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The role of FVIII/VWF concentrates in the treatment of von Willebrand disease

A B S T R A C T

Two are the goals of treatment of bleeding episodes in patients with von Willebrand disease (VWD): to correct the abnormal platelet adhesion due to reduced and/or dysfunctional von Willebrand Factor (VWF) and to increase the low level of Factor VIII (FVIII). Replacement therapy with plasma-derived FVIII/VWF concentrates is required for VWD patients who do not respond to desmopressin. Several factors should be taken into account to design and optimize the replacement therapy of VWD. As for other inherited bleeding disorders, the choice of a specific treatment requires an accurate diagnosis, which is of a particular relevance in VWD because of the heterogeneity of phenotypes.

Introduction

Virus-inactivated plasma-derived factor VIII (FVIII) and von Willebrand factor (VWF) concentrates are the mainstay of treatment for patients with von Willebrand disease (VWD) unresponsive to desmopressin.[1] Several of these products have been successfully used for the prevention or treatment of bleeding episodes in patients with VWD.[1] Despite this clinical evidence, most treatments are administered on an empirical basis and carefully designed prospective trials assessing the optimal dosage on adequate pharmacokinetics studies are very few. The characteristics of manufacturing procedures of FVIII/VWF concentrates and the relationship between *in vitro* assays of VWF and factor VIII coagulant activity (FVIII:C)[2,3] are shown in Table 1.

Which parameters should guide treatment?

Although a functional assay reflecting all the in vivo VWF activitities is not yet available, the Ristocetin cofactor activity of VWF (VWF:RCo) is universally accepted as the reference laboratory test. In addition, standardization of FVIII:C assays is recommended to provide quality of the assay in the clinical setting.[4] VWF:RCo and FVIII:C must be assayed very accurately at baseline conditions.

Determination of desmopressin (DDAVP) responsiveness in a non-bleeding state is a requirement in moderate type 1, 2A and 2M. If the increase of VWF and FVIII: C is good enough and long lasting, DDAVP should be the first line treatment. The treater should always consider the severity of the bleeding to be stopped or of the hemorrhagic risk related to the surgical procedures to be performed. A strict follow-up during the first 10-15 post-operative days is recommended especially in major surgery because delayed bleeding may occur until complete wound healing is achieved. A safe and efficacious emergency plan, using a second line therapy, should be in place in the event of unexpected bleedings, which may rarely occur in spite of adequate treatment.[5] A strict co-operation between the surgeon and the haematologist is a pre-requisite for a successful outcome.

When treating severe bleedings or during perioperative periods laboratory monitoring is recommended.

If there is no adequate response to DDAVP or the compound is contraindicated, FVIII/VWF concentrates are the first choice for prophylaxis of surgical bleeding or for treatment of bleeding episodes. The information on the labelled potency of each concentrate in terms of VWF:RCo and FVIII:C content should be available to the physician in order to select the most suitable product when replacement therapy is required. Several concentrates are available:

1. Cryoprecipitate, rarely used in Europe due to virus safety concerns but still available in USA and in emerging countries.
2. Intermediate purity FVIII/VWF concentrate
3. High purity FVIII/VWF concentrate
4. VWF concentrates
5. rDNA derived FVIII concentrates
6. Platelet concentrates

Table 2 summarizes the guidelines of the Italian Association of Haemophilia Centers (AICE) for the treatment of VWD according to the different types.[2]

Dosage regimens of replacement therapy

As for haemophiliacs, there is no general agreement on the standard dosages of replacement therapy in VWD. The results of a questionnaire submitted some years ago to treaters in Europe[6] were quite disappointing. To the question "How do you decide on the dosage to be used?", 33.3% answered that for major surgery FVIII level should be between 0.5 and 1.0

Table 1. Plasma-derived concentrates containing FVIII and VWF with published activity.

Product	*Purification*	*Virucidal method*	*VWF:RCo/Ag*	*VWF:RCo/FVIII*	*Manufacturer*
Wilfactin	Ion exchange Affinity CT	SD + Nanofiltration + Dry heat	0.7	60	LFB
Haemate® P	Polyelectrolyte Precipitation	Pasteurization	0.9	2.5-2.88*	CSL Behring
Wilate	Affinity & size exclusion CT	SD + Dry heat	1.0	0.8	Octapharma
Alphanate	Heparin ligand CT	SD + Dry heat	0.9	0.82(*)-1.2	Grifols-USA
Fanhdi	Precipitation + heparin ligand CT	SD + Dry heat	0.8	1.29(*)-1.6	Grifols-SP

*CT = chromatography; SD = solvent detergent; *cfr. Reference 2.*

Table 2. Recommendations of Italian Association of Hemophilia Centres for the treatment of VWD.

VWD phenotype	*First choice therapy*	*Second choice therapy*
Type 1	DDAVP	Tranexamic Ac., Estrogens
Type 2 A	FVIII/VWF concentrates	DDAVP
Type 2 B	FVIII/VWF concentrates	----------
Type 2 M	DDAVP & FVIII/VWF concentrates	----------
Type 2 N	DDAVP	----------
Type 3	FVIII/VWF concentrates	DDAVP, Platelet concentrates
Type 3 with alloantibodies	rDNA FVIII	----------

U/mL, 12.5% indicated that VWF:RCo should be between 0.6 and 0.8U/mL but 54% declared to base their therapy on both levels. As far as mucosal bleeding is concerned, the answers were: 33.3% of treaters aimed at reaching VWF:RCo levels between 0.8 and 1.0 U/mL, 20.8% between 0.2 and 1.0 U/mL and 20.8% the FVIII between 0.5 and 1.0 U/ml. Only 4% considered the correction of bleeding time a prerequisite for successful treatment of mucosal bleeding. Most physicians, 37.5%, established the dosage empirically, with doses ranging from 20 to 75 U/kg of body weight.

From a general point of view, to estimate the loading dose we have to take into account that, as for type A haemophiliacs, 1 IU/kg of FVIII in the concentrate usually induce a 2 U/dL increase in FVIII:C in the recipient. For VWF:Rco, in contrast, the gain is a bit lower, 1.5 U/dL. Thus, the following formula should be considered:V:

Factor VIII:C: 1U/Kg = 2% rise in plasma dose = % desired FVIII rise x wt (kg) x 0.5

VWF:RCo: 1U/kg = 1.5% rise in plasma dose = % desired VWF:RCo rise x wt (kg) x 0.67

As to FVIII, one should also consider the endogenous synthesis of this protein that normally occurs when the specific carrier is provided to VWD patients.

To design the correct dosage, the type of the bleeding episode must be considered: for example, mucosal bleeding, especially from the gastro-intestinal tract, is difficult to stop, while soft tissue bleeding after surgery or trauma can be managed more easily, except in open wound procedures, like tonsillectomy. Baseline FVIII:C and VWF levels, VWD subtype, previous bleeding history, response to DDAVP, presence of an inhibitor should also be taken into account.[10]

Apart from the failure of treatment, a potential risk of treatment is represented by the occurrence of thromboembolic complications[11-12] when the FVIII:C level largely exceeds the upper normal limit. This is the reason why an accurate laboratory monitoring of FVIII:C level must be performed during replacement therapy in VWD, first and foremost when a sustained half life of VWF can determine a continuous increase of endogenous synthesis. Avoiding excessively high levels of VWF/FVIII can reduce the risk of thrombotic complications. A crucial point, though still a matter for controversy, is the correction of bleeding time.[13-14]

The choice of the concentrates

There is a general consensus that low FVIII:C level is the most important predictor of soft tissue and surgical bleeding in patients with VWD. As for haemophilia A, this deficiency must be corrected in order to achieve a completely normal clotting ability; otherwise the release of Tissue Factor, and subsequent binding and activation of FVII, cannot be amplified by positive feedback pathways involving FVIII to achieve an adequate thrombin generation. This could be particularly relevant for trauma and surgery, when the accidental or intentional damage of soft tissues leads to TF release. Mucosal bleedings need the correction of abnormal platelet adhesion and aggregation caused by the reduced or abnormal function of VWF. Thus, a concentrate also able to correct bleeding time, which reflects the role of VWF in inducing platelet adhesion to the subendothelium, may be more advisable to stop mucosal bleedings in VWD patients. Unfortunately, the correction of bleeding time lasts a few hours only or is inconsistent when cryoprecipitate or Intermediate Purity FVIII/VWF concentrates

are used, and only some minutes with the use of High Purity or Ultra-High purity concentrates. The correction of bleeding time is more likely to occur in presence of all the array of VWF multimers, which rarely occurs with commercial concentrates or cryoprecipitate. In this regard, it has been demonstrated that the transfusion of normal platelet concentrates containing Ultra-large High molecular weight multimers of VWF was able to fully correct the persisting prolonged bleeding time after administration of cryoprecipitate1 hour before in type 3 VWD patients.[15]

Notwithstanding these considerations, several studies have demonstrated that nearly all these concentrates are clinically useful in controlling or preventing bleeding in VWD. Furthermore, a recent study demonstrated a 100% success rate in a group of 12 patients with VWD on prolonged prophylaxis (up to 735 days) with twice or thrice a week infusions of Haemate® P for recurrent gastrointestinal (47% of cases) or joint bleedings (35%).[16]

Pharmacokinetic approach

The heterogeneity of VWD is very impressive and the variability of response to replacement therapy should call for a strictly tailored treatment design. The identification of the loading dose and of subsequent maintenance doses requires the availability of well-defined pharmacokinetics (PK) parameters. Unfortunately in most PK studies conducted in VWD patients,[17-20] blood samples were collected for the first 24 hours only after the end of infusion. These studies do not fulfil the golden rule of general pharmacokinetics: the concentration of drug must return to the baseline value at the end of single dose kinetics. There are also intrinsic difficulties in conducting PK studies in VWD :

1. FVIII/VWF concentrates behave very differently in types 1, 2 , and 3 VWD patients
2. the final formulation of the product has a great impact on the PK
3. the VWD patients are not generally very acquainted and compliant with PK procedures, except prior to surgery
4. at least 3 different assays, FVIII:C, VWF:Ag, VWF:RCo, should be performed
5. the FVIII:C level is the total sum of the administered amount, if present in the final formulation, and endogenous synthesis.

However, very recently a large international prospective multicenter study has determined the feasibility of dosing an intermediate purity FVIII/VWF concentrate (Haemate® P) based on pharmacokinetics in the management of 28 VWD patients undergoing elective surgery (21). A PK-guided median VWF:RCo loading dose of 62.4 IU/Kg was administered and a mean postoperative VWF:RCo levels of 62-73 IU/dL was obtained. Hemostasis was rated as excellent or good in 96.3% of subjects on the day of surgery and 100% on the next day and on day 14. Thus, selection of loading dose of the concentrate on the basis of VWF PK proved feasible and safe.

Only with pure VWF concentrates containing very low FVIII the endogenous synthesis of FVIII:C in type 3 VWD can be evaluated, provided that two assumptions are true: the rate of FVIIIC synthesis is constant and the FVIIIC shows an exponential decay. The second assumption was demonstrated by PK studies in VWD type 3 by infusion of monoclonal or rDNA FVIII concentrates, completely free of VWF. Two independent groups[22,23] were able to demonstrate in these patients a very rapid exponential decay of FVIII:C. Based on these findings, the following formula was defined[24-26] to fit the FVIII:C curve: $FVIII:C = A0+(A1+k1t)\, e(-k2t)$, where k1= synthesis rate of FVIII:C (U/dL/h),

Table 3. The three most important pharmacokinetic parameters of VWF:Ag, VWF:RCo, FVIII:C decay in 5 VWD type 3 patients after a single dose infusion of Intermediate (I.P.) and High Purity (H.P.) FVIII/VWF concentrate.

VWF:Ag

Patient	Clearance (mL/h/kg)		MRT (h)		VdArea (mL/kg)	
	I.P.	H.P.	I.P.	H.P.	I.P.	H.P.
#1	1.35	3.07	13.14	11.55	20.88	48.22
#2	1.94	3.58	14.38	12.14	30.30	44.85
#3	1.74	2.84	19.91	17.94	36.10	54.48
#4	1.20	3.59	13.99	10.43	17.45	43.86
#5	0.82	1.93	55.79	17.43	45.02	35.79

VWF:RCo

Patient	Clearance (mL/h/kg)		MRT (h)		VdArea (mL/kg)	
	I.P.	H.P.	I.P.	H.P.	I.P.	H.P.
#1	2.34	6.37	5.31	5.07	13.38	83.52
#2	2.98	15.23	11.39	7.15	36.23	144.00
#3	2.81	10.06	13.14	12.09	39.64	140.80
#4	1.61	6.92	18.44	8.01	30.90	67.45
#5	2.29	12.23	19.78	13.25	49.34	163.14

FVIII:C

Patient	Clearance (mL/h/kg)		MRT (h)		VdArea (mL/kg)	
	I.P.	H.P.	I.P.	H.P.	I.P.	H.P.
#1	0.10	-1.20	375.63	-75.17	37.51	86.80
#2	0.77	1.89	58.30	62.78	44.40	119.54
#3	0.03	1.27	300.00	50.34	42.70	65.50
#4	0.17	4.38	319.25	13.93	53.77	64.15
#5	1.05	3.51	66.10	19.93	70.72	75.09
Haemophilia A population*	3.85±1.94		15.90±7.10		58.20±20.13	

**crf. reference 27*

k2=decay rate of FVIII:C (U/h), A0= baseline FVIII:C, and A1=infused FVIII:C.

A model independent method has been used to evaluate the decay of FVIII/VWF concentrates in 5 patients, type 3 or severe type 1, attending the Haemophilia Centre in Florence, after a single dose administration of an Intermediate purity (Haemate® P) and of a High purity concentrates, on the basis of the labelled FVIII:C potency of 40 and 80 U/kg b.w. respectively. The design of the study was randomized and cross-over. Plasma samples were collected at baseline, 15, 30, 45 minutes and 1. 3, 6, 12, 24 and 48 hours after the end of infusion. The results of PK parameters are reported in table 3. For comparison, the pattern of FVIII:C decay in haemophiliacs[27] has been included. VWF:Ag and VWF:RCo decay can be easily and exactly analyzed by the Model Independent method. High Purity concentrate showed a faster Clearance (Cl), a shorter Mean Residence Time (MRT), and a larger Volume of distribution Area (VdArea) compared with Intermediate Purity concentrate. Nonetheless, the decay of VWF:RCo is always steeper than that of VWF:Ag, indicat-

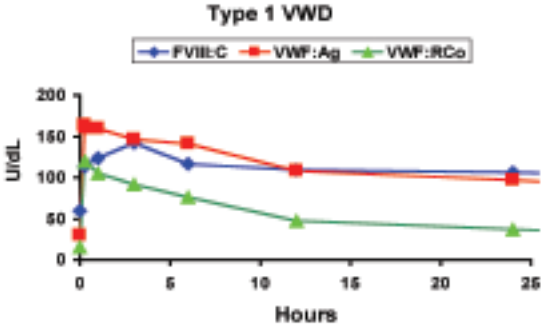

Figure 1. Typical increase of FVIII:C in a severe type 1 VWD patient after infusion of an intermediate purity FVIII/VWF concentrate. The observation time is too short to evaluate the true decay of FVIII:C and VWF:Ag, but is suitable enough for evaluating VWF:Rco, which shows a faster return to the baseline value.

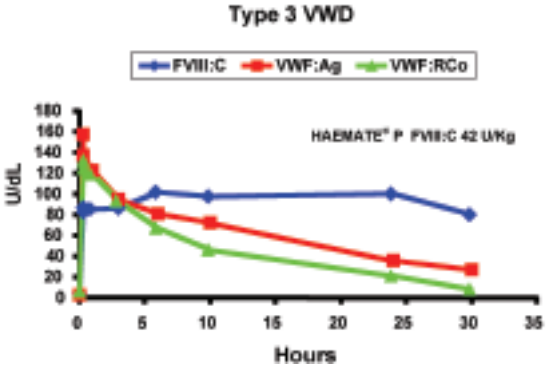

Figure 2. Pharmacokinetic evaluation in a type 3 VWD patient infused with an intermediate purity FVIII/VWF concentrate. Due to the stabilizing effect of the transfused VWF, a secondary raise of FVIII:C levels is observed around 6 hours after the infusion and FVIII:C levels remain stable for about 24 hours. VWF:Ag and VWF:RCo show a brisk increase immediately after infusion, with a consensual progressive decrease.

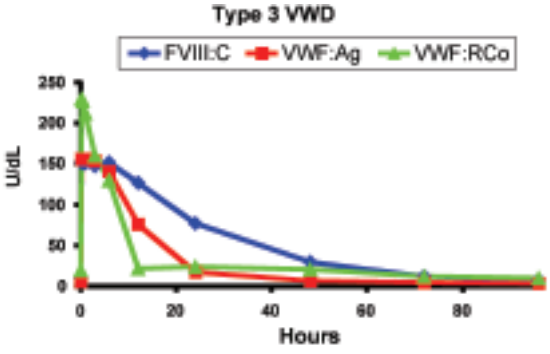

Figure 3. Pharmacokinetic evaluation in a type 3 VWD patient infused with an intermediate purity FVIII/VWF concentrate. After a short plateau, limited to the first 5 hours post-infusion, FVIII:C decreases more rapidly, similarly to the pattern observed for VWF:Ag and VWF:RCo.

ing a more rapid decrease of the functional property of the protein, probably due to the proteolysis of VWF contained in the concentrates.[28] On the contrary, the pattern of FVIII:C decay should be interpreted with caution. The Cl of FVIII:C is definitely very small, sometimes negative, because of a plateau or increase in plasma level, which also results in a very long MRT. Rather, the VdArea, more reliable than In Vivo Recovery, is similar to that observed in haemophiliacs. However, the Model independent method is not suitable to describe the complex decay of FVIII:C, especially when the circulating activity is the sum of exogenous and endogenous FVIII:C. A characteristic increase and/or plateau of FVIII:C has been reported in Figures 1 and 2 after infusion of Intermediate Purity concentrate in a severe type 1 and a type 3 VWD patient. Similar in vivo behaviour with Intermediate Purity concentrate was well documented in the first study.[29] Only a more complex mathematical procedure taking into account the fall off of FVIII:C after the initial phase of increase or plateau, can approach the pharmacodynamics of FVIII:C in VWD patients. Unfortunately, the timing of this PK studies should have been prolonged at least up to 96 hours.[30] As shown in Figure 3, after the first 5-6 hours, the decay of FVIII:C in a type 3 VWD patient is very similar, i.e. bi-exponential, to that observed in haemophilia A patients.

Only well designed and standardized cross-over PK studies, according to the FVIII/IX SSC of ISTH, as well as a new mathematical approach could, in the future, allow treaters to identify the best treatment for VWD patients.

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