M. di von Willebrand acquisita

- Malattia acquisita dell'emostasi caratterizzata da difetto funzionale o strutturale del VWF
- Probabilmente sottodiagnosticata
- Manifestazioni emorragiche spesso solo dopo traumi, interventi chirurgici o manovre invasive maggiori effettuate in pazienti con patologie associate a VWD acquisito

Principali meccanismi patogenetici nella m. di von Willebrand acquisita

- **Aumentata clearance VWF**:

- Autoanticorpi specifici neutralizzanti le funzioni del VWF
- Autoanticorpi non neutralizzanti il VWF formanti complessi immuni
- Assorbimento del VWF su cellule neoplastiche
- Aumentata degradazione proteolitica del VWF
- Perdita dei multimeri ad alto pm in condizioni di alto shear stress (stenosi aortica, LVAD)

- Ridotta sintesi o rilascio di VWF: Ipotiroidismo

M. di von Willebrand acquisita
Manifestazioni cliniche

(Registro Internazionale Thromb Haemostas 2000

- Sintomi emorragici modesti nel 72% dei casi, prevalentemente cutaneo-mucosi

- Emorragie maggiori: post-chirurgiche, post-manovre invasive, gastroenteriche, epistassi profuse ricorrenti

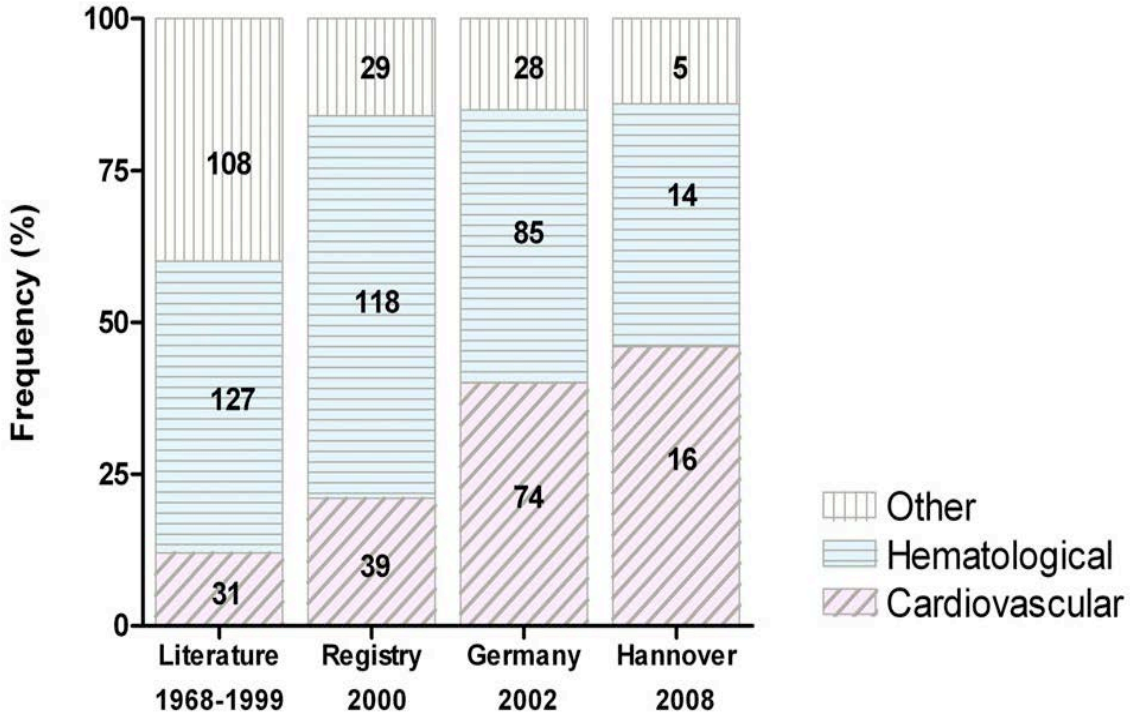
Dati dal Registro Internazionale aVWS

(266 casi letteratura e 186 casi riportati nel registro)

(Thromb Haemostas 2000,84,245-9)

- M. linfoproliferative/gammopatie monoclonali 48%
- M. Mieloproliferative 15%
- Neoplasie 5%
- M. Autoimmuni 2%
- M. Cardiovascolari 21%
- Miscellanea 9% (da farmaci, ipotiroidismo, diabete, uremia,sarcoidosi, teleangectasia, rettocolite ulcerosa, m di Crohn)

The Current Changing Spectrum of AVWS-Associated Disorders



Tiede A et al, Blood 2011

Differential Diagnosis Between AVWS and VWD

Aspect	In favor of AVWS	In favor of VWD	Limitations
Personal history	Late onset of bleeding	Early onset of bleeding	Variable penetrance of VWD
	Uneventul surgery before onset of bleeding	No uneventful surgery or no previous high risk situations	
Family history	Negative	Positive	Variable penetrance of VWD
AVWS-associated disorder	Present	Absent	Coincidental presence of highly prevalent disorders, *e.g.* MGUS in the elderly
Laboratory evaluation	Presence of inhibitor or VWF-binding antibodies	VWF gene mutation	Low frequency of detectable inhibitors in AVWS
			Alloantibodies in rare cases of VWD type 3
Treatment response	Remission after treatment of underlying disorder	Normal recovery and half-life of VWF-containing concentrate	Cannot be assessed before treatment
	Response to IVIG (in IgG MGUS associated AVWS	Sustained response to desmopressin	
	Short-lived response to VWF containing concentrates or desmopressin		

Diagnostica di laboratorio aVWS

- Allungamento aPTT*
- Ridotti valori VWF:RCo, VWF:Ag*, VIII:C*, VWF:CBA, RIPA*
- PFA-100 allungato*
- Alterazione multimeri VWF a pattern variabile

* Possono essere normali

Approfondimento diagnostico nel aVWS

- Ricerca di anticorpi neutralizzanti il VWF:RCo o il VWF:CBA su miscela 1:1 con plasma normale dopo incubazione 1-2 ore a 37° C (+ solo 10-15% dei casi)
- Ricerca di anticorpi non neutralizzanti, ma in grado di accelerare la clearance del VWF,con test ELISA utilizzando come antigene VWF ricombinante (falsi positivi con il VWF plasma derivato per presenza di antigeni dei gruppi sanguigni)

- Risposta alla DDAVP di breve durata

- Ridotto recupero dopo infusione di concentrato di FVIII/VWF

Obiettivi del trattamento nella aVWS

- Terapia dell'emorragia in atto
- Trattamento della malattia di base (se presente) associata a comparsa del difetto di VWF
- Profilassi emostatica per manovre invasive o per interventi chirurgici

Proposte terapeutiche nella aVWS

- Trattamento della condizione di base che ha condotto alla sindrome

- Trattamento o profilassi del sanguinamento:

- **DDAVP** quando non controindicazioni all'uso e nei casi responsivi
- **Concentrati di FVIII ricchi in VWF** alla dose calcolata in relazione al recupero e alla farmacocinetica in vivo

- IgG ev nelle MG (più sensibili le IgG) per blocco dei Recettori Fc reticoloendoteliali nella milza e incremento del catabolismo degli autoanticorpi

Altre opzioni terapeutiche nella aVWS

- rFVIIa (90 µmcg/kg): almeno 3 dosi a distanza di 3 ore (*possibili complicanze trombotiche nei soggetti a rischio)*

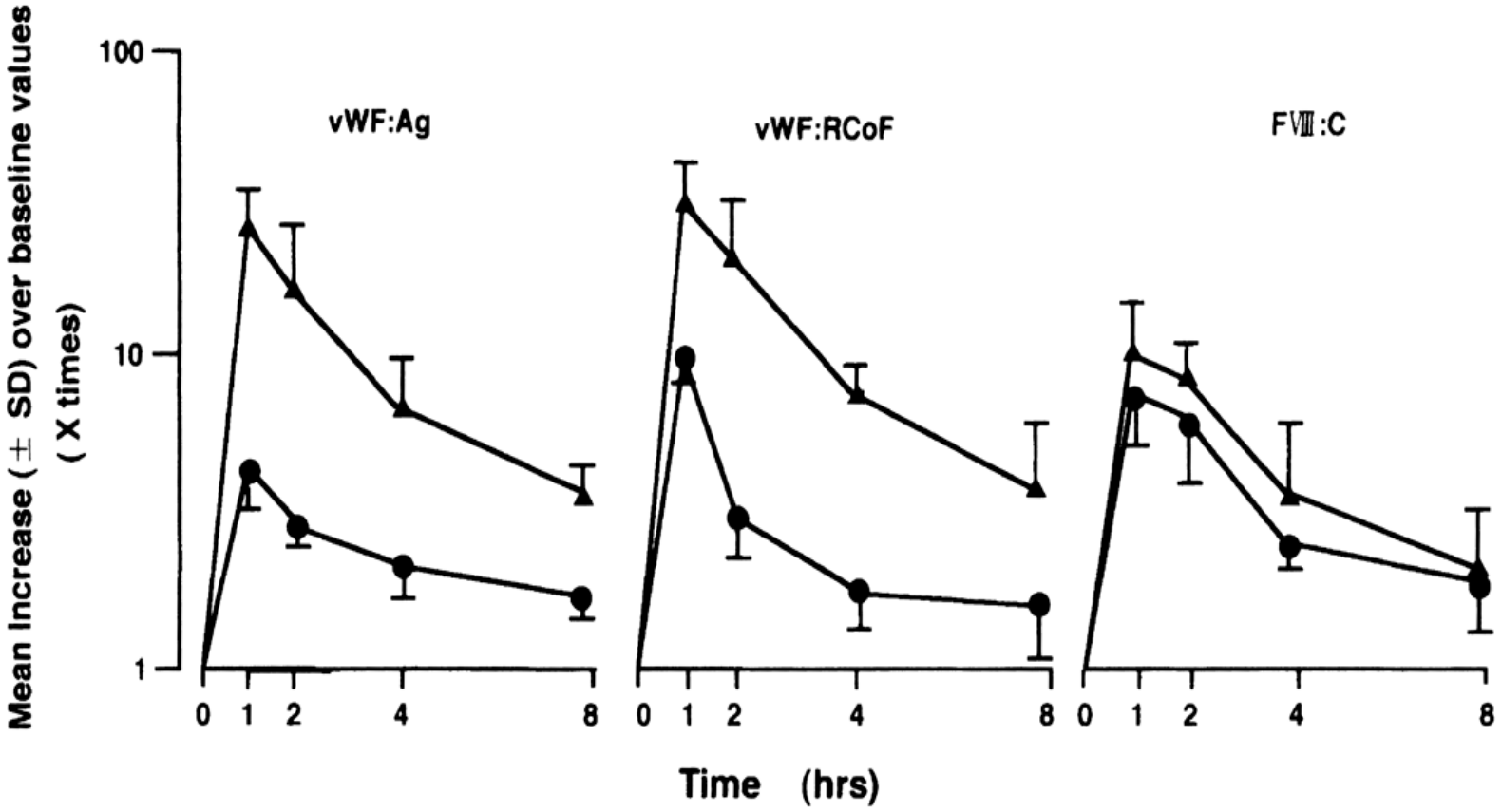
- Antifibrinolitici: ac tranexamico (20-25 mg/kg ogni 8-12 ore) *indicati nelle emorragie in sedi ad alto potenziale fibrinolitico locale (mucose)*

- Plasmaferesi: utilizzata in soggetti con gammopatia monoclonale IgM

Therapeutic Options in AVWS According to Underlying Disorder

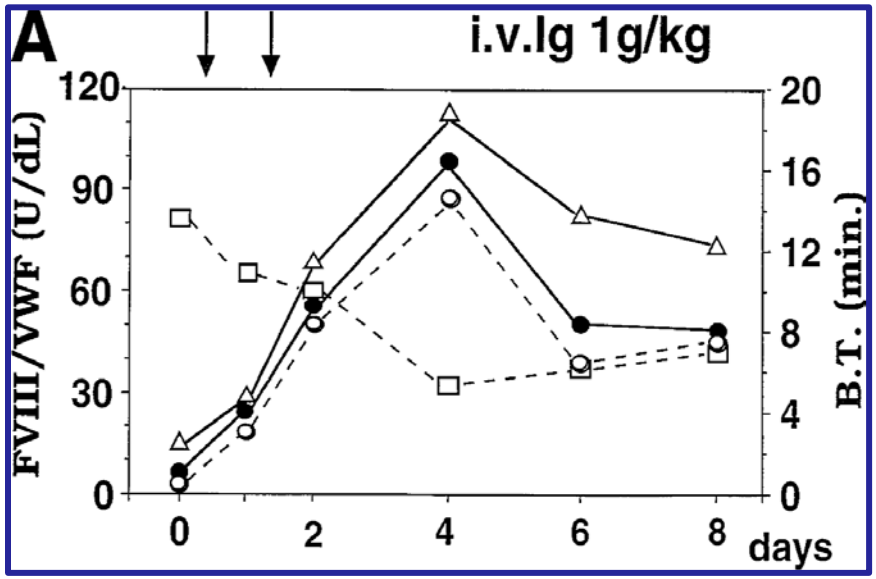
Underlying disorder	Causal treatment	Additional treatment options
Autoimmune disorders		**IVIG (only IgG-MGUS or anti-VWF IgG), plasmapheresis or immunoadsorption, antifibrinolytics, VWF-containing concentrate, rFVIIa**
Systemic lupus erythematosus	Steroids, cyclophosphamide	
Lymphoproliferative disorders		
MGUS	Usually untreated	
Lymphoma, multiple myeloma	Chemotherapy according to entity	
Cardiovascular		
Aortic valve stenosis and other anomalies with increased sheer stress	Corrective surgery	VWF-containing concentrate, antifibrinolytic
Dysfunctional heart valve prosthesis, LVAD	Corrective surgery if applicable	Reduce or withdraw anticoagulation, VWF-containing concentrate
Myeloproliferative neoplasia		**Withdraw aspirin (if applicable), desmopressin, antifibrinolytics, VWF-containing concentrate**
Essential Thrombocythemia	Cytoreductive therapy, chemotherapy or stem cell transplantation in case of progression	
Polycythemia vera	Phlebotomy, cytoreductive therapy chemotherapy or stem cell transplantation in case of progression	
Chronic myeloid leukemia	Tyrosine kinase inhibitors, stem cell transplantation	

Biological Response to DDAVP in Inherited VWD *versus* AVWS

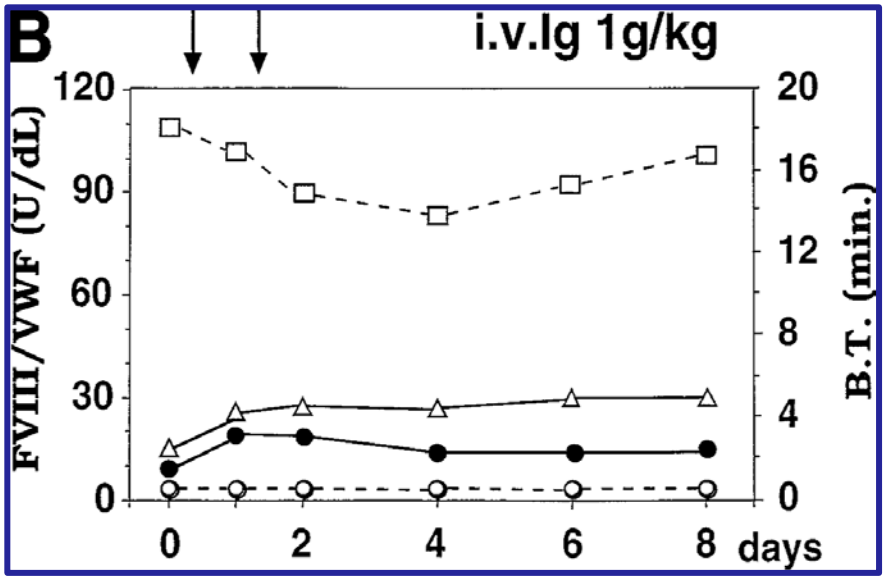


Differente risposta alle Ig nella aVWS associata a gammopatie monoclonali

IgG-MGUS

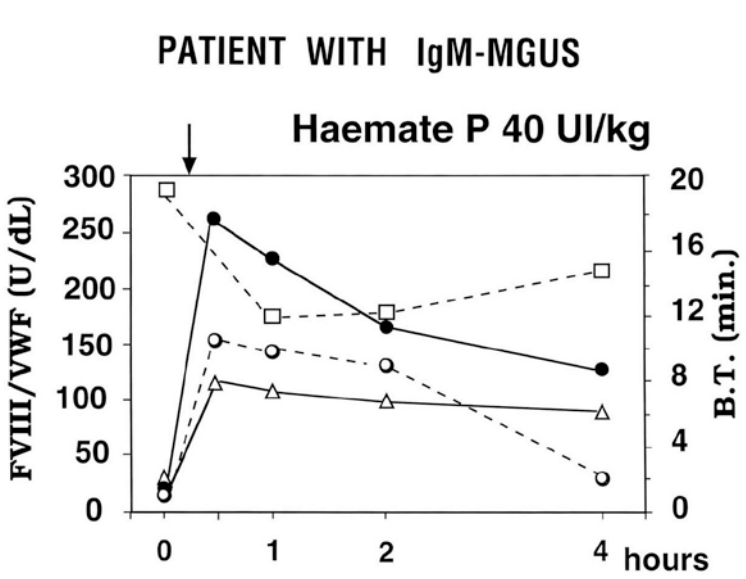


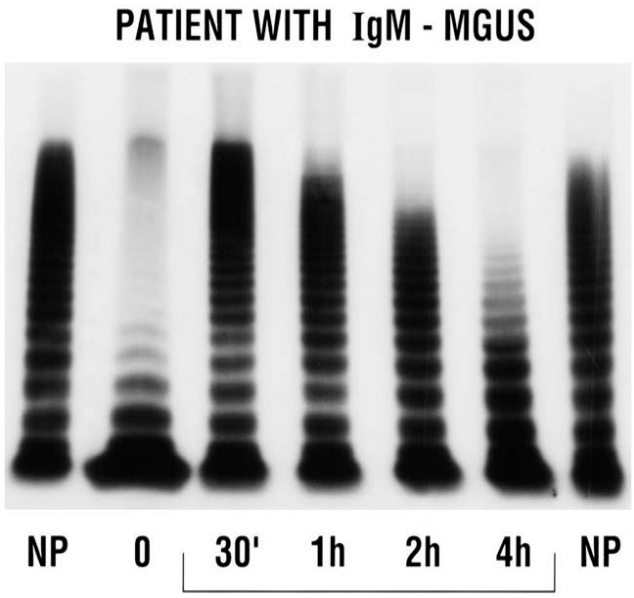
IgM-MGUS



Federici et al, Blood 1998

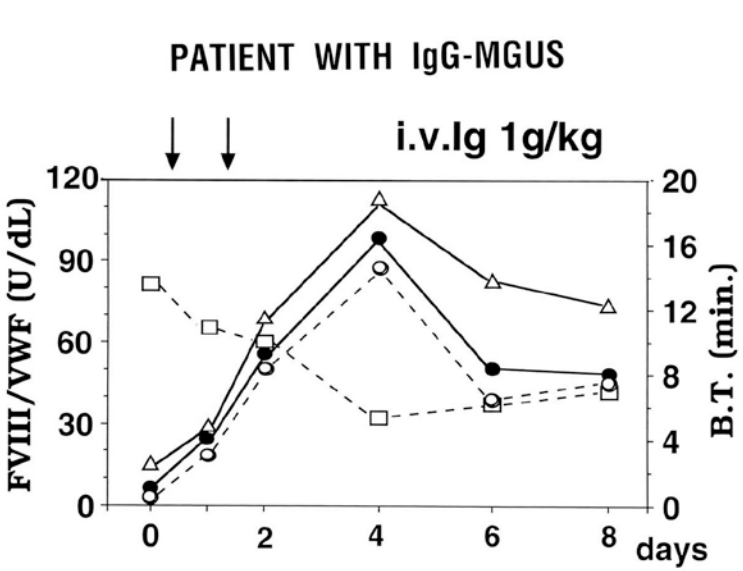
VWF/FVIII Concentrates in AVWS Associated with IGM-MGUS

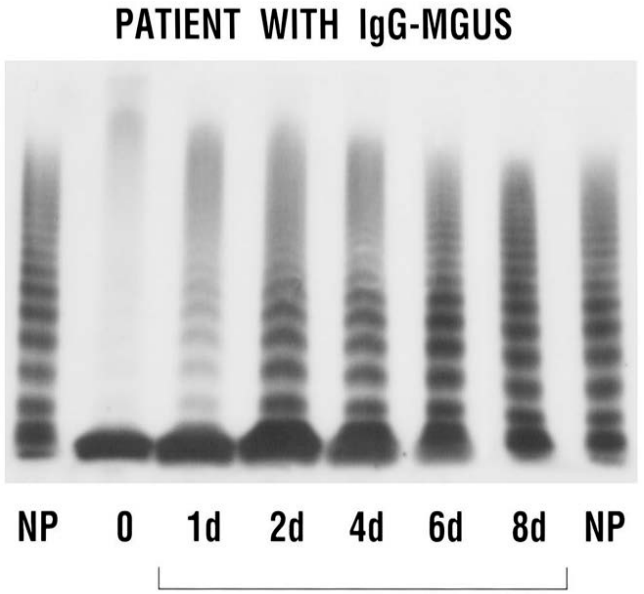




Federici AB et al, Blood 1998

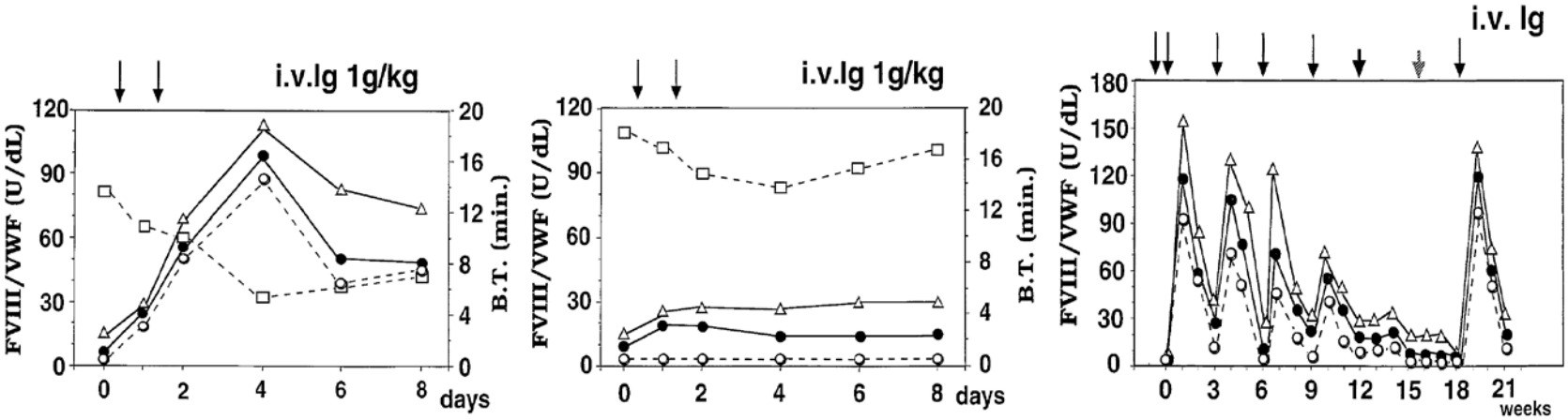
High Dose IV Immunoglobulin in AVWS Associated with IGG-MGUS





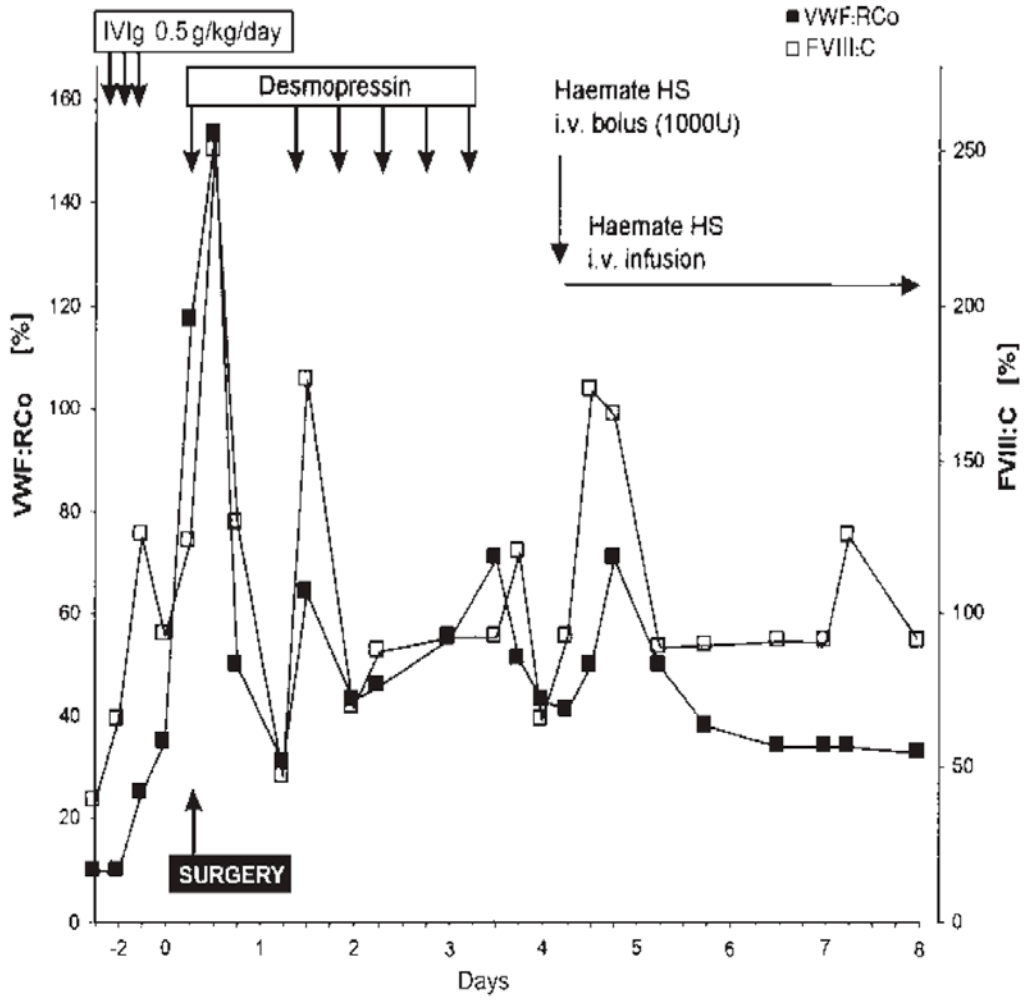
Federici AB et al, Blood 1998

High Dose IV Immunoglobulin: not Always Effective in AVWS



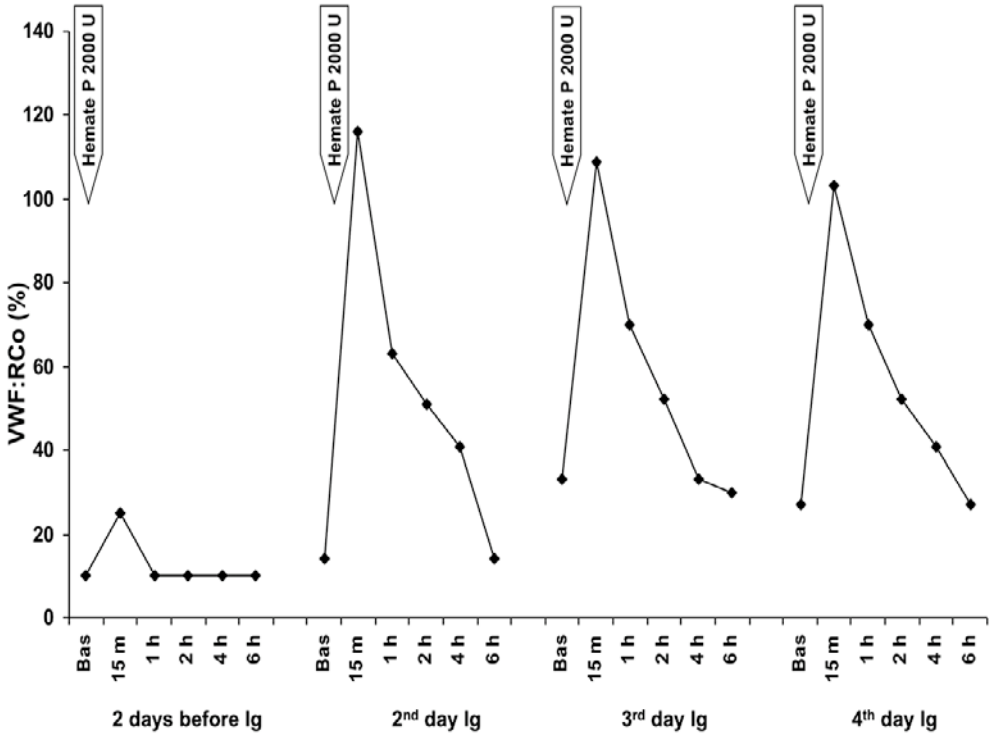
Federici AB et al, Blood 1998

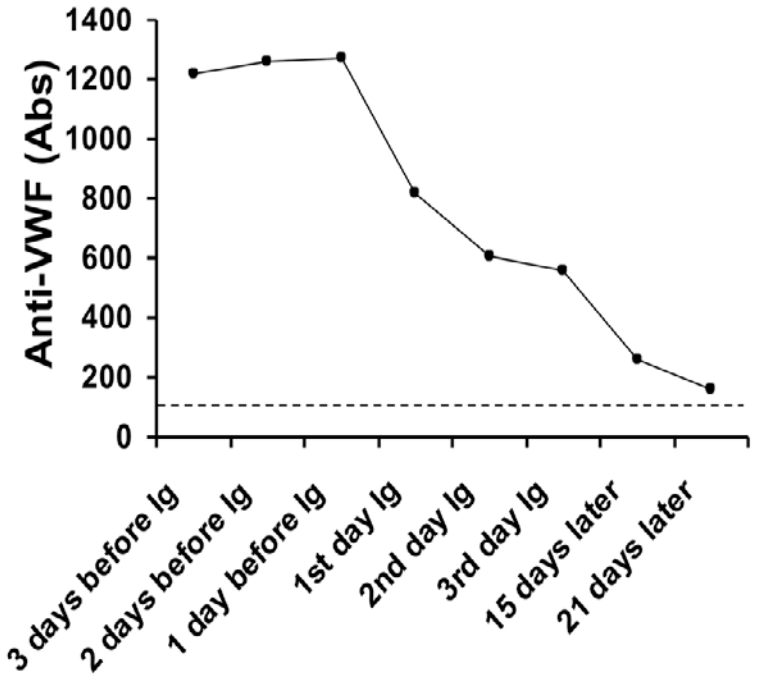
High Dose IV IG + DDAVP or Concentrates in AVWS with Urgent Bleeds/Surgery



Michiels JJ et al, Semin Thromb Hemost 2006

High Dose IV IG + VWF Concentrates in Acute Patients with AVWS





Cugno M et al, Exp Hematol Oncol 2014

Recombinant FVIIa in AVWS
Unresponsive to Standard Drugs

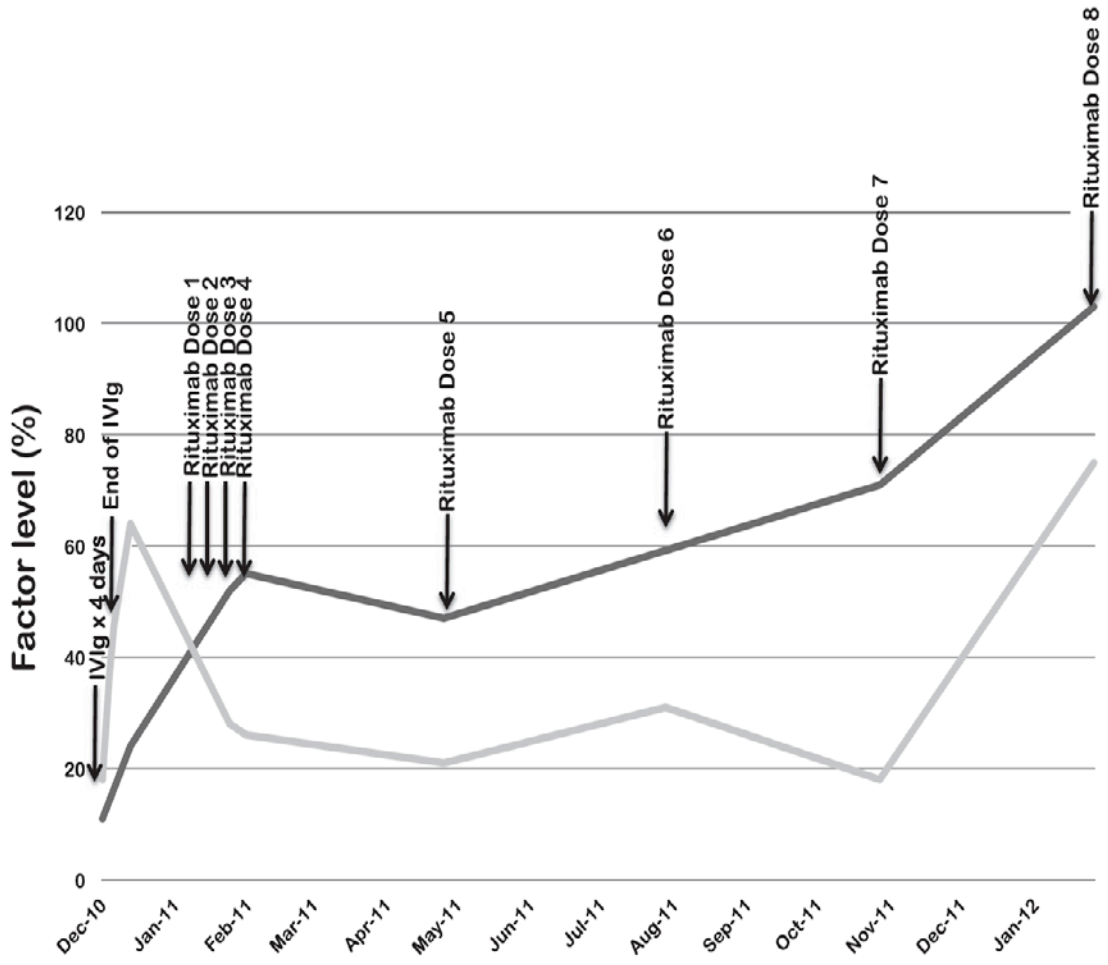
Successful *treatment with rFVIIa* in a patient with AVWS associated with MGUS and severe bleeding resistant to standard therapy:

90 ug/kg (bolus) + 17.5 ug/Kg/h for 6 days of rFVIIa

Friederich PW et al, Am J Hematol 2001

High Dose IV IG + RITUXIMAB

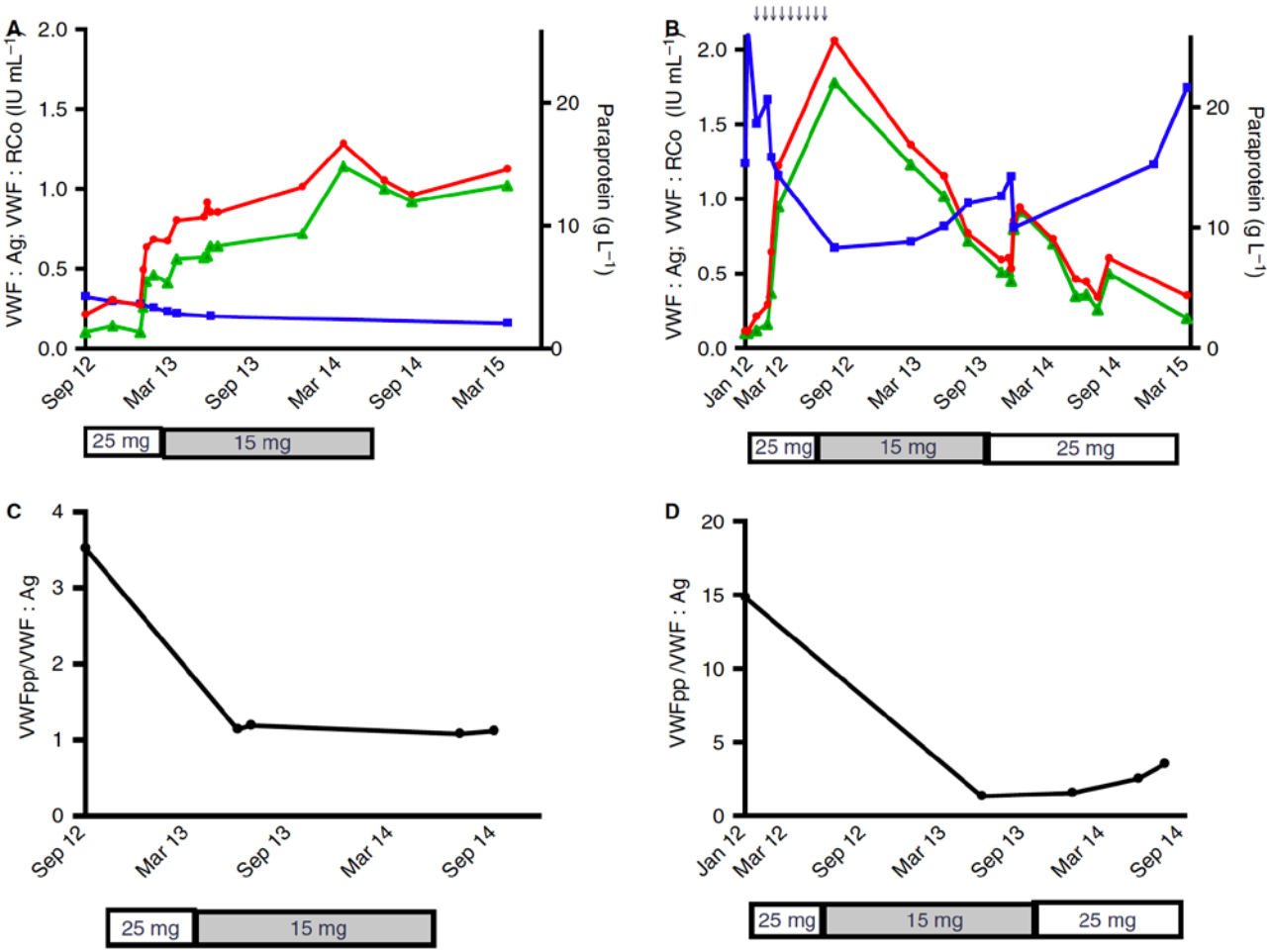
Case Report



Kanakry JA & Gladstone DE, Transfusion 2013

Lenalidomide as a novel treatment for refractory acquired von Willebrand syndrome associated with monoclonal gammopathy

M. LAVIN,*† T. M. BROPHY,† O. RAWLEY,† J. M. O'SULLIVAN,† P. J. HAYDEN,‡ P. V. BROWNE,‡ K. RYAN,* N. O'CONNELL* and J. S. O'DONNELL*†



J Thromb Haemost. 2016;14:1200-5.

Management of AVWS in 2017
Discussion

Despite many reports and recommendations, the diagnosis of AVWS remains difficult in most cases and therapeutic approaches are not standardized

Clinical prospective studies are required in large number of patients with centralized diagnosis of AVWS to assess specific therapies according to the actual mechanisms causing AVWS