Principles of care for the diagnosis and treatment of von Willebrand disease

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ABSTRACT

Von Willebrand disease is a common autosomal inherited bleeding disorder caused by quantitative or qualitative defects of von Willebrand factor, a multi-adhesive protein that binds platelets to exposed subendothelium and carries factor VIII in circulation. As a result of von Willebrand factor deficiency or abnormality, levels of factor VIII, the protein deficient in hemophilia A, may be variably reduced. Clinical manifestations are mainly represented by mucous membrane and of soft tissue bleeding. Their severity is variable depending on the degree of von Willebrand factor and factor VIII reduction. While a clear-cut diagnosis is easy in severe von Willebrand factor reductions, the advantage of pursuing a definite diagnosis in mild or dubious cases should be weighed against the risk of over-medicalization. The aim of treatment is to correct the dual defect of hemostasis caused by the abnormal/reduced von Willebrand factor and the concomitant deficiency of factor VIII. Desmopressin is the treatment of choice for type 1 von Willebrand disease patients with factor VIII and von Willebrand factor levels of 10 U/dL or over who have proved responsive to a test-infusion with the compound. Von Willebrand factor/factor VIII concentrates are needed when desmopressin is ineffective (mainly type 2 and 3 von Willebrand disease).

Introduction

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, with a prevalence of approximately 1-2% according to population studies,[1] but clinically relevant cases have a 10-fold lower prevalence.[2] The disorder is mainly transmitted in an autosomal dominant manner and is caused by the deficiency or abnormality of VWF, which is required for platelet adhesion to subendothelium to occur and serves as carrier of FVIII, protecting it from early inactivation by the activated protein C (APC) system.[3] The recommended nomenclature for the two proteins and their activities is reported in Table 1. Several extensive reviews have recently been published on the pathophysiology, diagnosis and treatment of VWD to which the reader is referred.[3-10] The aim of the present review is to provide a concise practical outline of the diagnosis and treatment of VWD in Europe that could be useful for the general hematologist.

Diagnosis

The diagnosis and appropriate classification of VWD usually requires an array of tests (Table 2) together with the evidence of a bleeding history, usually also present in other family members. The diagnosis should be undertaken in a specialized center for bleeding disorders that is capable of performing such assays accurately and providing the patients with a balanced view of their bleeding risk. When a diagnostic process is initiated, the physician should always take into consideration the practical advantage and the patient perspective of a specific diagnosis of VWD in any given patient, avoiding the risk of over-medicalization of patients with dubious or mild bleeding history.[8] A slightly reduced VWF level can be found even in normal subjects and bleeding symptoms are also frequently reported by 'normal' subjects.[11-13] For this reason, the patient should be interviewed about his/her bleeding history using a structured, written questionnaire to improve the quality of data collection and to reduce both intra- and inter-observer variability. Since in many cases the deficiency is mild and the risk of bleeding small, it is recommended that diagnosis be pursued especially in the presence of a significant bleeding history, obtained by using specifically designed questionnaires.[13,14] Collected data must be unambiguously interpreted to verify if the bleeding history is compatible with a bleeding disorder, and for this purpose a bleeding score (BS), accounting for both the number and the severity of the bleeding symptoms, may be useful. The BS is generated by summing the severity of all bleeding symptoms reported by a subject, and graded according to an *a priori* scale.[13,15] Previous experience from the International Multicenter Study suggests that a bleeding score of 3 or over in males and of 5 or over in females could be considered as a useful cut off to identify adults with a bleeding diathesis in whom it is worth measuring VWF-related activities.[13] A novel questionnaire has been recently endorsed by the International Society on Thrombosis and Haemostasis (ISTH) to assess bleeding symptoms for the diagnosis of bleeding disorders.[16]

The diagnosis of VWD is then based on the presence of reduced VWF:RCo (or VWF:CB) (<40 U/dL), with a further characterization of VWD type based on assessment of VWF:Ag, FVIII and multimer pattern. In general, VWF levels

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below 30 U/dL have been shown to be strongly associated with a significant clinical severity as assessed by a bleeding score[17] and the presence of mutations in the *VWF* gene.[18] However, levels under 40 U/dL and the presence of other relatives with equivalent levels are similarly a crucial clue for the diagnosis of mild VWD.[14] In these cases, bleeding history is milder and treatment usually rests on avoidance of anti-platelet drugs and antifibrinolytics as required.

Pediatric cases should be evaluated by using less stringent criteria. Mucocutaneous bleeding symptoms (e.g. epistaxis and bruising) are common in childhood and are not necessarily caused by a congenital bleeding disorder. A recent study that used the same bleeding questionnaire adopted for adults showed that with minimal modifications it is useful also in a pediatric setting, with a threshold score for a significant bleeding history of 2 or over.[19] Table 3 summarizes a practical multistep approach to the diagnosis.

Clinical manifestations

Clinical expression of VWD is usually mild in type 1, with increasing severity in type 2 and type 3. In general, the severity of bleeding correlates with the degree of the reduction of FVIII. Mucocutaneous bleeding (epistaxis especially during childhood, menorrhagia, easy bruising) is a typical, prominent manifestation of the disease and may affect the quality of life. However, the rate of spontaneous bleeding may be low even in patients with severe VWF deficiency.[20] Bleeding after dental extraction is the most frequent post-operative bleeding manifestation. Since FVIII is usually only mildly reduced, manifestations of a severe coagulation defect (hemarthrosis, deep muscle hematoma) are rarely observed in type 1 VWD and are mainly post-traumatic. On the contrary, in type 3 VWD, the severity of bleeding may sometimes be similar to that of moderate hemophilia. Gastrointestinal bleeding may be particularly frequent and difficult to manage, especially in patients lacking high

Table 1. Recommended nomenclature of factor VIII/von Willebrand factor complex.

Factor VIII	
Protein	FVIII
Antigen	FVIII:Ag
Function	FVIII:C
Von Willebrand factor	
Mature protein	VWF
Propeptide	VWFpp
Antigen	VWF:Ag
Ristocetin co-factor activity	VWF:RCo
Collagen binding capacity	VWF:CB
Factor VIII binding capacity	VWF:FVIIIB

Table 2. Basic and discriminating laboratory assays for the diagnosis of VWD.

Test	Pathophysiological significance	Diagnostic significance
Ristocetin Co-factor activity using formalin-fixed platelets and fixed ristocetin concentration (1 mg/mL) (VWF:RCo)	VWF-GP Ib interaction as mediated by ristocetin *in vitro* (ristocetin, normal platelets, patient's plasma)	"Functional test"; most sensitive screening test. Sensitivity low for levels < 10 U/dL, difficulties in standardization
GPIb binding assays "VWF:RCo" (new nomenclature under development)	Measure interaction between VWF and captured rGPIbα fragment in the presence of ristocetin or with mutant pseudo-VWD rGPIbα without ristocetin	Promising new tests proposed as substitutes for VWF:RCo; validation on larger patient series required
Immunological assay with polyclonal antibody (VWF:Ag)	Antigen concentration	Correlates with VWF:RCo in type 1; reduced VWF:RCo/VWF:Ag (< 0.6) suggests type 2 VWD; level < 3 U/dL suggests type 3 VWD
Factor VIII procoagulant activity (one-stage clotting assay) (FVIII:C)	FVIII-VWF interaction	Not specific, but useful for patient management; disproportionately reduced compared to VWF in type 2N VWD
Bleeding time (Ivy method)	Platelet-vessel wall VWF-mediated interaction	Not specific; correlates with platelet VWF content in type 1 VWD. Widely dismissed, historical test
Binding of VWF to collagen (VWF:CB)	VWF-collagen interaction	Correlates with VWF:RCo in type 1 VWD; some collagen preparations more sensitive to high molecular weight multimers
Binding of FVIII to VWF (VWF:FVIIIB)	FVIII-VWF interaction	Allows identification of type 2N
Ristocetin-induced platelet aggregation using patient platelets (RIPA)	Threshold ristocetin concentration inducing patient's platelet-rich plasma aggregation	Allows the discrimination of type 2B, characterized by reduced threshold; absent in type 3 at every ristocetin concentration
Multimer analysis (intermediate resolution gel)	Multimer composition of VWF	Presence of full range of multimers in type 1; high and intermediate molecular weight multimers absent in type 2A and high molecular weight multimers absent in type 2B; multimers absent in type 3
Closure time PFA-100	Simulates primary hemostasis after injury to a small vessel	More sensitive than BT in screening for VWD; specificity unknown; more data needed before recommending for clinical laboratory
Propeptide assay (VWFpp)	Measures the amount of VWFpp released in plasma	Increased VWFpp/VWF:Ag ratio identifies patients with shortened VWF survival after desmopressin; still for research purposes

molecular weight multimers in plasma.[21] Bleeding after delivery is rarely observed in type 1 since FVIII/VWF levels tend to correct at the end of pregnancy in mild type 1 cases, whereas type 2A and 2B and type 3 females usually need replacement therapy post-partum to prevent immediate or delayed bleeding. Post-operative bleeding may not occur even in more severely affected type 1 patients, whereas in type 3 prophylactic treatment is always required.

Classification

VWD is classified into three different types (Table 4).[6] Types 1 and 3 VWD reflect the partial or (virtually) complete quantitative deficiency of VWF, while type 2 VWD reflects qualitative defects of VWF. Type 1 is the most common form of VWD and is predominantly transmitted as an autosomal dominant trait often with incomplete penetrance (not all cases that inherit a VWF mutation demonstrate bleeding symptoms). Type 1 VWD is characterized by an equivalent mild to moderately severe reduction of VWF antigen (VWF:Ag) and ristocetin co-factor activity (VWF:RCo) in plasma. VWF multimers are essentially normal and certainly with a normal profile of high molecular weight forms, while plasma levels of FVIII are reduced, usually in proportion to VWF but often FVIII is higher than VWF. The severity of mucocutaneous bleeding symptoms usually correlates with the degree of their VWF and FVIII deficiencies. Type 2A is inherited mainly with an autosomal dominant pattern and the hallmark is represented by the lack of large and intermediate size VWF multimers. The laboratory hallmark of the most typical and frequent forms of type 2B is the heightened ristocetin induced platelet aggregation (RIPA) with mild to moderate thrombocytopenia and the absence of large multimers in plasma. In type 2M VWD the VWF multimer distribution is normal, but platelet-dependent VWF activities (VWF:RCo and/or von Willebrand factor collagen binding (VWF:CB)) are reduced. Type 2N is characterized by recessive inheritance, with mildly reduced or normal levels of VWF:Ag and VWF:RCo and a normal multimer pattern in most cases. Low plasma levels of FVIII (typically 5-40 U/dL) result from the decreased plasma half-life of FVIII, which cannot bind to VWF as a consequence of a qualitative abnormality of VWF. Type 3 VWD is inherited as an autosomal recessive trait and is characterized by undetectable levels of VWF (usually < 3 U/dL) and very low levels of FVIII (typically 1-5 U/dL), which may cause a more severe bleeding tendency characterized not only by mucocutaneous hemorrhages but also by hemarthroses and hematomas as in moderately severe hemophilia.

Table 3. A simplified practical approach to the diagnosis of von Willebrand disease.

1. VWD diagnosis should be considered within the context of an appropriate personal and/or familial bleeding history. The use of a standardized questionnaire for history collection is advisable to appreciate the severity of the bleeding tendency.
2. Other common hemostatic defects should be excluded by performing a platelet count, APTT, PT and PFA-100 (or bleeding time).
3. If personal and/or familial bleeding history is significant, VWF:RCo assay should be carried out at this stage. If not possible, VWF:Ag assay or VWF:CB assay should be performed. VWF:Ag < 3 U/dL suggests type 3 VWD. VWF:Ag and VWF:RCo and FVIII:C should be measured on the same sample to assess the presence of a reduced VWF:RCo/VWF:Ag ratio (a ratio < 0.6 suggest type 2 VWD) or FVIII:C/VWF:Ag (a ratio < 0.6 suggests type 2N VWD, to be confirmed by binding study of FVIII to patient's VWF).
4. If any of these tests is below 40 U/dL, the diagnosis of VWD should be strongly considered.
5. Other family members with a possible bleeding history should be evaluated. Finding another member with bleeding and reduced VWF strongly supports the likelihood of diagnosis.
6. Aggregation of patient platelet-rich plasma in the presence of increasing concentrations of ristocetin (0.25, 0.5, 1.0 mg/mL, final concentration) should be assessed. Aggregation at low concentration (< 0.5 mg) suggests type 2B (or platelet type) VWD.
7. Multimer pattern using an intermediate resolution gel should be evaluated. Lack of high molecular weight multimers suggests type 2A and/or 2B. Presence of full complement of multimers suggests type 1 (or 2N, 2M). Absence of multimers in type 3. Analysis of the triplet structure will help identify variants with increased or decreased cleavage. Repetition of the multimer gel in low resolution agarose may be helpful in confirming the presence/lack of HMW multimers.
8. VWF genetic analysis could be advisable for differential diagnosis of mild hemophilia A *vs.* 2N VWD in males, hemophilia A carriership *vs.* 2N VWD in females and for type 2B VWD *vs.* platelet type-VWD.
9. VWF genetic analysis may be required for prenatal diagnosis in type 3.

Table 4. Classification of von Willebrand disease, modified from Sadler *et al.*[6]

Quantitative deficiency of VWF	
Type 1	Partial quantitative deficiency of VWF
Type 3	Virtually complete deficiency of VWF
Qualitative deficiency of VWF	
Type 2	Qualitative deficiency of VWF
Type 2A	Qualitative variants with decreased platelet-dependent function associated with the absence of high and intermediate-molecular-weight VWF multimers
Type 2B	Qualitative variants with increased affinity for platelet GPIb
Type 2M	Qualitative variants with decreased platelet-dependent function not caused by the absence of high-molecular-weight VWF multimers
Type 2N	Qualitative variants with markedly decreased affinity for factor VIII

Molecular diagnosis

VWF is synthesized by endothelial cells and megakaryocytes. The gene coding for VWF (*VWF*) has been cloned and located at chromosome 12p13.2.[22] It is a large gene of approximately 178 kilobases and containing 52 exons. Recent years have witnessed an outstanding widening of knowledge of the molecular basis of VWD. After the initial characterization of type 2A and 2B cases caused by mutations in exon 28 of *VWF*, coding for the critical region of the mature subunit involved in binding to platelet glycoprotein Ib (GpIb), several studies have reported the identification of causative mutations in all other types.[23] While the discussion of these aspects is beyond the scope of this document and is dealt with in detail in other papers,[23,24] it should be borne in mind that the routine characterization of *VWF* mutations is not usually required for the general treatment of these patients, apart from a few exceptions (Table 3). The identification of type 2N mutations, which is suspected in the presence of a marked reduction in FVIII:C in comparison to *VWF* and is confirmed by the FVIII-VWF binding test (VWF:FVIIIB), is important for genetic counseling to exclude the presence of the state of carrier for hemophilia A. The identification of VWF gene mutations in suspected type 2B cases allows its distinction from platelet-type VWD, characterized by a similar phenotype but with mutations located in the *GP1BA* gene. Homozygosity for a large gene deletion or nonsense mutation may be associated with appearance of antibodies against *VWF*. These antibodies may be very difficult to demonstrate and several laboratory tests, still not standardized, are required.[25] In these patients, replacement therapy may be not only ineffective, but also stimulate an anaphylactic reaction upon treatment. Prenatal diagnosis for type 3 in families with patients showing a heavy bleeding history or inhibitors could be suggested.

Treatment

The severity of the bleeding tendency is usually proportional to the degree of the primary deficiency of VWF and to that of the secondary deficiency of FVIII, as VWF is the carrier of FVIII in circulating plasma.[3,10] Thus, in VWD the aim of therapy is to correct the dual defect of hemostasis, i.e. the abnormal platelet adhesion-aggregation and the abnormal intrinsic coagulation due to low FVIII levels. Desmopressin (DDAVP) and replacement therapy with VWF/FVIII concentrate or VWF concentrates devoid of FVIII are the mainstay of treatment (Table 5). Combined estrogen-progestogen drugs and antifibrinolytic agents (tranexamic acid and epsilon aminocaproic acid) can also play a significant role in the treatment.[4,8]

A practical approach to the treatment of von Willebrand disease

Desmopressin (DDAVP)

The first step is to carry out a test with desmopressin. Candidates are those patients with basal FVIII and/or VWF:RCo below 30 U/dL. Patients with higher levels are very likely to respond and do not routinely require biological testing, although a test infusion may be useful in unraveling additional VWF abnormalities (e.g. shortened VWF half-life).

Desmopressin (1-deamino-8-d-arginine vasopressin) is a synthetic analog of vasopressin originally designed for the treatment of diabetes insipidus.[4,8] DDAVP increases VWF and FVIII plasma concentrations in patients with mild hemophilia A and VWD by provoking release of stored VWF.[4,8] DDAVP is cheap and carries no risk of transmitting blood-borne viruses. DDAVP (Emosint®, Minirin®) is usually administered subcutaneously, when a concentrated formulation is available, or intravenously at a dose of 0.3 μg/kg (for intravenous administration DDAVP is diluted in 50-100 mL saline and infused over 30 min). This treatment increases plasma VWF-FVIII levels 2-4 times above the basal levels within 30-60 min. In general, hemostatically useful VWF-FVIII levels are measured in plasma for 6-8 h. Infusions can be repeated every 12-24 h depending on the type and severity of the bleeding episode.[4,8] The drug is also available as an intranasal spray (Octostim®) which can, however, result in variable adsorption with a lower increase in FVIII/VWF.

Because responses in a given patient and within a family are consistent on different occasions,[26] a test infusion of DDAVP is required to establish the individual response pat-

Table 5. Suggested flow-chart for the treatment of von Willebrand disease.

• Consider the use of tranexamic acid for the treatment or prevention of bleeding in mild cases or as an adjunctive therapy in more severe cases.
• A DDAVP test infusion is recommended, especially in patients with VWF < 30 U/dL, measuring FVIII:C, VWF:Ag and VWF:RCo levels at 1 h (peak) and at least 4 h (clearance).
• Ideal candidates for treatment are those with levels post-infusion >50 U/dL.
• Patients with heightened RIPA should be excluded (risk of thrombocytopenia).
• Bleeding episodes and minor surgical or invasive procedures should be covered with DDAVP.
• Consider FVIII/VWF concentrates for major surgery when prolonged hemostatic coverage is required since sustained clinically useful levels (> 50 U/dL) are difficult to maintain with DDAVP alone.
• In patients treated repeatedly with DDAVP, measure the FVIII:C and VWF:RCo responses to monitor the development of tachyphylaxis.
• DDAVP should be used cautiously: - in children < 2 years, due to the risk of hyponatremia (limit fluid intake); - in elderly patients with atherosclerosis (risk of ischemic complications); - limit fluid intake (< 1 liter) in adults for 24 h after DDAVP.
• Pregnant VWD women responsive to DDAVP can be safely treated (0.3 μg/kg for 3-4 days) at the time of parturition after umbilical section if FVIII or VWF is not >50 U/dL to avoid excessive bleeding. DDAVP may also be used during the first trimester for invasive procedures.
• Oral tranexamic acid should be considered to lessen bleeding during the late post-partum period.

tern. A response to DDAVP is assessed at least after 1 h (peak) from the infusion and is defined as an increase of at least 3-fold over baseline levels of FVIII activity (FVIII:C) and VWF:RCo, reaching plasma levels of at least 30 U/dL.[27,28] It is also important to measure FVIII:C and VWF:RCo plasma levels at 4 h post-DDAVP infusion, in order to determine the pattern of clearance of these moieties.[29] In fact, a significant percentage of patients may have a very short half-life of FVIII and VWF despite a rapid transient normalization of these moieties soon after administration, with return to baseline occurring completely after 2-4 h.[28,29] Measurement of VWF:RCo and FVIII:C 4 h after DDAVP will provide useful information to plan appropriate treatment especially for major surgery where sustained normal FVIII/VWF levels are required.

DDAVP is usually effective in patients with type 1 VWD and baseline VWF and FVIII levels higher than 10 U/dL,[28] while in other VWD types there is significantly less response to DDAVP.[27] In type 2B, DDAVP is contraindicated because of the transient appearance or aggravation of thrombocytopenia leading to an increased risk of bleeding, although a few patients have clinically benefited from its use.[30,31] Patients with type 3 VWD are unresponsive to DDAVP. Tachycardia, headache and flushing are frequent, mild adverse-effects of DDAVP and can often be attenuated by slowing the rate of infusion or by using the subcutaneous route. Tachyphylaxis (the progressive reduction in responsiveness after repeated treatments) is the main limitation to the use of DDAVP and should be considered when repeated doses are anticipated.[32] Hyponatremia and volume overload due to the antidiuretic effect of DDAVP occur rarely, but small children who have received closely repeated infusions are particularly at risk.[33] To avoid this complication, fluid intake should be limited during DDAVP treatment. Finally, this drug should be used cautiously in patients with uncontrolled hypertension, recent myocardial infarction or stroke, or suffering from angina, as thrombotic events have been reported to occur following its use.[34,35] DDAVP can also be safely used at the time of parturition in responsive VWD women with low FVIII:C and VWF:RCo levels, and it has been safely used in the first trimester of pregnancy to cover invasive procedures such as villocentesis and amniocentesis.[36,37] Table 5 reports the recommendations on the use of DDAVP in VWD patients.

Replacement therapy

Those patients in whom a test infusion with desmopressin is not able to achieve clinically useful FVIII and/or VWF levels are candidates for replacement therapy

Candidates for replacement treatment should be vaccinated against hepatitis B, although the risk of infection by commercial concentrates nowadays is very small. Vaccination against hepatitis A is similarly advisable[38] although recommendations vary amongst different groups.[39] VWF and FVIII levels in VWD can be normalized by the infusion of virally-inactivated plasma-derived concentrates containing both these proteins and these concentrates are the mainstay of treatment for patients not candidates for the use of DDAVP. A recombinant VWF concentrate is under investigation but at present no indications on its use can be given. Several intermediate and high-purity products containing both VWF and FVIII are licensed in Europe for treatment of VWD (Table 6). After infusion, the half-life of FVIII:C is usually approximately twice that of VWF:Ag (~20-24 h *vs.* ~10-14 h) because of the endogenous production of FVIII.[4]

Theoretically, products labeled for VWF content and with a VWF/FVIII ratio around 1 should be preferred[4,8] since the expected rise post-infusion can be easily predicted. However, there is no evidence from retrospective or prospective clinical studies that VWF/FVIII products differ with regards to hemostatic efficacy.[40,42] The goal of treatment in patients undergoing major surgery is to maintain FVIII plasma levels around 80-100 U/dL for at least a couple of days and trough level above 50 U/dL for an additional 5-7 days thereafter. A loading dose of 50 U/kg of VWF:RCo is usually given in severe cases 30 min-1 h before surgery, followed by similar daily doses for the next two days. A single or daily doses for 2-3 days of 20-60 IU/kg of VWF:RCo (depending on the severity of bleeding) are hemostatically effective for treating spontaneous bleeding episodes or for preventing bleeding during invasive procedures in patients with factor levels at baseline of less than 10 U/dL (Table 7). Not all countries label VWF/FVIII concentrates with their VWF:RCo content and in these cases FVIII content must be used to guide replacement therapy. The accumulation of FVIII infused together with that endogenously synthesized and stabilized by the infused VWF may lead to very high FVIII:C concentrations in plasma (> 150 U/dL) when repeat-

Table 6. VWF/FVIII concentrates licensed for the treatment of von Willebrand disease in Europe.

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 Laboratory	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	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 h)	0.59±0.1	2.45±0.3
Immunate	Baxter	Ion exchange chromatography	S/D + vapor heat (60°C, 10 h)	0.47	1.1
Wilate	Octapharma	Ion exchange + size exclusion Chromatography	S/D + dry heat (100°C, 2 h)	-	0.9
Wilfactin	LFB	Ion exchange + affinity	S/D, 35 nm filtration, dry Heat (80°C, 72 h)	≈ 0.95	≈50

VWF: von Willebrand factor; RCo: ristocetin co-factor; Ag: antigen; FVIII: factor VIII; S/D: solvent/detergent; D: detergent. # Data from ref.[40,41]

Table 7. Suggestions for replacement therapy of von Willebrand disease.

- **Spontaneous bleeding episodes**: single or daily doses of 20-60 IU/kg of VWF to maintain FVIII:C levels > 30 U/dL until bleeding stops (usually 2-4 days)[1].
- **Major surgery**: daily doses of 50-60 IU/kg of VWF to maintain pre-operative FVIII:C and VWF:RCo levels of 80-100 U/dL until 36 h postoperatively and then > 50 U/dL until healing is complete (usually 5-10 days).[1]
  - Measure plasma levels of FVIII:C (and VWF:RCo) every 12 h on the day of surgery, then every 24 h.
  - Usual thrombo-prophylactic treatment with LMWH should be implemented in patients at high risk of venous thrombosis.
- **Minor surgery**: daily or every other day doses of 30-60 IU/kg of VWF to maintain FVIII:C level > 30 U/dL until healing is complete (usually 2-4 days)[1].
- Dental extractions or invasive procedures: single dose of 30 IU/kg of VWF to maintain FVIII:C level > 50 U/dL for 12 h[1].
- **Delivery and puerperium**: daily doses of 50 IU/kg VWF to maintain FVIII:C level > 50 U/dL for 3-4 days.
- Long-term secondary prophylaxis with VWF/FVIII concentrates may be considered for patients with severe VWD and recurrent bleeding in dangerous sites (i.e. gastrointestinal bleeding, hemarthroses, epistaxis in children).
- Possible indications for VWF concentrates devoid of FVIII include major elective surgery, particularly when repeated infusions are foreseen in patients at high risk for thrombosis (old age, cancer surgery, orthopedic surgery) and long-term prophylaxis (i.e. for target joints, recurrent gastrointestinal bleeding, recurrent epistaxis in children).
- All plasma concentrates containing VWF must be avoided in type 3 VWD patients with alloantibodies because of the risk of anaphylactic reactions. Recombinant FVIII, administered at very high doses by continuous intravenous infusion, or recombinant activated factor VII can be used instead.

Dosing should be based on VWF:RCo content where this is available. [1]These doses are indicated for VWD patients with severely reduced FVIII:C/VWF:RCo levels (less than 10 U/dL).

ed and closely spaced infusions of concentrate are given, especially to cover major surgery. Because VWD patients have an intact endogenous production of FVIII and in order to avoid excessive post-infusion FVIII:C levels, a highly purified plasma VWF concentrate containing very little FVIII has been developed for exclusive use in VWD (Wilfactin®).[43] However, as post-infusion levels of FVIII:C rise slowly reaching a peak between 6 and 8 h, co-administration of a priming dose of FVIII may be required if prompt hemostasis is required in patients with baseline FVIII:C levels of 30 U/dL or lower.[44] In patients with high basal levels of FVIII, the concentrate could be useful when prolonged treatment is anticipated (e.g. secondary prophylaxis).

Sustained high plasma levels of FVIII:C may increase the risk of venous thrombosis, especially in the presence of circumstantial risk factors (e.g. cancer) when repeated infusions of VWF/FVIII concentrates are necessary, such as during surgical procedures. FVIII:C plasma levels should be measured daily, in order to avoid values in excess of 150 U/dL.[45,46] Primary standard prophylaxis with the use of low molecular weight heparin (LMWH) in VWD patients undergoing surgery is safe and advised at least during replacement therapy.

Secondary long-term prophylaxis

Some patients with severe forms of VWD (FVIII:C levels < 5 U/dL) may have frequent hemarthroses or recurrent spontaneous bleeding (e.g. gastrointestinal bleeding and epistaxis) which can benefit from secondary long-term prophylaxis. Clinical experience with secondary prophylaxis in VWD has been rated as excellent or good in the large majority of case series, despite using different schedules of administration.[47-49] However, prospective trials are needed to better evaluate the cost-effectiveness of this approach and the impact on patient's quality of life in comparison with on-demand therapy.

Treatment of patients with anti-VWF alloantibodies

Life-threatening anaphylactic reactions may occur in rare patients with type 3 VWD (typically homozygous for gene deletions or nonsense mutations) who develop alloantibodies[50] when treated with concentrates containing VWF. The risk of alloantibody formation in patients with large deletions may not be as high as previously thought at least for some deletions.[51] These patients can be effectively treated with recombinant FVIII, administered by continuous intravenous infusion, or with recombinant activated factor VII.[52,53]

Adjunctive and adjuvant therapies

Platelet concentrates (1 unit obtained by apheresis or 1 unit from random donors every 10-20 kg/body weight) may be of help in the very rare situations in which bleeding continues despite adequate replacement therapy.[54] This treatment provides platelets with a normal content of VWF and they can susbstitute for patient's platelets lacking or with an abnormal VWF which could be responsible for the persistence of bleeding.

Antifibrinolytic agents (i.e. tranexamic acid and epsilon aminocaproic acid), given orally, intravenously or topically, are useful alone or as adjuncts to replacement therapy (DDAVP or VWF/FVIII concentrates) for the prevention or treatment of bleeding in mucosal tracts, characterized by a high fibrinolytic activity.[55] Thus, they may be sufficient for the management of less severe forms of mucosal bleeding, epistaxis, menorrhagia or dental procedures and generally in mild VWF deficiencies. Furthermore, these agents are useful in association with replacement therapy during minor or major surgery involving mucosal surfaces. Tranexamic acid should be administered at a dose of 10-15 mg/kg 3-4 times a day, or more frequently if used as mouthwash for oral surgery or bleeding, and aminocaproic acid at a dose of 50-60 mg/kg every 4-6 h. These drugs are contraindicated in the management of urinary tract bleeding because of the risk of ureteral clots and hydronephrosis.

Estrogens-progestogen preparations may be useful to reduce the severity of menorrhagia in women with VWD, including those with type 3.[4,8]

Treatment of women with von Willebrand disease

There are special therapeutic problems related to physiological events such as menstruation, pregnancy and parturition in women of childbearing age. Up to 20% of women with menorrhagia may have mild VWD[56] and up to 70-80% of women with VWD may experience this symptom.[17,57] Treatment options (antifibrinolytics, oral contraceptives, etc.) are similar to those adopted in women without a bleeding disorder, with the exception of desmopressin or therapy with VWF/FVIII containing products. In general, it seems preferable to avoid combined oral contraceptives (COC) at menarche or initially in young girls if the patients respond to antifibrinolytics, such as tranexamic acid (oral or parenteral) given three times a day for 4-5 days or aminocaproic acid every 4 h for the same time period. Oral contraception may be preferred for older individuals under the initial supervision of a gynecologist. A levonorgestrel-releasing intrauterine device (Mirena®) has proved to be efficacious and safe in primary menorrhagia and has also been proposed for use in women with inherited bleeding disorders.[58] Endometrial ablation can also be used in older women without further reproductive needs. Iron supplementation is often required for patients with significant menorrhagia.

Pregnant women with VWD are at increased risk of postpartum hemorrhage if untreated.[56] In patients with VWD types 1 or 2, the levels of VWF and FVIII rise 2- to 3-fold during the second and third trimester, but fall to baseline levels soon after delivery.[37,59] However, in VWD 2B the increase of the abnormal VWF can cause or worsen thrombocytopenia.[60] In general, VWD patients should be monitored for VWF:RCo and FVIII:C at least once during the third trimester of pregnancy.[37] The risk of bleeding is minimal when FVIII:C and VWF:RCo levels are around or higher than 50 U/dL.[4,8,37] In type 1 VWD pregnant women with FVIII:C and/or VWF levels lower than 30 U/dL, the administration of DDAVP usually after umbilical clamping and for 3-4 days thereafter may be necessary.[37] The same approach, with less infusions can be applied to those with VWF over 30 and below 50 U/dL. Recent experience, however, suggests the possibility of initiating treatment immediately before delivery, without evident side effects for the mother or the newborn.[61]

Oral antifibrinolytic agents can be used during this period to prevent delayed postpartum bleeding. In type 3 VWD women, VWF and FVIII do not increase during pregnancy and thus VWF/FVIII concentrates may be required during pregnancy to control intermittent vaginal bleeding and at delivery or for Cesarean section. This latter procedure should be reserved only for the usual obstetrical indications. If performed, VWF:RCo and FVIII:C peak levels should be at least 50 U/dL.[4,8] Invasive management of delivery with ventouse, rotational forceps, etc. should be avoided as the risk of bleeding for the neonate is potentially raised.

Conclusions

The use of a conservative approach to the diagnosis of VWD allows the identification of patients for whom a specific treatment is needed to prevent or treat bleeding. In this way, the prevalence of clinically significant VWD is estimated to be at least similar to moderate-severe hemophilia. Although outstanding progress has been made in unraveling the molecular basis of the various VWD types and in clarifying the pathophysiology of the disease, treatment remains primarily that of discriminating patients who respond to desmopressin from those who need replacement therapy. The therapeutic armamentarium for VWD is sufficiently effective and safe to avoid the risk of intractable bleeding, while the risk of adverse effects due to overtreatment should not be overlooked.

Appendix

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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