to the observation of their rapid cleavage by endogenous ADAMTS13.[24] The phase 1 study was a prospective, multicenter, randomized, controlled trial of safety, tolerability and PK of vonicog alfa, combined with a fixed ratio (1.3:1) of rFVIII, compared to Haemate-P® which exhibits a VWF:RCo/FVIII ratio of 2.5. Twenty-six subjects were randomized to blinded dual-crossover PK profiles, comparing a single dose of rVWF/rFVIII (50 VWF:RCo IU/kg and 38.5 FVIII:C IU/kg) with a single dose

Table 1. VWF/FVIII concentrates licensed for the treatment of von Willebrand disease in Europe and North America.

Product	Manufacturer	Purification	Viral inactivation	VWF:RCo/Ag# (Ratio)	VWF:RCo/FVIII# (Ratio)
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)	0.47±0.1	0.91±0.2
Factor 8Y	BioProducts	Heparin/glycine precipitation	Dry heat (80°C, 72 h)	0.29	0.81
Fanhdi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)	0.47±0.1	1.04±0.1
Haemate P/Humate P	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 h)	0.59±0.1	2.45±0.3
Talate	Takeda	Ion exchange chromatography	S/D + vapor heat (60°C, 10 h)	0.47	1.1
Wilate	Octapharma	Ion exchange chromatography + size exclusion	S/D + dry heat (100°C, 2 h)	-	0.9
Wilfactin	LFB	Ion exchange chromatography + affinity chromatography	S/D, 35 nm filtration, dry Heat (80°C, 72 h)	≈0.95	≈50
Veyvondi	Takeda	immune-affinity chromatography	-	1.16±0.25	>100

VWF, von Willebrand factor; RCo, ristocetin cofactor; Ag, antigen; FVIII, factor VIII; S/D, solvent/detergent.

Table 2. Main pharmacokinetic parameters after Haemate P in the different types of Willebrand disease.[14]

Parameter	VWD type	VWF:RCo (Median (IQR)	VWF:Ag (Median (IQR)
Terminal half-life (h)	1	22.1 (14.5–30.8)	29.1 (19.7–34.6)
	2A	15.1 (11.4–26.4)	21.2 (20.6–27.7)
	2M	14.9 (14.9–14.9)	17.3 (17.3–17.3)
	3	8.8 (5.1–13.8)	14.6 (14.3–16.5)
	All	15.6 (9.0–28.4)	20.6 (16.2–29.0)
MRT (h)	1	26.9 (19.5–35.3)	39.9 (27.1–43.7)
	2A	17.9 (13.3–27.0)	28.3 (26.4–32.9)
	2M	21.0 (21.0–21.0)	22.6 (22.6–22.6)
	3	11.6 (8.5–19.1)	20.7 (20.4–23.5)
	All	19.7 (11.9–28.3)	26.7 (22.8–36.0)

of pd-VWF/FVIII (50 VWF:RCo U/kg and 25 FVIII:C IU/kg) (Table 3.) Within 1 h after infusion, patients treated with rVWF/rFVIII showed a high VWF:RCo level, while VWF:Ag levels were lower than in subjects treated with the pd-VWF/FVIII. A longer VWF:Ag plasma half-life was observed with rVWF/rFVIII (25.5 h) as compared to pd-VWF/FVIII (17.9 h), similar to the VWF collagen binding (VWF:CB) activity (24.4 *vs* 16.4 h). Consequently, FVIII levels within the normal range were attained and maintained over time. No thrombotic complications were observed during the study including the early post-infusion period when ULMs were detected in plasma. Indeed, the enzymatic degradation by endogenous ADAMTS13 was rapid, as indicated by the appearance of typical VWF cleavage products 15 min post-infusion. PK data obtained in the phase 1 study were confirmed in the phase 3 trial:[25] the mean half-life of VWF:Rco activity resulted 21.9±8.4 h and it was shown that VWF:RCo, VWF:Ag and VWF:CB significantly increased after a single rVWF administration and that rFVIII does not influence VWF PK parameters.[25]

VWF-containing concentrates in the surgical setting

If not properly dosed, repeated infusions of pd-VWF/FVIII for severe bleeding episodes or major surgery may lead to accumulation of FVIII in plasma over time with consequent increased risk of deep vein thrombosis, pulmonary embolism, and cardiovascular complications.[26,27] Several factors influence FVIII and VWF half-lives in the surgical setting, including inter-individual PK variability, consumption of FVIII/VWF, tissue damage that may induce the release of normal or abnormal VWF from endothelial cells, and other medical conditions such as infection and/or inflammation.

A retrospective study analyzed the perioperative management of 148 surgeries in 103 patients using Haemate-P®.[28] The results indicated a significant risk of overtreatment across all VWD types, as many patients had high VWF levels (65, 53 and 57% in type 1, 2 and 3 patients, respectively) and exceeded predefined FVIII target levels (i.e., ≥20 U/dL; 91, 72 and 73% in type 1, 2, and 3 patients, respectively). In another prospective study exploring the efficacy and safety of Wilate® as hemostatic treatment in 125 VWD patients who underwent 125 surgical procedures (63 major), a subgroup analysis including 47 patients who received more than 3 infusions showed no accumulation of FVIII in plasma.[29]

To mitigate the risk of off-target treatment, daily monitoring of FVIII plasma levels, alongside VWF activity, is suggested during major surgery to ensure FVIII level remains below 150 IU/dL.[27] Alternatively, the use VWF concentrates with low or no FVIII, such as Wilfactin® or Veyvondi®/Vonvendi® alfa may help to prevent excessive FVIII accumulation. However, for these FVIII-free products, a priming dose of FVIII is necessary when baseline FVIII levels are below 30 IU/dL, as endogenous FVIII takes approximately 6-8 h to reach the desired peak following rVWF infusion.[30] This priming dose could be avoided starting rVWF administration 12 h before surgery. In fact, evidence from a phase 3 surgical trial, where patients received the first rVWF dose 12-24 h before surgery, showed that majority of procedures were managed with rVWF alone, without the need for FVIII priming doses.[31]

Anatomical Therapeutic Chemical (ATC) classification and summary of product characteristics (SmPC) of VWF-containing concentrates

The ATC system was specifically developed to classify pharmaceutical preparations' active ingredients according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. Concentrates for the clinical management of VWD are grouped into two distinct ATCs, depending on whether they contain FVIII/VWF (B02BD06); Haemate-P®/Humate-P®, Fanhdi®, Wilate®, Talate®) or only VWF (B02BD09; Wilfactin®, Veyvondi®/Vonvendi®). This depends on assignment of ATC codes based on the mechanism of action rather than therapeutic use. However, it is to be considered that there are other peculiarities that influence the choice and prescription of different products. For example, Veyvondi®/Vonvendi® is licensed for use in adult patients (≥18 years of age) only. Talate® is limited to VWD patients with FVIII deficiency only in case no specific preparations effective in treating this disease are available.

International guidelines recommendations

The ASH/ISTH/NHF/WFH guidelines on the management of VWD "conditionally recommend" the use of long-term prophylaxis in VWD patients with a history of severe and frequent bleeds.[32] Prophylaxis is defined as a period of at least 6 months of treatment consisting of VWF replacement administered at least once weekly with VWF-containing concentrates. The rec-

Table 3. Half-life of rVWF-rFVIII *vs* Haemate-P.[24]

	Number of Type 3 VWD patients	VWF:RCo	VWF:Ag	FVIII:C
Non-compartmental half-life (h)				
rVWF-rFVIII (SD)	17	16.4 (6.7)	23.2 (7.9)	26.7 (9.0)
pdVWF-pdFVIII (SD)	15	13.0 (4.2)	15.3 (3.8)	22.6 (5.3)
Half-life (h)				
rVWF-rFVIII (SD)	16	16.3 (7.1)	25.5 (6.7)	-
pdVWF-pdFVIII (SD)	15	14.4 (6.7)	17.9 (3.5)	-

ommendation was aimed to reduce the number of bleeding episodes without taking into consideration biases and imprecisions due to the small number of patients included in different studies, while no consistent data are available to evaluate possible differences between different products. However, there is no doubt that effective prophylaxis may be achieved by the use of concentrates containing different amounts of VWF. A phase 3 study on rVWF prophylaxis in patients with severe VWD clearly demonstrated that this approach can reduce spontaneous bleeding events in patients previously receiving on-demand VWF therapy and maintain at least the same level of hemostatic control in patients switched from prophylaxis with pd-VWF to rVWF, with a favorable safety profile.[33]

Furthermore, the ASH/ISTH/NHF/WFH guidelines panel suggests: i) targeting both FVIII and VWF activity levels above 0.50 IU/mL for at least 3 days after major surgery; ii) increasing VWF activity levels to >0.50 IU/mL in patients undergoing minor surgery or invasive procedures; and iii) targeting a VWF activity level range between 0.50 and 1.50 IU/mL in women who require or desire neuraxial anesthesia during labor.[32] Therefore, these guidelines highlight the importance of normalizing both VWF and FVIII:C for major surgery, using FVIII/VWF concentrates or adding FVIII concentrates when rVWF or high purity pd-VWF concentrates are used. In addition, the recently published Italian guideline recommends that FVIII levels are maintained above 0.50 IU/mL in patients undergoing major surgery for at least 3 days after surgery when VWF activity cannot be monitored.[34]

Conclusions

VWF replacement therapy continues to evolve, with both plasma-derived and recombinant products demonstrating efficacy and safety in managing VWD. Several pd-VWF/FVIII concentrates and one high purity plasma-derived VWF concentrate are currently available for replacement therapy of VWD in Italy. These concentrates are characterized by variable content of VWF and FVIII, as well as heterogeneous multimer patterns. Their half-lives do not show significant differences. Vonicog alfa is the only rVWF concentrate currently available, which is yet not reimbursed in Italy. Unlike the available pd-VWF/FVIII concentrates, it contains an intact multimer pattern, including ULMs. The slower clearance of VWF:Ag of rVWF as compared to that of pd-VWF/FVIII concentrates may explain the enhanced stabilization of endogenous FVIII and the subsequent demonstration of efficacy even without rFVIII co-administration. The possibility to administer VWF alone, without FVIII, is an important treatment option for patients with VWD, especially relevant when repeated treatments are required for major surgeries or to prevent recurrent bleeding episodes. Furthermore, when choosing the most appropriate VWF-containing product, the opportunity to reduce the dose and/or increase the time interval between administrations or to use products with a low FVIII content, should be considered to avoid FVIII off-target levels and accumulation. In this light adequate laboratory monitoring of FVIII and VWF activity levels are advisable although not always easily available and accessible in all treatment centers. In conclusion, product selection should be tailored to each patient's needs, ensuring optimal bleeding control and minimizing thrombotic risk.

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