

# Management of Inherited von Willebrand Disease in 2006

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## ABSTRACT

The aim of treatment of von Willebrand disease (VWD) is to correct the dual defect of hemostasis (i.e., the abnormal platelet adhesion due to reduced and/or dysfunctional von Willebrand factor [VWF] and the abnormal coagulation expressed by low levels of factor [F] VIII). Desmopressin acetate (DDAVP) is the treatment of choice for type 1 VWD because it can induce release of normal VWF from cellular compartments. Prospective studies on biological response versus clinical efficacy of DDAVP in VWD types 1 and 2 are in progress to explore its benefits and limits as a therapeutic option. In type 3 and in severe forms of type 1 and 2 VWD, DDAVP is not effective, and for these patients plasma virally inactivated concentrates containing VWF and FVIII are the mainstay of treatment. Several intermediate- and high-purity VWF/FVIII concentrates are available and have been shown to be effective in clinical practice (bleeding and surgery). New VWF products almost devoid of FVIII are now under evaluation in clinical practice. Although thrombotic events are rare in VWD patients receiving repeated infusions of concentrates, there is some concern that sustained high FVIII levels may increase risk of postoperative venous thromboembolism. Dosage and timing of VWF/FVIII administrations should be planned to keep the FVIII level between 50 and 150 U/dL. Appropriate dosage and timing in repeated infusions are also very important in patients exposed to secondary long-term prophylaxis for recurrent bleedings.

**KEYWORDS:** von Willebrand disease, von Willebrand factor, desmopressin, factor VWF/FVIII concentrates, efficacy and safety of concentrates, secondary long-term prophylaxis

The management of von Willebrand disease (VWD) has been improved significantly during the last 80 years since 1926, when Erik von Willebrand described a novel bleeding disorder in a large family from Foglo on the islands of Aland in the Gulf of Bothnia. The better understanding of von Willebrand factor (VWF) structure and function, mainly derived from the clinical observations on patients with VWD, have

contributed significantly to development of more specific therapeutic approaches in VWD patients. The milestones of VWD management are summarized in Table 1. The goal of therapy for VWD is to correct the dual defects of hemostasis (i.e., abnormal platelet adhesion due to low VWF activities and the abnormal intrinsic coagulation pathway due to low factor [F] VIII levels).<sup>1-3</sup> Two therapeutic approaches are available to

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**Table 1 List of Milestones in VWD Clinical Management**

1	Bleeding time and first assays for FVIII in VWD (1950)
2	Cross-transfusion experiments by hemophilic plasma in VWD (1951)
3	Plasma and Cohn's fraction I in VWD (1957)
4	Pool's cryoprecipitate in VWD (1964)
5	Immunologic differentiation of classic hemophilia A and VWD (1971)
6	First report on the use of desmopressin in VWD (1977)
7	Multimeric structure of VWF and VWD 2A versus 2B variants (1980)
8	Pasteurized VWF/FVIII concentrate for VWD available in Europe (1981–1985)
9	Discovery of VWF gene by four independent groups (1985)
10	First crossover prospective trials with VWF/FVIII concentrates (1992)
11	Classification of VWD different types (1994)
12	Recombinant VWF tested in VWD dogs (1997)
13	National guidelines for diagnosis and management of VWD (1998–2002)
14	Prospective PK and clinical studies with high purity concentrates (2002–2006)

VWD, von Willebrand disease; FVIII, factor VIII; VWF, von Willebrand

manage VWD patients: (1) desmopressin acetate (DDAVP), which releases endogenous VWF from endothelial compartments; and (2) the transfusion of exogenous VWF contained in VWF/FVIII plasma-derived concentrates (substitutive therapy).

Additional therapies for the rare cases with VWD type 3 and alloantibodies also include recombinant FVIII devoid of VWF or recombinant activated FVII.

## DESMOPRESSIN

DDAVP (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of vasopressin, originally designed for the treatment of diabetes insipidus. The first successful clinical trial with DDAVP was in 1977; its aim was to avoid the use of blood products in mild hemophilia and VWD patients who needed dental extractions and other surgical procedures.<sup>4</sup> Following these early observations, DDAVP has been used widely for the

treatment of these diseases. The obvious advantage is that DDAVP is relatively inexpensive and carries no risk of transmitting blood-borne viruses. DDAVP is usually injected intravenously at a dose of 0.3 µg/kg diluted in 50 mL saline, infused during 30 minutes. This increases plasma VWF/FVIII three to five times above the basal levels within 30 to 60 minutes and, in general, high VWF/FVIII concentrations last for 6 to 8 hours. Because the responses in a given patient are consistent on different occasions, a test dose of DDAVP at the time of diagnosis helps to establish the individual response patterns.<sup>1–3</sup>

A recommended protocol for the DDAVP infusion test, with the clinical and laboratory parameters to be used to assess the biological response in each patient, is summarized in Table 2; the definition of biological response to DDAVP is also reported.<sup>2,5</sup> This test infusion also has been recommended in children.<sup>6</sup> Infusions can be repeated every 12 to 24 hours depending on the type and severity of the bleeding episode. However, most patients treated repeatedly with DDAVP become less responsive to therapy.<sup>1</sup> The drug is also available in concentrated forms for subcutaneous and intranasal administration, which can be convenient for home treatment.<sup>1</sup> Side effects of DDAVP are usually mild: such as transient tachycardia and headache. Hyponatremia and volume overload, due to the antidiuretic effects of DDAVP, also are relatively rare in children.

Despite the wide use of DDAVP in the clinical management of VWD patients, there are no large prospective studies on efficacy and safety aimed to determine the benefits and the limits of this therapeutic approach in VWD. A large observational study evaluating both biological response and clinical efficacy in more than 150 patients with VWD types 1 and 2 has been organized on behalf of the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee on VWF. For the first time, VWD patients will be enrolled not only to evaluate their biological response to DDAVP, but also to test efficacy and safety during repeated injections required for bleeding episodes and major or minor surgery, with a prospective clinical evaluation during the following 24 months.

**Table 2 Recommendations for the Infusion Test with DDAVP**

Infusion protocol	Administer in 30 min 0.3 µg/kg of DDAVP in 50 mL of saline; the same dosage can be administered also subcutaneously
Clinical and laboratory parameters	VWF/FVIII activities must be measured before and 0.5, 1, 2, and 4 h after the administration of DDAVP; bleeding time and platelet counts must be checked before and at least after 2 h after infusion
Definition of responsiveness	VWD patients should be considered responsive to DDAVP if after 2 h they show increases of baseline levels of FVIII:C and VWF:RCo by at least three times, with levels of at least 30 U/dL and bleeding time of 12 min or less, when prolonged

DDAVP, desmopressin acetate; FVIII, factor VIII; VWF, von Willebrand factor; VWD, von Willebrand disease; C, coagulant; RCo, ristocetin cofactor activity.  
See Federici et al.<sup>2,5</sup>

## OTHER SYNTHETIC DRUGS FOR VWD

Antifibrinolytic amino acids are synthetic drugs that interfere with the lysis of newly formed clots by saturating the binding sites on plasminogen, thereby preventing its attachment to fibrin and making plasminogen unavailable within the forming clot. Epsilon aminocaproic acid (50 mg/kg four times a day) and tranexamic acid (15 to 25 mg/kg three times a day) are the most frequently used antifibrinolytic amino acids. Both can be administered orally, intravenously, or topically, and are useful alone or as adjuncts in the management of oral cavity bleeding, epistaxis, gastrointestinal (GI) bleeding, and menorrhagia. They should be avoided in the management of urinary tract bleeding.

Estrogens increase plasma VWF levels, but the response is variable and unpredictable, so they are not widely used for therapeutic purposes. It is common clinical experience that the continued use of oral contraceptives is very useful in reducing the severity of menorrhagia in women with VWD, even in those with type 3 disease, despite the fact that VWF/FVIII levels are not modified.

## SUBSTITUTIVE THERAPY WITH PLASMA-DERIVED CONCENTRATES

VWF/FVIII concentrates are indicated in type 3 VWD, in type 2B because DDAVP can induce transient thrombocytopenia, and in all types 1 and 2 patients who are not responsive to DDAVP or who may have contraindications to its use. Minimal requirements for plasma-derived VWF/FVIII concentrates in VWD management are the following: (1) they must contain VWF and some FVIII:coagulant (C); (2) they should be treated using virucidal methods; and (3) before clinical use, they should be tested for pharmacokinetics (PK) and efficacy in retrospective and prospective clinical trials in relatively large numbers of VWD patients. Among several concentrates containing VWF, only four have been evaluated extensively in PK trials as well as in retrospective or prospective efficacy studies in VWD (reviewed by Federici<sup>7</sup>).

The Alphanate Study Group published results of PK and clinical efficacy studies in 2002. This was the first study to enroll not only type 3 (n = 12), but also type 2A (n = 5) and type 1 (n = 18) VWD patients. An important finding in this study was that, in VWD type 3, the half-life of FVIII:C was twice that of VWF:antigen (Ag) due to the endogenous FVIII:C. Efficacy results showed that 75% of bleeding episodes were controlled with one or two infusions, and 71% of patients who received prophylactic treatment for surgeries or invasive procedures had good clinical responses. In another retrospective study, 22 VWD patients in Italy received Fanhdi (Grifols, Barcelona, Spain), a concentrate similar to Alphanate (Alpha Therapeutics, Los

Angeles, CA). Excellent to good clinical responses were seen in 92% of bleeding episodes and in 93% of surgical procedures, despite the relative loss of high molecular weight VWF multimers in the product.

Haemate P/Humate-P (ZLB Behring, Marburg, Germany), an intermediate-purity VWF/FVIII concentrate, has been used widely in VWD and has been considered the gold standard in management of this disorder. This product was introduced into clinical practice in Europe (Haemate P) in 1984 and in the United States (Humate-P) in 1999. The first PK study of Haemate P, published in 1998, was a single-center evaluation involving six type 3 VWD patients. Clinical efficacy data were collected retrospectively, and showed excellent to good responses for 99% of surgeries (n = 73) and for 97% of bleeding episodes (n = 3440). Results of a large retrospective study organized by the Canadian Hemophilia Centers were published in 2002. Other published studies include a retrospective analysis of Haemate P/Humate-P efficacy and safety in preventing bleeding during surgery or invasive procedures in 26 Italian VWD patients, as well as two prospective, multicenter, open-label, nonrandomized studies conducted in the United States on Haemate P/Humate-P used in urgent bleeding and urgent surgical events.<sup>7</sup>

Another plasma-derived VWF concentrate with low FVIII:C levels was introduced in France in 1992 and the first PK study in type 3 VWD was published in 1996.<sup>7</sup> An improved version of this concentrate, which is almost devoid of FVIII:C, was evaluated in two large French and European studies, and PK data are now available.<sup>7</sup> Results in type 3 VWD show no major differences in VWF:ristocetin cofactor activity (RCo) and VWF:Ag for the concentrates that did or did not contain FVIII:C. As expected, the only difference was an approximate 6-hour delay in FVIII:C increase with the concentrate devoid of FVIII:C; therefore, administration of exogenous FVIII:C is recommended in type 3 VWD cases of acute life-threatening bleeding episodes or emergency surgeries.<sup>7</sup> Clinical efficacy results of the French and European studies are expected in 2006.

Data derived from PK and clinical studies have contributed to more appropriate use of VWF/FVIII concentrates. For the specific activity of concentrates, it is important to derive the degree of VWF/FVIII product purity, whereas VWF:RCo/Ag and VWF:RCo/FVIII ratios can be considered markers of VWF/FVIII protein activity. The accumulation of FVIII:C that is infused together exogenously with that synthesized endogenously and stabilized by the infused VWF may cause very high FVIII levels when multiple infusions are given to cover major surgery. There is some concern that sustained high FVIII levels may increase the risk of postoperative deep vein thrombosis (DVT); however, DVT are rare events that have been reported only in VWD patients receiving repeated VWF/FVIII

**Table 3 Doses of FVIII-VWF Concentrates Recommended in VWD Patients Unresponsive to DDAVP**

Type of Bleeding	Dose (IU/kg)	Number of Infusions	Objective
Major surgery	50	Once a day or every other day	Maintain FVIII > 50 U/dL for at least 7 days
Minor surgery	30	Once a day or every other day	FVIII > 30 U/dL for at least 5–7 days
Dental extractions	20–40	Single	FVIII > 30 U/dL for up to 6 hours
Spontaneous or posttraumatic bleeding	20–40	Single	FVIII > 30 U/dL for up to 6 hours

Dosage is given in units of FVIII because all VWF/FVIII concentrates are labeled in FVIII units in Italy.

FVIII, factor VIII; VWF, von Willebrand factor.

(From Federici AB, Castaman G, Mannucci PM. Guidelines for the diagnosis and management of VWD in Italy. *Haemophilia* 2002;8:607–621.)

concentrate infusions to maintain clinical hemostasis after surgery.<sup>8</sup> Therefore, when using repeated injections of VWF/FVIII concentrates for recurrent bleeding episodes and especially after major surgery, we suggest daily monitoring of FVIII:C levels and adjustment of the VWF/FVIII concentrate dose to keep the patient's FVIII:C levels between 50 and 150 IU/dL. The minimal VWF:RCo levels to maintain sufficient hemostasis in VWD have not yet been determined in prospective studies; however, preliminary retrospective data from a large cohort of well-characterized Italian VWD patients suggest that VWF:RCo levels > 30 IU/dL are associated with a low incidence of spontaneous mucosal bleedings.<sup>9</sup> The dosages of concentrates with the most correct therapeutic approaches according to VWD types are summarized in Tables 3 and 4.

### TREATMENT OF PATIENTS WITH ALLOANTIBODIES TO VWF

For the rare patients with type 3 VWD who develop anti-VWF alloantibodies after multiple transfusions, the use of VWF concentrates not only is ineffective, but may even cause postinfusion anaphylaxis due to the formation of immune complexes.<sup>10</sup> These reactions may be life threatening. To overcome this drawback, a patient undergoing emergency abdominal surgery was treated with recombinant FVIII, because this product, which contains no VWF, could not cause anaphylactic reactions. In view of the very short half-life of FVIII without its VWF carrier, recombinant FVIII had to be administered by continuous intravenous infusion, at very large doses, to keep FVIII levels above 50 IU/dL for 10 days

after surgery.<sup>11</sup> Another possible therapeutic approach is recombinant activated factor VII (rFVIIa), which can be used in VWD with alloantibodies according to the same dosage and regimens as for hemophilia A patients with inhibitors.<sup>12</sup> However, the contemporary use of both recombinant FVIII and of activated FVIIa should be avoided because of the risk of thrombosis.<sup>13</sup> Because only few data on efficacy and safety on the use of recombinant FVIII and FVIIa are available currently, prospective cross-over studies should be designed to determine the best therapeutic approach in these rare cases.

### THE USE OF VWF/FVIII CONCENTRATES IN THE SECONDARY LONG-TERM PROPHYLAXIS OF VWD

Patients with severe forms of VWD may have frequent hemarthrosis, especially in cases with FVIII levels below 20 IU/dL. Mucosal bleedings are the most frequent in VWD because they can occur not only in VWD type 3, but also in types 1, 2A, 2B, and 2M; all are characterized by VWF:RCo below 10 IU/dL.<sup>2,9</sup> There are rare patients with chronic GI bleeds, with or without demonstrated vascular lesions localized in the GI tract, who have been treated on demand every day or every other day for more than 1 year in the attempt to stop such bleeding. In several cases the identification and local interventions at the site of vascular angiodysplasia and Dieulafoy's lesions could stop bleeding and solve the problem.<sup>13</sup> Unfortunately, in most cases the site of bleeding cannot be found and therefore large doses of VWF/FVIII concentrates are required to control the bleeding and reduce the need for transfused packed red

**Table 4 Management of Different Types and Subtypes of VWD**

Type	Treatment of Choice	Alternative and Adjunctive Therapy
1	Desmopressin	Antifibrinolytics, estrogens
2A	VWF/FVIII concentrates	
2B	VWF/FVIII concentrates	
2M	Desmopressin	VWF/FVIII concentrates
2N	Desmopressin	VWF/FVIII concentrates
3	VWF/FVIII concentrate	Desmopressin, platelet concentrates
3 with alloantibodies	Recombinant FVIII	Recombinant activated FVII

FVIII, factor VIII; VWF, von Willebrand factor.

blood cells (PRBCs) to maintain physiological levels of hemoglobin. Compared with patients with hemophilia A and B who have been exposed to secondary long-term prophylaxis mainly to prevent degeneration of the joints, little retrospective or prospective data on secondary long-term prophylaxis in VWD are available. The largest experience regarding secondary long-term prophylaxis has been collected in VWD in Sweden in 35 patients with severe forms of VWD.<sup>14</sup>

Another study regarding secondary long-term prophylaxis was performed in a large cohort of VWD patients followed by our group. This is a cohort study on 452 VWD patients regularly followed up at our Center for at least 3 years;<sup>15</sup> 89 of 452 cases (20%) were treated with VWF/FVIII concentrates during the last 2 years because of one or more bleeds, and 11 of 89 (12%) were included in a long-term prophylaxis program because of frequent recurrence of bleeds at the same sites. Effectiveness of prophylaxis was based on resolution/reduction of bleeding as well as on numbers of transfused PRBCs and days of hospitalization. Safety was measured by monitoring side effects and FVIII levels before and after every injection during the first 3 weeks of prophylaxis.<sup>15</sup> Prophylaxis was started because of GI bleeds in seven patients with VWD types 3 (n = 1), 2A (n = 4), 2M (n = 1), and 1 (n = 1), and for joint bleeds only in VWD type 3 (n = 4). Prophylaxis could stop bleeding in eight patients and largely reduced hospitalization for PRBC transfusions in the remaining three patients. When prophylaxis was compared with previous on-demand regimen in all 11 cases, the annual total FVIII IU of concentrate as well as number of PRBC used and days in hospital were significantly reduced. As for safety, FVIII levels were always < 180 IU/dL in all VWD and no side effects, including thrombosis, were observed. These two retrospective studies suggest that cost effectiveness of these prophylaxis regimens versus on-demand therapy should be investigated further in large, prospective studies.

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