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Use of von Willebrand Factor Concentrate in Inherited von Willebrand Disease: How Often Is It Useful to Add Factor VIII?

Von Willebrand factor (VWF) is a multimeric glycoprotein with multiple roles in hemostasis, such as protecting factor VIII (FVIII) in peripheral blood and facilitating platelets binding to endothelial collagen via the GPIb-IX-V complex [1]. Von Willebrand disease (VWD) is an autosomal inherited bleeding disorder characterized by quantitative (types 1 and 3) or qualitative (type 2) VWF defects. It constitutes the commonest inherited bleeding disorder with a reported prevalence of approximately 1 in 1000 individuals [2] and leads mostly to mucocutaneous bleedings [3].

Hemostatic drugs prescribed to VWD patients can be desmopressin, VWF concentrates, cryoprecipitate andor antifibrinolytics. Desmopressin releases endothelial VWF and FVIII but requires prior testing, because the response can be, in some patients, insufficient [5]. When the use of desmopressin is not possible and/or antifibrinolytic therapy is not sufficient, the hemostatic treatment of VWD is based on the administration of VWF concentrates, either plasma-derived or recombinant. To date, most of the concentrates used worldwide consist in a combination of plasma-derived (pd) VWF containing variable levels of FVIII. One pdVWF concentrate, mostly used in France, contains negligible amounts of FVIII. At a time when the marketing of recombinant VWF concentrates, without any associated FVIII, is considered, it seemed interesting to evaluate the proportion of patients with inherited VWD for whom the addition of FVIII concentrates would be required at first injection during replacement therapy.

When using VWF concentrate without FVIII and if there is an associated FVIII deficiency (FVIII activity (FVIII:C) level <40 IU/dL) the addition of FVIII concentrates may be required for an immediate normalization of coagulation, at least at the beginning of treatment. After this initial correction of FVIII levels, VWF replacement therapy allows for stabilization and normalization of the patient's endogenous FVIII. When VWF is administered to a VWD patient, the subsequent increase in FVIII:C levels takes about 6 hours [4]. In patients with basal FVIII:C within normal values, initial administration of FVIII concentrates is by contrast dispensable.

From cohorts of patients followed in two French Clinical Hemostasis Centers (Nantes and Tours), we evaluated, for each type of inherited VWD, the percentage of VWD patients with FVIII levels <40 IU/dL for whom the hemostatic response to desmopressin was insufficient, thereby imposing substitutive FVIII treatment at the first injection. Data from all VWD patients were extracted from a regional database (NHEMO/BERHLINGO), approved by French regulatory authorities for care and research studies. In this database, medical characteristics of a confirmed diagnosis are reported for each patient with a hemostatic disorder followed in one of the 2 centers. Parameters considered for the diagnostic of VWD were ristocetin cofactor activity (VWF:RCo), VWF antigen (VWF:Ag), and FVIII:C levels.

Complete response to desmopressin was defined as an increase of both VWF:RCo and FVIII:C ≥50 IU/dL within 2 hours after a single desmopressin administration of 0.3 μg/kg. In other situations, response was considered insufficient [6].

The response to desmopressin was not tested in all patients with moderately low VWF levels (VWF:RCo between 30 and 50 IU/dL) because of a reported usually good response in this population [7].

Basal FVIII:C levels were collected in 1477 patients with different types of VWD, as reported in Table 1. Among them, 1070 patients (72.4%) had a FVIII:C level ≥40 IU/dL and thus did not require FVIII infusion. Among the 407 patients with FVIII:C <40 IU/dl, 72 were known to have a contra-indication to or inefficacity of desmopressin (i.e. VWD type 2B or 3) and 152 had been tested for desmopressin. Among the latter, 72 displayed an insufficient response to desmopressin. Conversely, 80/152 patients (34%) showed a complete response to desmopressin indicating that the first injection could be performed without substitutive therapy. These results obviously do not take into account any comorbidity such as coronary or heart failure that would contra-indicate the use of desmopressin. Patients with FVIII:C >40 IU/dL, or with a complete response to desmopressin represented 1150/1477 (78%) patients from this cohort. These did not require FVIII infusion and could be treated either with desmopressin or VWF concentrates without any additional FVIII. Conversely, 144/1477 (9.7%) would need either pdVWF containing FVIII or FVIII concentrate with their first dose of rVWF.

Due to the data extraction method and the database used, it is likely that this cohort is very reliable and representative of real-life. Indeed, for more than 10 years, all patients identified as having VWF deficiency in our centers have been prospectively integrated into the NHEMO care database, used for research purposes in its anonymous version (BERHLINGO).

All in all, considering the entire cohort, it appears that at least 78% of VWD patients do not require FVIII infusion at the time of the first injection. This could be slightly underestimated since information about the use of desmopressin is lacking for 183 patients (12%). Omitting these 183 patients, 1150 of 1294 (88.8%) patients appear not to require FVIII infusion at first injection. This is based on FVIII basal level ≥40 IU/dL or complete response to desmopressin that can be used at first injection. These results do not take into account the response to desmopressin among patients with FVIII ≥40 IU/dL which can be used in the majority of situations [8]. This information seems important in face of the therapeutic options available to physicians in the management of VWD patients nowadays, namely the administration of Desmopressin or VWF without any FVIII concentrate which appears to involve the large majority of patients. This is of particular interest from a medico-economic point of view.

Table 1
FVIII:C levels and response to desmopressin according to VWD type in a study cohort of 1477 patients. FVIII, Factor VIII; VWD, Von Willebrand disease; VWF:RCo, Von Willebrand factor ristocetin cofactor activity

	Patients	FVIII:C >40 IU/dL	FVIII:C <40 IU/dL	Response to desmopressin in patients with FVIII:C <40 IU/dL	
	n	n (%)	n (%)	Tested n	Complete response n (%)
VWD Type 1 (VWF:RCo <30 IU/dL)	810	677 (83.6)	133 (16.4)	34	26 (76.5)
Low VWF levels (VWF:RCo 30–50 IU/dL	130	120 (92.3)	10 (7.7)	10	10 (100)
VWD Type 2A (IIA)	39	27 (69.2)	12 (30.8)	10	5 (50)
VWD Type 2A (IIE)	72	52 (72.2)	20 (27.8)	13	9 (69.2)
VWD Type 2B	117	80 (68.4)	37 (31.6)	/	/
VWD Type 2 M	59	42 (71.2)	17 (28.8)	15	0 (0)
VWD Type 2 M (2A-like)	73	33 (45.2)	40 (54.8)	33	2 (6.1)
VWD Type 2 N	105	14 (13.3)	91 (86.7)	28	25 (89.3)
VWD Type 2 “unclassified”	37	25 (67.6)	12 (32.4)	9	3 (33.3)
VWD Type 3	34	0 (0)	34 (100)	/	/
VWD Type 3 with inhibitor	1	0 (0)	1 (100)	/	/
Total	**1477**	**1070**	**407**	**152**	**80**

Declaration of Competing Interest

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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