Prospective Observation on the Use of Von Willebrand Factor (VWF) Concentrates in a Large Cohort of Type 3 Von Willebrand Disease (VWD) patients: Interim (22-months) Analyses on 116 Cases enrolled into the 3Winters-Ips Project.

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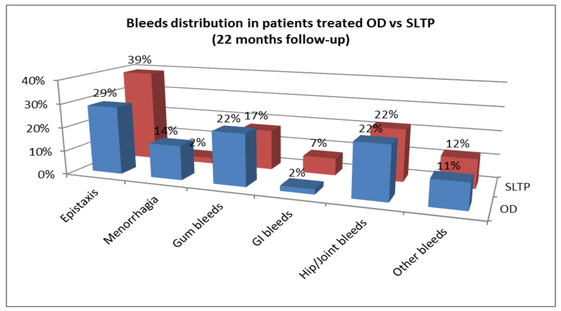
Objectives:

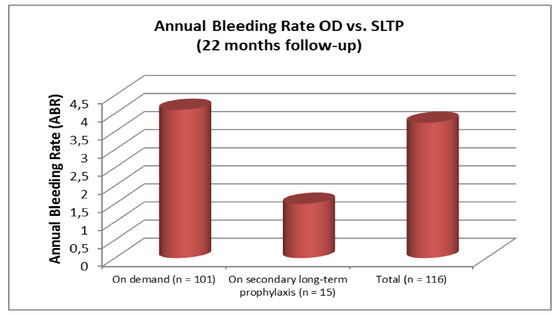
The type *3* Von *W*illebrand *Inter*national *R*egistrie*S* *I*nhibitor *P*rospective *S*tudy (*3WINTERS-IPS*) is a no-profit, investigator initiated, multicenter, European-Iranian observational, retrospective and prospective study on patients with diagnosis of type 3 VWD. Patients with type 3 von Willebrand Disease (VWD3) have markedly reduced levels of von Willebrand factor (VWF) and very severe bleeding phenotype. Due to the recessive inheritance pattern, VWD3 is by definition a rare bleeding disorder (1:Million) but its prevalence may increase in countries like Iran with consanguineous marriages. Our aim was to identify the VWF genetic defects in a cohort of European and Iranian patients with previously diagnosed VWD3 enrolled into the 3WINTERS-IPS project.

Methods:

A total of 260 previously diagnosed VWD3 cases were enrolled into the study from 18-EU and 7-IR investigation sites (retrospective registries) and reassessed by 5 expert labs for phenotypic and genotypic analyses to confirm VWD3 diagnosis (central confirmation). Only 201/260 (77%) cases with centrally confirmed VWD3 diagnosis were included into the 24-month clinical observation (prospective phase) registered as NCT02460458 into Clinical-Trials.gov. All the clinical and laboratory data were reported by investigators into the database online organized by a CRO under the direct supervision of the Scientific Coordinators.

Management of VWD3 cases during follow-up	N. of cases under management		Treatment during follow-up			N. of events during follow-up		Events during follow-up			VWF concentrates use during follow-up	
	N.	%	Type	N.	%	N.	events/patient/year	Type	N.	events/patient/year	Type	IU VWF:RCo/patient/year
N. of cases with at least 1 bleeding during follow-up	116	58%	On demand	101	87%	796	3,74	On demand	755	4,1	On demand	15396
			On seconday long-term prophylaxis	15	13%			On seconday long-term prophylaxis	41	1,5	On seconday long-term prophylaxis	100144
N. of cases with at least 1 surgery during follow-up	31	15%	On demand	26	84%	46	0,81	Major	10	0,2	During surgeries	12289
			On seconday long-term prophylaxis	5	16%			Minor	36	0,6		





Results:

Clinical results on the efficacy and safety of VWF concentrates during the 22 months observation were assessed on 116/201 (58%) VWD3 patients (EU=41/IR=75), who experienced at least one bleeding episode during the follow-up, with the following sex (M/F) and age (Mean-SD, Median) distribution: 56/60 and 24.4-17.2, 23.5. Being a non-interventional study, the therapeutic approaches such as on demand (OD) or secondary long-term prophylaxis (SLTP) with the assigned VWF concentrates with or without FVIII – n. of patients (FANHDI – 5 cases, HAEMATE-P – 50 cases, VONCENTO – 5 cases, WILATE – 16 cases, WILFACTIN – 8 cases, NOVOSEVEN – 2 cases) were decided by local investigators. The number of VWD3 treated OD/SLTP were 101/15 with SLTP cases only at EU sites. To compare the results of OD/SLTP groups, data obtained were divided by case number and by months to calculate the mean (range) annual bleeding rate (ABR). ABR observed after 22 months of follow-up in OD/SLTP is 4.1/1.5 with nose (29%), gum (22%), joint (22%), uterus (14%) bleeds being the most frequent sites. A total of 11 cases treated SLTP did not report any bleeding events during the 22-month observation. To manage (OD) or prevent (SLTP) bleeds the mean consumption of VWF:RCo units of VWF concentrates per patient/year were 15396 and 100144 VWF:RCo units, respectively. During follow-up VWD3 patients under OD/SLTP were exposed to 10/36 minor/major surgeries with an average of 12289 VWF:RCo Units used per surgery. Efficacy of the different VWF concentrates was reported as good/excellent during bleeds and surgeries. No side effects related to VWF concentrates were reported by investigators: no additional anti-VWF antibodies were found after the use of VWF concentrates.

Conclusions:

Based on this interim analysis on the largest cohort of VWD3 currently under prospective observation, the frequency of spontaneous bleeds assessed by ABR seems lower than expected by the severe VWF defect of VWD3. So far, the use of SLTP seems to reduce the ABR. However, a longer prospective observation (from 2 to 5 years) with 3WINTERS-IPS-EXTENDED is required to characterize bleeding phenotype of VWD3 patients and to prepare recommendations on the appropriate use (OD/SLTP) of the VWF concentrates .