Secondary long-term prophylaxis in von Willebrand disease: an Italian cohort study

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A B S T R A C T

Patients with severe forms of von Willebrand's disease (VWD) may have frequent episodes of mucocutaneous bleeding and also of hemarthrosis or hematomas. However, little retrospective or prospective data on secondary long term prophylaxis in VWD are available. Aim of this study was to evaluate the efficacy and safety of fixed regimens of prophylaxis with factor VIII/VWF concentrates in our cohort of VWD patients with recurrent joint and gastrointestinal (GI) bleeds. This is a cohort study on 452 VWD patients enrolled in our database until December 2004. 89/452 cases (20%) were treated with FVIII/VWF concentrates during the last two years because of one or more bleedings and 11/89 (12%) were included in a long term prophylaxis program because of frequent recurrence of bleeds at the same sites. Patients were given 40 FVIII IU/Kg of high- (Alphanate, Fanhdi) or intermediate-purity (Haemate-P) concentrates, two-three times a week to maintain FVIII and VWF levels higher than baseline during prophylaxis. Effectiveness of prophylaxis was based on resolution/ reduction of bleeding as well as on numbers of packed red blood cells and days of hospitalization. Safety was measured by monitoring side effects and FVIII levels before and after every injection during the first three weeks of prophylaxis. All the 11 patients were severe with VWF:RCo baseline levels below 10 U/dL. Prophylaxis was started because of GI bleeds in 7 patients with VWD type 3 (n=1), 2A (n=4), 2M (n=1) and 1 (n=1) and for joint bleeding only in VWD type 3 (n= 4). Prophylaxis could stop bleeding in 8 patients and largely reduced hospitalization for blood transfusions in the remaining 3. FVIII levels were always below 180 U/dL in all VWD and no side effects, including thrombosis, were observed. Secondary long-term prophylaxis by high-and intermediate purity FVIII/VWF concentrates is effective and safe in severe forms of VWD. Cost-effectiveness of these prophylaxis regimens versus on demand therapy should be investigated in large prospective studies.

Key words: von Willebrand disease, prophylaxis

Von Willebrand disease (VWD) is the most frequent inherited bleeding disorder, caused by quantitative (types 1 and 3) or qualitative (type 2) defects of von Willebrand factor (VWF). It is inherited in an autosomal dominant or recessive pattern, but women are usually more symptomatic.[1,2] The goal of therapy for VWD is to correct the dual defects of hemostasis, ie, abnormal platelet adhesion and the abnormal intrinsic coagulation pathway due to low factor VIII (FVIII:C) levels.[3] Two therapeutic approaches are available to manage VWD patients: a) the release of endogenous VWF from endothelial compartments induced by desmopressin (DDAVP), the synthetic derivative of anti-diuretic hormone; b) the transfusion of exogenous VWF contained in FVIII/VWF plasma-derived concentrates. An infusion trial with DDAVP at the time of diagnosis has been recommended in all VWD type 1 and 2 (except type 2B) and criteria for biological response to DDAVP have been recently described.[4] FVIII/VWF 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 because of epilepsy or major cardiovascular problems. Minimal requirements for plasma-derived FVIII/VWF concentrates in VWD management are the following: 1) they must contain VWF and some FVIII:C; 2) they should be treated by virucidal methods; 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.[1-3] Among several concentrates containing VWF, only four have been extensively eval-

Table 1. Characteristics of FVIII/VWF-concentrates used in this cohort study.

Products (Manufacturer)	*Purification*	*Viral inactivation*	*Specific activity* (IU/mg protein)*	*VWF:RCo/Ag† (ratio)*	*VWF:RCo/FVIII† (ratio)*	*Other proteins*
Alphanate (Grifols Biologicals)	Affinity chromatography (heparin)	Solvent/detergent + dry heat 72 hrs at 80°C	>100	0.94	1.21	Albumin +
Fanhdi (Instituto Grifols)	Affinity chromatography (heparin)	Solvent/detergent + dry heat 72 hrs at 80°C	>100	0.83	1.48	Albumin +
Haemate P (ZLB Behring)	Multiple precipitation	Pasteurization 10 hrs at 60°C	40 ± 6	0.96	2.54	Albumin +

**Specific activity measured as FVIII before adding albumin as stabilizer. †VWF:RCo values are not available in the technical description of all concentrates: therefore only the mean values calculated by producers on different concentrate stocks could be reported. Modified from Federici et al.2*

uated in pharmacokinetic (PK) trials as well as in retrospective or prospective efficacy studies in VWD.

The Alphanate Study Group published results of PK and clinical efficacy studies in 2002.[5] 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, half-life of FVIII:C was twice that of VWF: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, a concentrate similar to Alphanate. Excellent-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.[6]

Haemate P/Humate-P, an intermediate-purity FVIII/VWF concentrate, has been widely used 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,[7] was a single-center evaluation involving six type 3 VWD patients. Clinical efficacy data were collected retrospectively, and showed excellent-good responses for 99% of surgeries (n=73) and for 97% of bleeding episodes (n=344).[7] Results of a large retrospective study organized by the Canadian Hemophilia Centers were published in 2002.[8]

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,[9] as well as two prospective, multicenter, open-label, nonrandomized studies conducted in the U.S. on Haemate P/Humate-P used in urgent bleeding and urgent surgical events.[10,11]

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.[12] An improved version of this concentrate, which is almost devoid of FVIII:C, was evaluated in two large French and European studies and data on PK are now available.[13] Results in type 3 VWD show no major differences in VWF: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.[13] Clinical efficacy results of the French and European studies are expected in 2005.

Data derived from PK and clinical studies have contributed to more appropriate use of FVIII/VWF concentrates. It is important to note that FVIII/VWF concentrates have different compositions, based on varying FVIII:C and VWF protein contents, and different specific activities based on degree of purity. Therefore, before using commercially available FVIII/VWF products, hematologists should know product details such as specific activities, and VWF:RCo/Ag and VWF:RCo/FVIII:C ratios. Specific activity is important to derive the degree of FVIII/VWF product purity, while VWF:RCo/Ag ratio can be considered a surrogate marker of VWF protein activity. The accumulation of FVIII:C that is exogenously infused together with that endogenously synthesized 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 risk of postoperative deep vein thrombosis (DVT), as suggested by several recent epidemiologic studies.[14] Rare DVT events have been reported in VWD patients receiving repeated FVIII/VWF concentrate infusions to maintain clinical hemostasis after surgery.[15,16] In some of these cases, very high FVIII:C levels (> 400 U/dL) may have occurred because the daily concentrate doses were based on correction of BT.[17] Therefore, when using repeated injections of FVIII/VWF concentrates for recurrent bleeding episodes and especially after major surgery, we suggest daily monitoring of FVIII:C levels and adjusting the FVIII/VWF concentrate dose to keep the patient's FVIII:C levels between 50 and 150 U/dL. The minimal VWF:RCo levels to maintain sufficient hemostasis in VWD has 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 U/dL are associated with a low incidence of spontaneous mucosal bleedings.[18]

The use of FVIII/VWF concentrates in the secondary long-term prophylaxis of VWD

Patients with severe forms of VWD may have frequent episodes of hemarthrosis, especially in those cases with FVIII levels below 20 IU occurring in VWD type 3 and some cases with severe forms of type 1 and 2. Mucosal bleeding are the most frequent in VWD because they can occur not only in the rare cases of VWD type 3, but also in those VWD with type 1, 2A, 2B and 2M, all characterized by VWF:RCo below 10 IU.[18] In particular, GI bleeds have been reported not infrequently not only in VWD type 3 but also in type 2A and 2B and can be associated with vascular angiodysplasia.[19] There are 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 one 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.[20] Unfortunately, in most cases the site of bleeding cannot be found and therefore large doses of FVIII/VWF concentrates are required to control the bleeding and reduce the need of packed red blood cell (PRBC) transfused to maintain physiological levels of hemoglobin. Compared to 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 few data are sometimes included as additional experience in large retrospective studies[8] or are described in detail as case reports.[21] The largest experience on secondary long-term prophylaxis has been collected in VWD in Sweden in 35 patients with severe forms of VWD.[22] All patients were severe VWD type 3 (n=28) , 2B (n=4), 2A (n=2) and 1 (n=1). Most of these patients were receiving at least one injection per week for one year: 3 additional patients were also receiving intermittent prophylaxis for menorrhagia. Berntorp and Petrini have demonstrated a substantial reduction of bleeding episodes since initiation of treatment. Moreover, patients who began prophylaxis at a young age (younger than 5 years) to prevent nose and mouth bleeds have had no joint bleeds and have no clinical signs of arthropathy.[22] Such a long-term prophylaxis treatment has been safe with no cases of thrombosis and no viral transmission among patients who received virus-treated FVIII/VWF concentrates.

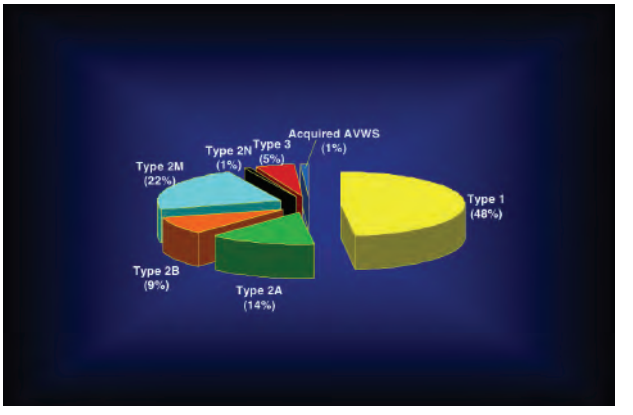

Figure 1. Distribution of VWD types (percent of cases) among the 452 patients enrolled in the database of the Angelo Bianchi Bonomi Hemophilia Center until December 2004.

The Italian cohort study on secondary long-term prophylaxis in VWD

During the last two years we have evaluated the efficacy and safety of secondary long term prophylaxis with FVIII/VWF concentrates in our large cohort of Italian VWD patients followed up at the Angelo Bianchi Bonomi Hemophilia Thrombosis Center. The distribution of different VWD types classified according to the recommendations of the ISTH-SSC on VWF and re-evaluated following the diagnostic flow-chart approved by the Italian Association of Hemophilia Centers[2] are shown in Figure 1. Among the 452 cases enrolled in our database on December 2004, 89 (20%) patients with more severe forms of VWD have been treated with FVIII/VWF concentrates for the last 24 months. Eleven out of 89 (12%) were included in a program of secondary long-term prophylaxis because

Table 2. Main clinical and laboratory features of VWD patients before enrollment into a program of secondary long-term prophylaxis.

Pt. n.	VWD type	Sex	Age	Baseline levels VWF:RCo /FVIII:C (IU/dL)		Site of bleeding (n. of episodes) (IU/dL)	Current management during the previous year		
							Concentrate (FVIII U/ year)	PRBC (Transfused U/year)	Time spent in H (days/year)
#1	1^{low}	F	63	3	36	G. I. tract (3)	450.000	18	28
#2	2A	M	74	5	45	G. I. tract I (3)	530.000	12	32
#3	3	F	33	< 1	5	Joints (5)	238.000	0	10
#4	3	F	15	< 1	3	Joints (4)	65.000	0	5
#5	3	M	50	< 1	4	G. I. tract (3)	850.000	8	10
#6	3	M	28	< 1	3	Joints (3)	150.000	0	7
#7	2A	F	79	3	37	G. I. tract (4)	750.000	38	46
#8	2A	M	83	8	27	G. I. tract (5)	312.000	11	15
#9	2M	M	70	7	27	G. I. tract (3)	350.000	5	11
#10	2A	M	48	6	38	G. I. tract (3)	380.000	9	18
#11	3	F	24	< 1	3	Joints (3)	160.000	0	12

PRBC: Packed Red Blood Cell; H: Hospital.

Table 3. Outcomes of bleeding episodes in VWD patients enrolled into a program of secondary long-term prophylaxis.

Pt. n.	Site of bleeding	FVIII/VWF concentrate Total U/year/type	Duration of prophylaxis (mos. /exposure days)	Max FVIII levels before/after	Type of improvement on the bleeding episodes		
					Bleeding	n. PRBC	Days in H
#1	G.I. tract	300.000/Haemate-P	12/100	75/152	Reduced	6	10
#2	G.I. tract	312.000/Alphanate	7/84	81/148	Stopped	2	8
#3	Joints	48.000/Haemate-P	3/24	10/98	Stopped	0	3
#4	Joints	48.000 /Haemate-P	3/24	12/ 103	Stopped	0	2
#5	G.I. tract	600.000/Fanhdi	10/120	49/119	Reduced	4	2
#6	Joints	72.000/Fanhdi	3/24	61/148	Stopped	0	1
#7	G.I. tract	630.000/Fandhi	15/210	126/174	Reduced	12	9
#8	G.I. tract	200.000/Fanhdi	12/100	65/165	Stopped	4	3
#9	G.I. tract	150.000/Fanhdi	3/36	80/145	Stopped	2	1
# 10	G.I. tract	180.000 /Fanhdi	5/60	39/120	Stopped	4	2
# 11	Joints	90.000/Haemate-P	3/30	52/136	Reduced	0	2

PRBC: Packed Red Blood Cell; H: Hospital.

of recurrent (at least three times) bleeding at the same sites, mainly localized in the GI tract and in the joints. The clinical and laboratory features of these 11 patients, together with sites of recurrent bleeds and management during the year before prophylaxis, are summarized in Table 2. The three FVIII/VWF concentrates used in our patients are labeled in Italy only as FVIII activity and are different in their specific activity, FVIII/VWF:Ag and VWF:RCo/Ag ratios (Table 1). Therefore, VWD patients enrolled into long-term prophylaxis were given 40 FVIII U/Kg of the high- (Alphanate, Fanhdi) or intermediate-purity (Haemate-P) concentrates according to their annual therapeutic plans previously assigned After the first bolus injection, two types of prophylactic regimens were given to maintain FVIII and VWF higher than baseline levels: 40 FVIII U/Kg twice a week in case of joint bleeding and every-other day or three times a week in case of GI bleeding. Effectiveness of prophylaxis was based on resolution/reduction of bleeding as well as on numbers of transfused PRBC and days of hospitalization. Safety was measured by monitoring side effects and FVIII levels before and after every injection during the first three weeks of prophylaxis.

All the 11 patients were severe with VWF:RCo baseline levels below 10 U/dL. Prophylaxis was started

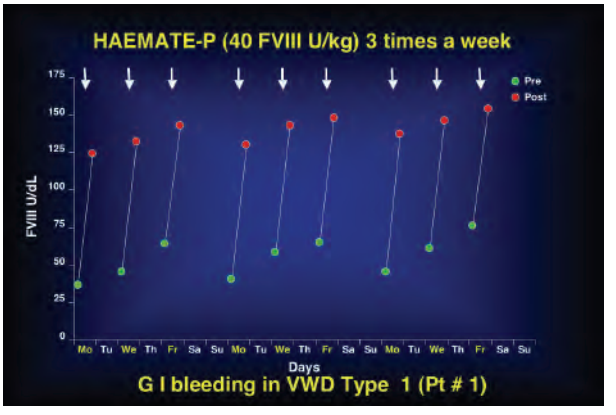

Figure 2. Changes of FVIII:C levels before and after repeated injections of the FVIII/VWF concentrate. 40 FVIII U/Kg of HAEMATE-P were given three times a week to prevent GI bleeding in patient # 1 with VWD type 1 (Tables 2 and 3).

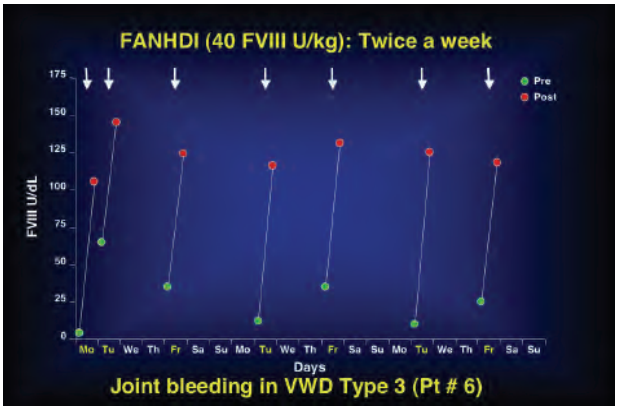

Figure 4. Changes of FVIII:C levels before and after repeated injections of the FVIII/VWF concentrate. 40 FVIII U/Kg of FANHDI were given twice a week to prevent joint bleeding in patient # 6 with VWD type 3 (Tables 2 and 3).

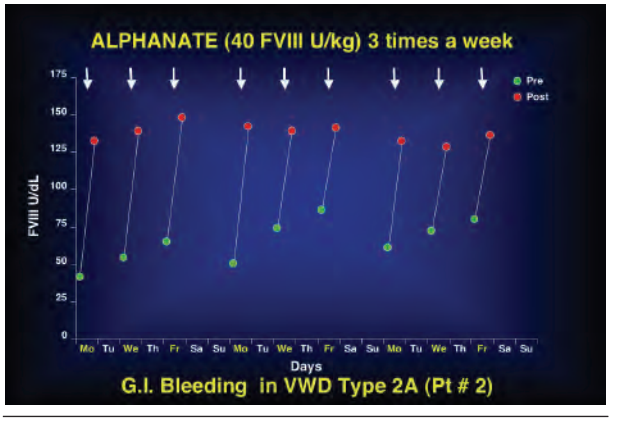

Figure 3. Changes of FVIII:C levels before and after repeated injections of the FVIII/VWF concentrate. 40 FVIII U/Kg of ALPHANATE were given three times a week to prevent GI bleeding in patient # 2 with VWD type 2A (Tables 2 and 3).

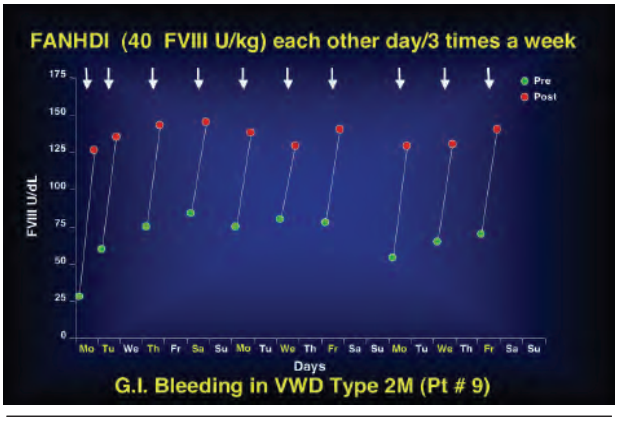

Figure 5. Changes of FVIII:C levels before and after repeated injections of the FVIII/VWF concentrate. 40 FVIII U/Kg of FANHDI were given every other day and three times a week to prevent GI bleeding in patient # 9 with VWD type 2M (Tables 2 and 3).

because of GI bleeds in 7 patients with VWD type 3 (n=1), 2A (n=4), 2M (n=1) and 1 (n=1) and for joint bleeding only in VWD type 3 (n= 4), as shown in Table 2. Prophylaxis could stop bleeding in 8 patients and largely reduced hospitalization for blood transfusions in the remaining 3: in several cases, lower amounts of concentrates were used during prophylaxis than during the previous year when therapy was on demand (Table 3).

For the safety of our patients, we decided to monitor the first three weeks of prophylaxis by testing always FVIII levels before and after each infusion of concentrates. All the three concentrates given to the patients at the same dosage of 40 FVIII U/Kg , according to the two regimens proposed, could induce concentrations of FVIII not higher than 180 IU/dL also in patients with VWD type 2A and 2M, characterized by relatively normal level of FVIII at baseline. As examples, four patterns of FVIII changes measured during the first three weeks of prophylaxis before and after the three different concentrates, given to patients with VWD type 3, 2A, 2A and 1 are shown in Figures 2-5.

Conclusions and perspectives

Our preliminary results obtained in a single Center have confirmed other previous experiences that secondary long-term prophylaxis is feasible non only in hemophiliacs but also in patients with VWD. Such pro-

phylaxis can be effective by using fixed doses of all the double FVIII/VWF concentrates commercially available in Italy and recommended for VWD management. No major/minor side effects including thrombosis were observed in all VWD patients, because FVIII levels during repeated injections are not too high. Large multicenter prospective studies should be designed to better determine the inclusion criteria of VWD patients, the appropriate regimens and dosage of concentrates and, most importantly, the cost-effectiveness of prophylaxis versus on demand therapy.

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