Acquired von Willebrand disease in patients with Waldenström macroglobulinemia

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Introduction

Acquired von Willebrand disease (VWD) is uncommonly observed in patients with Waldenström Macroglobulinemia (WM), and necessitates treatment intervention. The clinical characteristics for WM patients with acquired VWD, as well as outcomes following therapy have not been well characterized.

Methods

We carried a retrospective study in patients with new diagnosed diagnosed WM who were evaluated at our institution, and tested for the presence of VWD. The presence of any VWD was evaluated by measuring levels of VW factor antigen (VWFAG), VW factor activity (VWFACT) and factor VIII (FVIII). Low-level VWD was diagnosed if VWFAG, VWFACT and FVIII levels were between 30% and 50%. VWD was diagnosed if VFWAG, VWFACT and FVIII were <30%. Univariate and multivariate logistic regression models were fitted to evaluate association of clinical factors and presence of any VWD. We also evaluated the effect of response to therapy on VWFAG, VWFACT and FVIII levels.

Table 1. Baseline characteristics per VWD status

	Total (n=320)	No VWD (n=271)	VWD (n=49)	p-value
Age >=65 years	170 (53%)	148 (55%)	22 (45%)	0.21
Male sex	180 (56%)	148 (55%)	32 (65%)	0.17
WBC >6 K/uL	149 (47%)	135 (50%)	14 (29%)	0.006
Hemoglobin <10 g/dl	67 (21%)	53 (20%)	14 (29%)	0.15
Platelet <100 K/uL	15 (5%)	14 (5%)	1 (2%)	0.34
Bone marrow >=50%	146 (46%)	123 (45%)	23 (47%)	0.84
Serum IgM <3,000 g/dl	173 (54%)	169 (62%)	4 (8%)	<0.001
Serum IgM 3,000-5,999 mg/dl	108 (38%)	85 (31%)	23 (47%)	
Serum IgM 6,000+ mg/dl	39 (12%)	17 (6%)	22 (45%)	
MYD88 mutation*	120 (96%)	95 (96%)	25 (96%)	0.96
CXCR4 mutation*	57 (46%)	37 (37%)	20 (77%)	<0.001

*MYD88 and CXCR4 status was available in only 125 patients.

Table 2. Logistic regression models for VWD

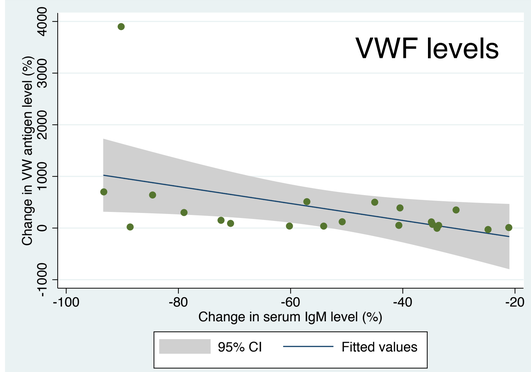
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age >=65 years	0.67 (0.37-1.25)	0.21		
Male sex	1.56 (0.83-2.95)	0.17		
WBC >6 K/uL	0.40 (0.21-0.78)	0.007	0.69 (0.32-1.47)	0.34
Hemoglobin <10 g/dl	1.65 (0.83-3.28)	0.16		
Platelet <100 K/uL	0.38 (0.05-2.98)	0.36		
Bone marrow >=50%	1.06 (0.58-1.96)	0.84		
Serum IgM 3,000-5,999 mg/dl	11.4 (3.83-34.1)	<0.001	11.1 (3.73-33.3)	<0.001
Serum IgM 6,000+ mg/dl	54.7 (16.9-177.3)	<0.001	48.7 (14.7-160.8)	<0.001
MYD88 mutation*	1.05 (0.11-9.84)	0.96		
CXCR4 mutation*	5.59 (2.06-15.2)	0.001		

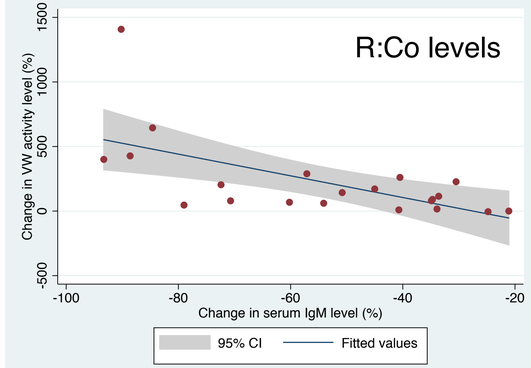
*MYD88 and CXCR4 were not included in the multivariate analysis (n=125 observations)

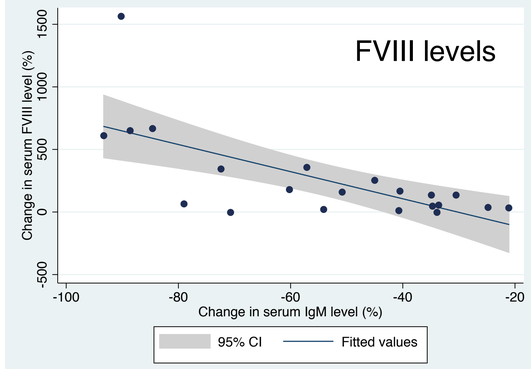
Table 3. VWD status before and after WM-directed therapy

	Before treatment	After treatment	p-value
Median FVIII (range)	21% (9-43%)	57% (30-183%)	<0.001
Median VWFAg (range)	21% (5-49%)	64% (15-200%)	<0.001
Median VWFAct (range)	23% (9-41%)	58% (19-196%)	<0.001
Median IgM (range)	6241 (3347-10,300)	2274 (406-6100)	<0.001
VWFAg/VWFAct/FVIII >50%	0 (0%)	14 (78%)	<0.001
VWFAg/VWFAct/FVIII 30-50%	6 (33%)	4 (22%)	
VWFAg/VWFAct/FVIII <30%	12 (67%)	0 (0%)	

Figure 1. Linear regression models for VWD and IgM response







Conclusions

- **Patients with WM can present with acquired VWD**
- **Acquired VWD seems to strongly correlate with high serum IgM levels and CXCR4 mutations.**
- **VWD improves and in most cases resolves with response to WM therapy and declining IgM levels.**
- **The depth of response to therapy correlates with the degree of improvement in VWD.**

Disclosures:
Castillo:
Pharmacyclics: Consultancy, Research
Millennium: Research Funding
Abbvie: Research Funding
Janssen: Consultancy, Research
Treon:
Pharmacyclics: Consultancy, Research