Evidence-based recommendations on the treatment of von Willebrand disease in Italy

Pier Mannuccio Mannucci[1], Massimo Franchini[2], Giancarlo Castaman[3], Augusto B. Federici[1], on behalf of AICE (Italian Association of Haemophilia Centres) other Authors are listed at the end of the manuscript

[1]Centro Emofilia e Trombosi Angelo Bianchi Bonomi, Dipartimento di Medicina e Specialità Mediche, Università di Milano e IRCCS Fondazione Ospedale Maggiore;[2]Centro di Immunoematologia e Trasfusionale, Dipartimento di Patologia e Medicina di Laboratorio, Università e Ospedale di Parma; [3]Divisione di Ematologia, Centro Emofilia e Trombosi, Ospedale San Bortolo, Vicenza, Italy

Background. von Willebrand disease (VWD) is the most common hereditary bleeding disorder affecting both males and females. It arises from quantitative or qualitative defects of von Willebrand factor (VWF) and causes bleeding of mucous membranes and soft tissues. The aim of treatment is to correct the dual defect of haemostasis caused by the abnormal/reduced VWF and the concomitant deficiency of factor VIII (FVIII).

Material and methods. This document contains evidence-based recommendations for the management of VWD compiled by AICE (the Italian Association of Haemophilia Centres). All the evidence supporting these recommendations are based on non-randomised comparative studies or case series, because randomised controlled clinical trials or meta-analyses are not available for this disease.

Results and conclusions. Desmopressin (DDAVP) is the treatment of choice for patients with type 1 VWD with FVIII and VWF levels of 10 U/dL or more, while VWF/FVIII concentrates are indicated for those who are unresponsive or insufficiently responsive to DDAVP (severe type 1, type 2 and 3 VWD). VWF concentrates devoid of FVIII, not yet licensed in Italy, may be considered for short-term prophylaxis in elective surgery or for long-term secondary prophylaxis.

Key words: von Willebrand disease, desmopressin, von Willebrand factor

Introduction

von Willebrand disease (VWD) is the most common genetic bleeding disorder, with its prevalence being approximately 1 to 2 percent according to population studies[1]. The severity of the bleeding tendency is usually proportional to the degree of the primary deficiency of von Willebrand factor (VWF) and to that of the secondary deficiency of factor VIII (FVIII), because VWF is the carrier of FVIII in circulating plasma[2, 3].

Inherited VWD has been classified into different types (Table I). Type 1 and 3 VWD are caused by the partial or virtually complete deficiency of VWF, while type 2 VWD is due to qualitative defects of VWF. Type 1 is the most common form of VWD[2,3] and is transmitted as an autosomal dominant trait with incomplete penetrance. Type 1 VWD is characterised by a mild to moderately severe reduction in plasma levels of VWF antigen (VWF:Ag) and ristocetin cofactor activity (VWF:RCo). In type 1 VWD, VWF is functionally normal, as is usually the pattern of plasma VWF multimers; the plasma levels of FVIII are usually reduced in proportion to the quantitative deficiency of the VWF. Type 1 patients manifest a spectrum of mucocutaneous bleeding symptoms, the severity of which usually correlates with the degree of their VWF and FVIII deficiencies. Type 2A is the most frequent form of VWD due to a qualitative defect of VWF and is inherited mainly with an autosomal dominant pattern. The hallmark of type 2A VWD is a

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Table I - Classification of von Willebrand disease

VWD type	Transmission	Pathogenic mechanism	Laboratory parameters					
			VWF:Ag	VWF:RCo	FVIII:C	VWF:RCo/ VWF:Ag	RIPA	Multimers
Type 1	AD	Partial quantitative deficiency of VWF	↓/↓	↓ /↓	↓ /↓	> 0.7	↓	Presence of all multimers
Type 2	AD, AR	Qualitative defects of VWF						
	2A	Decreased platelet-dependent VWF function	N/↓	↓	N/↓	< 0.7	↓	Lack of HMWM
	2B	Increased platelet-dependent VWF function	N/↓	↓	N/↓	< 0.7	↑	Lack of HMWM and of intermediate multimers
	2M	Decreased platelet-dependent VWF function	↓	↓	↓	< 0.7	↓	Normal
	2N	Decreased VWF affinity for FVIII	N	N	↓/↓	> 0.7	N	Normal
Type 3	AR	Complete deficiency of VWF	↓	↓ ↓		-	↓	Undetectable

N = normal; AD, autosomal dominant; AR, autosomal recessive; FVIII, factor VIII; FVIII:C, factor VIII coagulant; GP, glycoprotein; HMWM, high molecular weight multimers; RIPA, ristocetin-induced platelet agglutination; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor; ↓, ↓ , ↓ or ↑, ↑ , ↑ degrees of decrease or increase.

low VWF:RCo to VWF:Ag ratio (<0.7), with a lack of large and intermediate size VWF multimers and impaired ristocetin-induced platelet agglutination (RIPA) in platelet-rich plasma. Like type 2A, the inheritance pattern of type 2B VWD is mainly autosomal dominant. The laboratory hallmark of the most typical and frequent forms of type 2B VWD is heightened RIPA: this is usually accompanied by mild to moderate thrombocytopenia, mildly reduced to normal FVIII and VWF:Ag, reduced VWF:RCo and absence of large multimers in plasma, even though an intact multimeric pattern is seen in some patients. In type 2M VWD the distribution of VWF multimers is normal, but platelet-dependent VWF activities are reduced[2,3]. Type 2N VWD is characterised by normal levels of VWF:Ag and VWF:RCo and a normal multimeric pattern, but by low plasma levels of FVIII due to increased clearance of FVIII, which cannot bind to VWF as a consequence of a qualitative abnormality of VWF. Type 2N VWD therefore resembles mild haemophilia A, but its inheritance pattern is autosomal recessive. Type 3 VWD is inherited as an autosomal recessive trait and is characterised by undetectable levels of VWF in plasma (and platelets) and very low plasma levels (1-5 U/dL) of FVIII. Patients with type 3 VWD therefore have a severe bleeding tendency characterised not only by mucocutaneous haemorrhages but also by haemarthroses and haematomas, as in moderately severe haemophilia.

In VWD the aim of therapy is to correct the dual defect of haemostasis, i.e. the abnormal platelet adhesion-aggregation and the abnormal intrinsic coagulation due to low FVIII levels. The mainstays of treatment are autologous replacement therapy with desmopressin (DDAVP) and allogeneic replacement therapy with VWF/FVIII or VWF concentrates devoid of FVIII (Table II). There are also adjunctive treatments that act upon VWF-mediated haemostasis, i.e., platelet transfusion and combined oestrogen-progestogen drugs. Adjuvant therapies are antifibrinolytic amino acids, such as tranexamic acid and epsilon aminocaproic acid, which improve haemostasis without affecting plasma VWF levels[4,5]. On behalf of AICE (Italian Association of Haemophilia Centres), we present here clinical recommendations on the treatment of VWD, based on the levels of evidence described in table III, with a recommendation grading of A (evidence levels Ia or Ib), B (evidence levels IIa, IIb or III) or C (evidence level IV)[6]. The information contained in this review has been supported and signed off by the Directors of Italian Haemophilia Centres and was retrieved from several sources, including electronic searches in MEDLINE and the Cochrane database and hand searches of reviews and abstracts of the most important meetings on this topic. All the evidence supporting these recommendation is based on observational studies or case series, because randomised clinical trials and/or meta-analyses are not

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Table II - VWF/FVIII concentrates licensed in Italy for the treatment of von Willebrand disease and tested in clinical studies based upon efficacy and PK

Product	Manufacturer	Fractionation method (ratio)	Viral inactivation	VWF:RCo/Ag	VWF:RCo/FVIII
Alphanate	Alpha Therapeutics	Heparin ligand chromatography	S/D + dry heat, (80°C, 72h)	0.47 ±0.1*	0.91 ±0.2*
Fanhdi	Grifols	As above	S/D + dry heat (as above)	0.47 ±0.1*	1.04 ±0.1*
Haemate P	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 hr)	0.59 ±0.1*	2.45 ±0.3*

Abbreviations: VWF, von Willebrand factor; RCo, ristocetin cofactor; Ag, antigen; FVIII, factor VIII; S/D, solvent/detergent (TNBP/polysorbate 80); D detergent. *Means ± SD are derived from the analysis of 10 lots for each VWF/FVIII product. The analysis was independently done using in house methods at the Milan Hemophilia Center, not with the methods recommended to manufacturers by the European Pharmacopea.
Another VWF/FVIII product (Immunate) is licensed in Italy for VWD management. The characteristics of this product can be derived only from the information provided by the manufacturer[3], because this product was not made available for our independent analysis

Table III - Grades of recommendation and levels of evidence (see ref. 6)

Grade	Level	Type of evidence
A	Ia	Evidence obtained from meta-analysis of randomized-controlled trials.
	Ib	Evidence obtained from at least one randomized-controlled trial.
B	IIa	Evidence obtained from at least one well-designed controlled study without randomization.
	IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
	III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, cohort and case-control studies.
C	IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

currently available. These recommendations bring up to date previously published guidelines on the treatment (and diagnosis) of VWF produced by AICE[7].

Autologous replacement therapy

Desmopressin (DDAVP)

Desmopressin (1-deamino-8-d-arginine vasopressin) is a synthetic analogue of vasopressin originally designed for the treatment of diabetes insipidus[8]. It acts by inducing release of VWF into plasma by binding to the vasopressin V2 receptor and thereby activating cyclic adenosine monophosphate-mediated signalling in vascular endothelial cells[9]. DDAVP increases the plasma concentrations of VWF and FVIII (and tissue plasminogen activator) when administered to patients with mild haemophilia **A** and VWD[8]. The obvious advantages of DDAVP are that it is inexpensive and carries no risk of transmitting blood-borne viruses.

DDAVP (Emosint® Minirin®) is usually administered intravenously at a dose of 0.3 µg/kg diluted in 50 mL saline infused over 30 min. This treatment increases plasma VWF-FVIII 2-4 times above the basal levels within 30 min. In general, high VWF-FVIII concentrations last in plasma for 6-8 h. Infusions can be repeated every 12-24 hours depending on the type and severity of the bleeding episode[10,11]. The drug is also available in concentrated forms for subcutaneous and intranasal administration, which can be particularly convenient for home treatment.

Because responses in a given patient are consistent on different occasions, a test infusion of DDAVP at the time of diagnosis helps to establish the individual response patterns. Response to DDAVP is assessed at 1 hour (peak) after 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[10,11]. It is also important to

measure FVIII:C and VWF:RCo plasma levels at 4 hours post-DDAVP infusion, in order to determine the pattern of clearance of these moieties.

DDAVP is usually effective in patients with type 1 VWD and baseline VWF and FVIII levels higher than 10 U/dL. In a prospective study conducted by Castaman *et al.*[11] in 77 patients with type 1 VWD, complete responses (defined as post-infusion levels of FVIII:C and VWF:RCo of at least 50 U/dL) or partial responses (defined as post-infusion levels of FVIII:C and VWF:RCo less than 50 U/dL, but at least 3-fold the basal levels) were observed in 83% and 13% of the cases, respectively. In other types of VWD, responsiveness to DDAVP is less. Only 13% of type 2 VWD patients were found to be responsive in a prospective study by Federici *et al.*[11]. DDAVP may be useful and efficacious in type 2A VWD only when it is necessary to raise low FVIII:C levels, while it may be contraindicated in type 2B VWD because of the transient appearance or aggravation of thrombocytopenia leading to an increased risk of bleeding. There is limited experience with DDAVP in type 2M, but it may be used if a test dose indicates an adequate response. In type 2N, FVIII:C levels increase in response to DDAVP, but the protein may circulate for only a short time because the stabilising effect of VWF is impaired[10]. Patients with type 3 VWD are usually unresponsive to DDAVP.

Adverse effects. The main limitation to the use of DDAVP is the possible development of tachyphylaxis, i.e. the progressive reduction of responsiveness after repeated treatments[12]. Rather frequent but mild adverse effects of DDAVP are tachycardia, headache and flushing, which are imputable to the vasomotor effects of the drug and can often be attenuated by slowing the rate of infusion. Hyponatraemia and volume overload due to the antidiuretic effect of DDAVP occur rarely but a few cases have been described, mostly in small children after receiving closely repeated infusions[13]. To avoid this complication, fluid intake should be limited during DDAVP treatment. Finally, this drug should be used cautiously in elderly patients with established atherothrombotic disease, because cases of myocardial infarction and stroke have been reported following its use[13-15]. Because it does not cause uterine contraction[16], DDAVP can be safely used at the time of parturition in responsive VWD women with low FVIII:C and VWF:RCo levels, and in the first trimester of pregnancy to cover invasive procedures such as villocentesis and amniocentesis[16].

Table IV reports the evidence-based recommendations on the use of DDAVP in VWD patients.

Allogeneic replacement therapy

For those VWD patients in whom DDAVP is either ineffective (inadequate response or prediction of prolonged treatments with likelihood of tachyphylaxis) or contraindicated (type 2B VWD), VWF and FVIII levels can be restored by the infusion of virally-inactivated plasma-derived concentrates containing both these proteins. Four products containing VWF/FVIII are licensed in Italy for the treatment of VWD (Table 2): only three of them (Haemate P®, Alphanate® and Fandhi®) have been evaluated in prospective studies in terms of pharmacokinetics and efficacy[17-21].

VWF/FVIII concentrates

The pharmacokinetics and clinical efficacy results of the first prospective study in VWD were published in 2002[17]. This study included 53 patients receiving treatment with a doubly virus-inactivated VWF/FVIII concentrate for 87 bleeding episodes and in 39 patients receiving treatment before 71 surgical or invasive diagnostic procedures[17]. In patients with type 3 VWD, the half-life of FVIII:C was approximately twice that of VWF:Ag (23.8 hours versus 12.9 hours) because of the endogenous production of FVIII[17]. A good clinical response with this VWF/FVIII concentrate was observed in 86% of the spontaneous bleeding episodes and in 71% of surgical or invasive procedures[17]. A smaller prospective study has also been performed using Fandhi®, a concentrate manufactured using a process very similar to that for Alphanate®[18].

The VWF/FVIII concentrate Haemate P® has been used in VWD patients since the early 1980s. Two prospective studies have documented its safety and efficacy in acute spontaneous bleeding (excellent/good results in 98% of the cases) and surgical events (excellent/good results in 100% of the cases)[19,20]. A prospective study which applied pharmacokinetic analysis to the choice of doses in the management of surgical patients was recently conducted[21]. This trial enrolled 29 patients with VWD undergoing elective surgery and showed that Haemate P®, whose

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Table IV - Evidence-based recommendations on the treatment of von Willebrand disease.

Treatment	Level of evidence
a) Autologous replacement therapy (DDAVP)	
- A DDAVP test infusion measuring FVIII:C and VWF:RCo levels at 1 hour (peak) and 4 hours (clearance) is recommended before the clinical use of the drug, owing to within-patient consistency in response	Grade B, level III
- Bleeding episodes and surgical or invasive procedures should be covered with DDAVP in responsive patients unless contraindicated	Grade B, level III
- In type 1 with baseline VWF:RCo and FVIII:C levels > 10 U/dL, DDAVP is usually an effective treatment	Grade B, level III
- In type 2A, DDAVP may be used if a test infusion indicates an adequate response	Grade B, level III
- In type 2B, DDAVP is contraindicated	Grade B, level III
- In type 2M, DDAVP may be used if a test infusion indicates response	Grade C, level IV
- In type 2N, DDAVP may be effective but the half-life of FVIII is shortened	Grade C, level IV
- In type 3, DDAVP is ineffective	Grade B, level III
- In patients treated repeatedly with DDAVP, it is preferable to measure the FVIII:C and VWF:RCo responses in order to monitor the development of tachyphylaxis	Grade C, level IV
- DDAVP should be used cautiously in children < 2 years, due to the risk of hyponatremia (fluid intake should be limited); and in elderly patients with atherosclerosis due to the risk ischemic complications. Adults should limit fluid intake (< 1 liter) for 24 hours after DDAVP	Grade C, level IV
- Pregnant VWD women responsive to DDAVP can be safely treated (0.3 μg/kg for 3-4 days) at the time of parturition to avoid excessive bleeding. The same schedule should be adopted in pregnant women at the time of villocentesis and amniocentesis	Grade C, level IV
b) Allogeneic replacement therapy (VWF/FVIII or VWF concentrates)	
- Patients unresponsive to DDAVP or in whom DDAVP is contraindicated (inadequate response or prediction of prolonged treatments with risk of tachyphilaxis), should be treated with virus-inactivated plasma-derived VWF/FVIII concentrates	Grade B, level III
- Treatment of spontaneous bleeding episodes: daily doses of 20-60 IU/kg of VWF/FVIII to maintain FVIII:C levels > 30 U/dL until bleeding stops (usually 2-4 days)[1]	Grade B, level III
- Prophylaxis for major surgery: daily doses of 50 IU/kg of VWF/FVIII to maintain FVIII:C levels > 50 U/dL until healing is complete (usually 5-10 days)[1]	Grade B, level III
- Prophylaxis for minor surgery: daily or every other day doses of 30-60 IU/kg of VWF/FVIII to maintain FVIII:C level > 30 U/dL until healing is complete (usually 2-4 days)[1]	Grade B, level III
- Prophylaxis for dental extractions or invasive procedures: single dose of 30 IU/kg of VWF/FVIII to maintain FVIII:C level > 50 U/dL for 12 hours[1]	Grade B, level III
- Prophylaxis for delivery and puerperium: daily doses of 50 IU/kg to maintain FVIII:C level > 50 U/dL for 3-4 days	Grade B, level III
- Surgical procedures: measure plasma levels of FVIII:C and VWF:RCo every 12 hours on the day of surgery, then every 24 hours.	Grade B, level III
- A dosing pharmacokinetic study should be considered before major surgery, particularly for type 3 VWD patients	Grade B, level III
- In surgical VWD patients at high risk of venous thrombosis a thrombo-prophylactic treatment with LMWH should be implemented during treatment with VWF/FVIII concentrates, at the same doses and schedules that are recommended for non-VWD patients undergoing similar procedures	Grade C, level IV
- 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)	Grade C, level IV
- Possible indications for VWF concentrates devoid of FVIII include elective major 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)	Grade B, level III
- All plasma concentrates containing VWF must be avoided in type 3 VWD patients with alloantibodies because of the risk of anaphylactic reactions. Possible therapeutic approaches for these patients are recombinant FVIII, administered at very high doses by continuous intravenous infusion, or recombinant activated factor VII	Grade B, level III
c) Adjunctive and adjuvant therapies	
- Platelet infusions should be considered if bleeding occurs after adequate VWF/FVIII replacement therapy, particularly for gastrointestinal bleeding	Grade C, level IV
- Antifibrinolytic amino acids (i.e., tranexamic acid and epsilon aminocaproic acid) may be sufficient for the management of less severe forms of mucosal bleeding, menorrhagia, epistaxis, or dental procedures. They can also be used in association with replacement therapy (DDAVP or VWF/FVIII plasma concentrates) for treatment or prevention of mucosal-associated bleeding or for minor/major surgery involving mucosal surfaces	Grade B, level III
- Estrogens-progestogen preparations are useful in reducing the degree of menorrhagia in VWD women	Grade B, level III

[1]These dosage are indicated for VWD patients with severely reduced FVIII:C/VWF:RCo levels (less than 10 U/dL).

preoperative median VWF:RCo loading dose of 62.4 IU/kg was based on the pharmacokinetic study, provided excellent or good haemostasis in 96% of cases on the day of surgery and 100% in the next few days. Notably, this study demonstrated for the first time that the incremental recovery is constant over a wide range of doses of VWF/FVIII concentrate (dose linearity relationship) and that the pre-treatment pharmacokinetic results can provide a reliable basis for serial dosing decisions. A number of additional studies conducted retrospectively on Haemate P® Alphanate® and Fanhdi® matched the positive results of prospective studies[22-25].

On the whole, there is no evidence from retrospective or prospective clinical studies that these three products differ with regards to haemostatic efficacy, because no head-to-head clinical studies have been carried out. Hence, the following recommendations apply to all. Dosages given once daily or every other day and spanning from 20 to 60 IU/kg of VWF:RCo/FVIII:C (depending on the risk and severity of bleeding) are haemostatically effective in the treatment of spontaneous bleeding episodes or for preventing bleeding during surgical or invasive procedures in VWD patients with severely reduced factor levels (less than 10 U/dL). The accumulation of FVIII that is exogenously infused together with that endogenously synthesised and stabilised by the infused VWF may lead to very high FVIII:C concentrations in plasma (> 150 U/dL) when repeated and closely spaced infusions are given for severe bleeding episodes or to cover major surgery.

Adverse events. There is some concern that sustained high plasma levels of FVIII:C may increase the risk of deep vein thrombosis[26-28]. Therefore, 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. Treatment may also be monitored with VWF:RCo assays as a measure of VWF activity[21]. However, monitoring VWF:RCo alone may not be optimal during prolonged treatment, because the plasma levels of this moiety fall rapidly due to a relatively short half-life while, as mentioned above, FVIII:C levels continue to rise as a result of endogenous FVIII production (plasma half-life of VWF:RCo 8-10 hours versus plasma half-life of FVIII:C, 24-26 hours)[17]. We recommend primary prophylaxis with the use of low molecular weight heparin or corresponding anticoagulant drugs in VWD patients undergoing replacement therapy for major surgery and procedures at high risk of venous thromboembolism, at the same doses and schedules that are adopted in non-VWD patients at risk undergoing similar procedures.

Secondary long-term prophylaxis

Patients with severe forms of VWD (i.e., FVIII:C levels < 5 U/dL) sometime have frequent haemarthroses and may, therefore, benefit from secondary long-term prophylaxis, which should also be considered in patients with recurrent gastrointestinal bleeding and children with frequent epistaxis. The largest experience on secondary prophylaxis in VWD was gained in Sweden in 35 patients with severe VWD[29]. Secondary prophylaxis was retrospectively evaluated also in a cohort of 12 Italian VWD patients[30], who underwent 17 long-term secondary prophylaxis periods to prevent recurrent gastrointestinal or joint bleeding, with clinical responses rated as excellent or good in 100% of cases. However, more prospective trials are needed for a better evaluation of the cost-effectiveness of this approach versus on-demand therapy.

VWF concentrate devoid of FVIII

Because VWD patients have an intact endogenous production of FVIII and in order 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®) [31]. However, as post-infusion levels of FVIII:C rise slowly reaching a peak between 6 and 8 hours, co-administration of a priming dose of FVIII is necessary if prompt haemostasis is required in patients with baseline FVIII:C levels of 30 U/dL or lower. In a prospective study[32], 50 patients with clinically severe VWD (5 with type 1, 27 with type 2 and 18 with type 3) were treated with this VWF concentrate for a total of 139 spontaneous bleeding episodes and 108 surgical or invasive procedures, with an outcome judged excellent or good in 89% and 100% of the cases, respectively. Only 38% of the spontaneous bleeding episodes and as few as 12% of the surgical/invasive procedures (i.e., emergency procedures) needed the co-administration of a priming dose of FVIII concentrate together with the first VWF infusion. This VWF concentrate is not licensed in Italy

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at present. Potential indications for VWF concentrates devoid of FVIII include elective major surgery, particularly when repeated infusions are foreseen in patients at high risk of thrombosis (old age, cancer surgery, orthopaedic surgery), and also long-term prophylaxis (i.e., for target joints, gastrointestinal bleeding, recurrent epistaxis in children). More studies on these possible indications are warranted.

Treatment of patients with anti-VWF alloantibodies.

For those rare patients with type 3 VWD who develop alloantibodies (i.e., those homozygous for gene deletions or nonsense mutations), plasma concentrates containing VWF must be avoided because they often cause life-threatening anaphylactic reactions[33]. These patients can be effectively treated with recombinant FVIII, administered by continuous intravenous infusion, or with recombinant activated factor VII[34,35].

Table IV reports the evidence-based recommendations on the use of VWF/FVIII or VWF concentrates in VWD.

Adjunctive and adjuvant therapies

When mucosal tract haemorrhages are not controlled despite adequate VWF/FVIII replacement therapy, *platelet concentrates* (1 unit from random donors every 10 kg of body weight or 1 unit obtained by apheresis) are an adjunctive weapon that often helps to control bleeding[36,37]. Transfused normal platelets are thought to be haemostatically effective because they contain VWF that is transported and localised from the flowing blood at sites of vascular injury.

Antifibrinolytic amino acids. (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, characterised by a rich fibrinolytic activity[38]. Thus, they may be sufficient when given alone for the management of less severe forms of mucosal bleeding, such as epistaxis and menorrhagia, or for dental procedures. 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 every 8-12 hours and aminocaproic acid at a dose of 50-60 mg/kg every 4-6 hours. These drugs are contraindicated in the management of urinary tract bleeding. In a prospective, cross-over study of intranasal desmopressin and oral tranexamic acid in 117 women with menorrhagia and abnormal laboratory haemostasis (62% with platelet dysfunction, 15% with VWD and 23% with various coagulation defects), the latter was more effective in reducing menstrual blood loss[39]. Finally, oestrogen-progestogen preparations cause a variable increase of VWF, so that they may be a useful adjunctive weapon in the attempt to reduce the severity of menorrhagia in women with VWD, including those with type 3[40].

Table IV reports the evidence-based recommendations on the use of adjuvant and adjunctive therapies in VWD.

Pregnancy in women with von Willebrand disease

VWD also affects women of childbearing age, so that there are special therapeutic problems related to physiological events such as pregnancy and parturition. Pregnant women with VWD are at increased risk of post-partum haemorrhage if untreated (16-29% in the first 24 hours and 22-29% after 24 hours compared with 3-5% in the general population)[40]. In patients with type 1 or 2 VWD, the levels of VWF and FVIII rise two- to threefold during the second and third trimesters but fall to baseline levels after delivery. However, in type 2B VWD the increase of the abnormal VWF can cause or worsen thrombocytopenia[41,42]. In general, VWD patients should be monitored for VWF:RCo and FVIII:C once during the third trimester of pregnancy and within 10 days of the expected date of delivery. The risk of bleeding is minimal when FVIII:C and VWF:RCo levels are higher than 30 U/dL. In type 1 VWD pregnant women with FVIII:C levels lower than 30 U/dL, it may be necessary to administer DDAVP on the day of villocentesis or amniocentesis, if performed, and at parturition and for 3-4 days thereafter (see Table IV). In order to prevent late bleeding, VWF:RCo and FVIII:C levels should be checked and women monitored clinically for at least 2 weeks post-partum. In women with type 3 VWD, VWF and FVIII levels do not increase during pregnancy and thus VWF/FVIII concentrates are required to cover delivery or Caesarean section. The

latter should be reserved only for the usual obstetric indications.

Conclusions

Although an evidence-based evaluation of literature data (observational studies and case series) shows that the two main current treatments of VWD (desmopressin and VWF/FVIII plasma concentrates) are effective in controlling bleeding in most patients, a number of issues are still open, such as the optimal control of menorrhagia, recurrent gastrointestinal bleeding and the role of secondary prophylaxis. A recombinant preparation of VWF will soon undergo phase 1/2 studies and will presumably become available for replacement therapy in the near future. Finally, attempts to partially correct VWF defects through gene therapy are in progress. This therapeutic option is, however, less attractive than gene therapy for haemophilia, because VWD is not as severe and adequate therapeutic options are available.

Co-authors of the study

All the Italian Hemophilia Centres Association sites participating at the registry programme are listed below, in alphabetical order.

- Alessandria (Laura Contino),
- Arezzo (Arianna Accorsi),
- Bari - Policlinico (Nicola Ciavarella, Mario Schiavoni),
- Bari - Università (Francesco Antonio Scaraggi),
- Bologna (Giuseppina Rodorigo, Lelia Valdre'),
- Cagliari (Roberto Targhetta),
- Castelfranco Veneto (Giuseppe Tagariello, Paolo Radossi),
- Catania (Roberto Musso, Dorina Cultrera),
- Catanzaro (Gaetano Muleo, Piergiorgio Iannacaro),
- Cesena (Chiara Biasioli),
- Cremona (Sophie Testa, Adriano Alatri),
- Faenza (Daniele Vincenzi), Ferrara (Gianluigi Scapoli),
- Firenze (Massimo Morfini),
- Genova (Angelo Claudio Molinari, Elio Boeri, Daniela Caprino),
- Ivrea (Grazia Delios, Mauro Girotto),
- L'Aquila (Guglielmo Mariani, Mario Lapecorella),
- Macerata (Maria Teresa Carloni, Isabella Cantori),
- Milano (Elena Santagostino, Alessandro Gringeri),
- Modena (Marco Marietta, Paola Pedrazzoli),
- Napoli - Federico II (Giovanni Di Minno, Antonio Coppola),
- Napoli - Pausilipon (Corrado Perricone, Michele Schiavulli),
- Napoli - S. Giovanni Bosco (Angiola Rocino),
- Orvieto (Mauro Berrettini),
- Padova (Ezio Zanon),
- Palermo - Ospedale dei Bambini (Giacomo Mancuso),
- Palermo - Università (Sergio Siragusa, Alessandra Malato, Giorgia Saccullo),
- Parma (Annarita Tagliaferri, Franca Rivolta),
- Perugia (Alfonso Iorio, Emily Oliovecchio, Francesca Ferrante),
- Pescara (Alfredo Dragani),
- Piacenza (Agostino Rossi),
- Ravenna (Antonino Mancino, Patrizia Albertini, Silvia Macchi),
- Reggio Emilia (Marco D'Incà),
- Roma - Bambin Gesù (Giulio De Rossi - Matteo Luciani),
- Roma - Gemelli (Raffaele Landolfi),
- Roma - La Sapienza (Maria Gabriella Mazzucconi, Cristina Santoro),
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- Torino (Pier Carla Schinco),
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Correspondence: Pier Mannuccio Mannucci
Via Pace, 9
20122 Milan, Italy
e-mail: piermannuccio.mannucci@unimi.it