Von Willebrand disease and von Willebrand factor: an old story, a new perspective

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Chapter 4

How I treat gastrointestinal bleeding in congenital and acquired von Willebrand disease

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ABSTRACT

Gastrointestinal (GI) bleeding is distinctive of severe von Willebrand disease (VWD). It arises generally in older patients, requiring in most cases blood transfusion and hospitalization. The presence of arteriovenous malformations is often described when endoscopic examinations are performed. Patients with congenital type 3, 2A and 2B are those most frequently affected by this symptom, possibly due to the loss of high-molecular-weight multimers (HMWM) of von Willebrand factor (VWF). GI bleeding can also occur in patients affected by the acquired von Willebrand syndrome (AVWS). Endoscopic examination of the GI tract is necessary to exclude ulcers and polyps or cancer as possible causes of GI bleeding. In case of congenital VWD, prophylaxis with VWF/factor VIII (FVIII) concentrates is generally started after the GI bleeding events, but this therapy is not always successful. Iron supplementation must be prescribed to avoid chronic iron deficiency. Possible rescue therapies (high dose statins, octreotide, thalidomide, lenalinomide and tamoxifen) were described in few case-reports and series, while surgery may be necessary in emergency situations or in case of failure of the medical treatment to stop bleeding. In this article we present several clinical cases that highlight the clinical challenges of these patients and possible strategies for their long-term management.

INTRODUCTION

Von Willebrand disease (VWD) is caused by the congenital deficiency of von Willebrand factor (VWF), a multimeric protein involved in platelets adhesion and in blood coagulation (by transporting factor VIII and preserving it from clearance) [1]. VWD is classified into type 1 (partial quantitative deficiency with normal multimer profile), type 2 (qualitative deficiency, characterized by a discrepancy between function and antigen) and type 3 (severe quantitative deficiency) [2]. At present, in cases with severe VWD, patients are treated with plasma-derived concentrates containing FVIII and VWF (or VWF only) and the recently introduced recombinant VWF concentrate (Vonvendi). Adjuvant therapies as tranexamic acid are also used, especially in case of mucosal bleeding [3,4].

The acquired Von Willebrand Syndrome (AVWS) is a rare bleeding disorder, associated with several underlying diseases and different pathogenic mechanisms. In patients with hypothyroidism AVWS is associated with a decreased VWF synthesis, whereas in autoimmune diseases and in monoclonal gammopathies VWF is normally

produced but its clearance is increased by antibodies. In cases with aortic stenosis or left-ventricular assist devices (LVAD) increased VWF clearance is a result of high shear stress in the heart or device that unfolds VWF, increasing its susceptibility to proteolysis by ADAMTS-13 [5-6].

Recurrent GI bleeding is a distinctive symptom of VWD, especially in the elderly. The VWD Prophylaxis Network study reported angiodysplasia in 38% of the patients with at least one episode of GI bleeding [7], however a specific diagnosis may be challenging, requiring multiple endoscopic procedures. A large survey of 4503 VWD patients published in 1993 evaluated the association between VWD type and angiodysplasia, reporting angiodysplasia in 0% of type 1 patients, 2% of type 2 patients, 4.5% of type 3 VWD patients and in 11.5% of those with the AVWS [8]. This finding suggests the importance of an intact VWF multimeric structure to avoid GI bleeding. This hypothesis is supported by Castaman et al [9], who compared 46 type 2A patients (who lack HMWM) and 61 type 2M patients (who have normal multimers): in a period of 24 months 37% of type 2A patients had GI bleeding, compared to 3% of type 2M patients. The role of VWF in the regulation of angiogenesis was described [10], showing the molecular and cellular pathways whereby VWF regulates endothelial cell proliferation, migration and sprouting. Whether these mechanisms are more influenced by the amount of VWF that is available or by its quality (presence or absence of HMWM or presence of a defective protein that causes defective angiogenesis) remains to be understood.

Diagnosis, treatment and prophylaxis with VWF/FVIII concentrate

Case 1

A 48-year old woman with type 3 VWD was admitted for acute GI bleeding and anemia (melena and hemoglobin 7g/dL). The endoscopic study of her upper and lower GI tract found no ulcer nor active bleeding susceptible of endoscopic treatment. Double-balloon enteroscopy was performed and gave evidence of pre-pyloric and duodenal bleeding in the absence of ulcers (with no clear evidence of angiodysplasia).

Recent medical history: in the previous 3 years, 2 episodes of melena required red blood cell transfusions (4 units). Between events, the patient had mild to moderate chronic anemia, caused by iron deficiency. Cycles of oral iron therapy were recommended, with good correction of ferritin and hemoglobin levels. The patient denied evident traces of blood in her stools and refused to collect stools for occult blood testing.

Comorbidities: the patient received follow-up care for hepatitis C virus infection (caused by previous transfusions) and systemic lupus erythematosus. She presented with important arthropathy in ankles and elbows due to repeated joint bleeds since youth.

Therapy: during the acute phase of bleeding she received 6 units of red blood cells, supplementation with iron and folic acid, and hemostatic treatment with a VWF/FVIII concentrate (Humate-P), maintaining FVIII:C >50IU/dL and VWF:RCo >30 IU/dL in the first 7 days). A prophylactic regimen was proposed, but she refused and was discharged with oral supplementation with iron and folic acid.

Follow-up: the patient presented recurrent GI bleeding, requiring hospitalization, red blood cell transfusion and treatment with VWF/FVIII concentrates (4 episodes in 6 months with a total of 26 units red blood cells transfused). Upper GI tract endoscopy was performed at admission, finding an angiodysplastic lesion of the duodenum that was treated with argon-plasma coagulation. On subsequent admission duodenal bleeding without evident lesions (sine materia) was found at endoscopy and treated with hemoclips.

The patient finally accepted to begin a prophylactic regimen with VWF/FVIII concentrate (50 IU FVIII/Kg 3 times/week). In the following 12 months, she had one episode of acute GI bleeding, requiring 4 units of red blood cells and needed cycles of iron therapy for the following 2 years. The prophylactic regimen with Humate-P was reduced to 50 IU FVIII/Kg twice/week after 24 months (and to 40 IU FVIII/kg twice/week after an 2 additional years). The patient had no other episode of acute GI bleeding in the next 5 years and received no more iron therapy.

Discussion

Prophylaxis with a VWF/FVIII concentrate was effective in this patient. Nevertheless, other studies [11-13] showed that prophylaxis is less efficacious for GI bleeding compared to hemarthrosis (49% vs 86%) [11]. If we hypothesize that VWF deficiency causes an increased angiogenesis that leads to angiodysplasia, we would also expect that the vascular remodeling initiated by the prophylactic regimen would take some time. For this reason, the effectiveness of prophylaxis should be evaluated after a minimum of 12 months. Furthermore, we know that all plasma-derived VWF/FVIII concentrates that were used in the few published studies lack HMWM, and this could be another reason for their poor efficacy in patients with GI bleeding, especially in the short term. Accordingly, the new recombinant VWF concentrate (Vonvendi), which contains all

multimers (and also ultra large multimers) could be more effective in controlling GI bleeding, but this hypothesis has not yet been validated.
No evidence-based recommendation can be issued at the moment on the best timing to start (and also to stop) a prophylactic regimen nor on its dosing. It is our practice to initiate a prophylactic regimen (30-50 IU VWF/kg 2-3 times/week) after 2 episodes of GI bleeding (acute or chronic bleeding) and to carry it on for at least 2 years. The presence of other bleeding symptoms or arthropathy are reasons to carry it on even longer. In cases of severe type 3 VWD characterized by low levels of FVIII:C (<5IU/dL) and repeated joint bleeding, it is our current policy to begin prophylaxis in young patients. It will be interesting in the future to evaluate whether or not if this early strategy will be able to prevent GI bleeding later in life.

Rescue therapy in association to VWF/FVIII concentrate in congenital VWD.

Case 2.

An 83 year-old female with type 2B VWD (FVIII:C 57%, VWF:Ag 52%, VWF:RCo 10%, loss of HMWM, gene mutation p.R1306W and transient thrombocytopenia) was admitted for acute anemia and melena (hemoglobin 7g/dL). The endoscopic study of the upper GI tract found gastritis and several foci of gastric bleeding, that were partially treated with argon-plasma coagulation and hemoclips.
Recent medical history: in the previous 4 years, the patient had had 4 episodes of anemia associated with melena (on 1 occasion) or stools positive for blood. She was hospitalized and transfused with red blood cells on 1 occasion (2 units), and owing to an upper GI endoscopy positive for acute gastritis she was treated with a proton-pump inhibitor.
Comorbidities: chronic atrial fibrillation, HCV-related liver cirrhosis
Therapy: the patient received red blood cells transfusion (3 units), intravenous supplementation of iron, folic acid, VWF/FVIII concentrate (Humate-P, maintaining in the first 7 days VWF:RCo >30 IU/dL and avoiding FVIII:C >150 IU/dL), oral esomeprazole and tranexamic acid. After discharge she received esomeprazole and folic acid in association with intravenous iron supplementation.
Follow-up: the patient had recurrent GI bleeding with the need of red blood cell transfusions and episodic treatment with VWF/FVIII concentrates (3 episodes in 3 months, 10 red bloods cell units transfused). She underwent upper GI tract endoscopy that led to the treatment of bleeding (clips and argon-plasma coagulation for diffuse bleeding on the first occasion and subsequently treatment of lesions of the greater and

lesser curvature treated with argon-plasma coagulation and hemoclips). After 3 months, because of the frequent bleeding episodes, she was started on prophylaxis with a plasma derived VWF/FVIII concentrate (Humate-P, 40 IU FVIII/Kg 3 times/week). Despite prophylaxis, she had more episodes of recurrent acute GI bleeding, the need of red blood transfusion and hospitalization (4 occasions in the following 5 months, 20 U of red blood cells transfused). Because of the high transfusional need and poor quality of life, she was started on 80mg of high-dose atorvastatin per day. This therapy was continued for 6 months and then stopped for lack of efficacy (5 episodes of acute GI bleeding in 6 months, 20 U red blood cells transfused). It was then decided that the patient would start 5 mg of lenalinomide per day per 3 weeks, every 4 weeks, despite the thrombotic risk associated with atrial fibrillation. The patients had a prompt reduction in GI bleeding in the next 4 months (only 2 U of red blood cells transfused soon after the beginning of this therapy) but she developed neutropenia (<500/mm^3) after 5 months. After lenalinomide was stopped, GI bleeding restarted, with the associated need of weekly red blood transfusion every 7-14 days (follow-up 8 months).

Discussion

Control of GI bleeding can be particularly difficult in some patients: this was also reported in the PRO.WILL study, in which a single patient (in a group of 10) had 9 GI bleeding episodes (64% of the events) despite a prophylactic regimen [13]. In cases of recurrent acute GI bleeding that may be life-threatening and cause a significant worsening in quality of life, the clinician might choose a rescue therapy. Unfortunately, this choice can only rely on case reports or small case series, with the unavoidable publication bias of unsuccessful cases. In making the choice, the clinician must consider the whole medical history of the patient as well as the comorbidities and the possible side effects of the rescue therapy. Table 1 reports several rescue treatments used in patients with VWD and recurrent GI bleeding. Another important issue is when to stop prophylaxis and/or the rescue treatment. Unfortunately, no data are available on the long-term follow-up of these challenging patients. In patients with type 2 VWD the decision to carry on the prophylactic regimen may be difficult. Our opinion and practice in these patients, in the absence of evidence-based data, is to carry it on for at least 1 year since the last bleeding episode, to perform the search for occult blood in the stools, and to evaluate full blood count and iron balance every 6 months after stopping prophylaxis, so that possible chronic GI bleeding can be diagnosed and handled early.

Recurrent GI bleeding associated with type 1 VWD.

Case 3

A 70 year-old female with type 1 VWD (historic levels at 33 years: FVIII:C 60 IU/dL, VWF:Ag 35 IU/dL, VWF:RCo 35 IU/dL, with a normal multimeric pattern, gene mutation p.C1927R) was admitted for hematemesis and anemia (hemoglobin 7.3g/dL, FVIII:C 113%, VWF:Ag 60%, VWF:RCo 40%). Endoscopy revealed diffused inflammation of the gastric mucosa.
Medical history: the patient had had a previous episode of GI bleeding in her youth and another one 4 years ago.
Therapy: the patients received DDAVP, proton-pump inhibitor, oral supplementation with iron and folic acid.
Follow-up: she had recurrent GI bleeding (6 episodes in 6 months, 11 units of red blood cells transfused). After 6 months of follow-up, despite near normal VWF levels and a normal distribution of multimers, due to her repeated episodes of GI bleeding prophylaxis with a plasma-derived VWF concentrate was started (Wilfactin, 40 IU VWF/kg twice/week, increased to 3 times/week after 6 months). Prophylaxis was carried out for 12 months without stopping GI bleeding (9 units of red blood cells were transfused). After this period, the patient was diagnosed with a breast cancer. After surgery she was treated with tamoxifen (20mg/day). Since the start of this drug GI bleeding ceased and the patient received no more blood transfusion. The prophylaxis with the VWF concentrate was discontinued after GI bleeding stopped (1 month after the beginning of tamoxifen.

Discussion

GI bleeding due to angiodysplasia is typically associated VWD types characterized by the loss of HMWH, but it can be seldom present also in patients with mild VWD and in elderly normal subjects. In normal individuals angiodysplasia is associated to 4-7% of upper non-variceal bleeding, 35-66% of small bowel occult bleeding and 3-40% of colonic bleeding episodes [14]. We cannot be sure that the GI bleeding in this patient was really triggered by the mild congenital VWD. The increasing levels with aging of VWF:RCo observed in her (affected by type 1 VWD), is also described in the Dutch cohort by Sanders et al. In this large group of patients, increasing levels of VWF activity were not associated with an improvement of the bleeding phenotype [15]. Also, in our patient the GI bleeding shortly preceded the diagnosis of breast cancer,

Table 1. Rescue therapies in congenital VWD and AVWS associated to monoclonal gammopathy or autoimmune diseases.

Therapy	Patient number	Dose	Outcome and follow-up	Previous unsuccessful therapies	Possible mechanism	reference
Estrogen/ progesteron	1 (type 2B VWD)	Estradiol patch (50 µg twice/week for 3 weeks on and 1 week off), medroxyprogesterone acetate 5 mg/day (days 16-21)	control of GI bleeding, follow-up 11 months	Not reported	VWF and FVIII increase	30
Danazol	2 (type 2B VWD)	500 mg/day	Pt 1: control of GI bleeding but discontinued after 2 years for severe liver toxicity; follow-up 6 years Pt 2: control of GI bleeding, follow-up 18 months	Pt 1: VWF/FVIII concentrate prophylaxis, ε-aminocaproic acid, octreotide Pt 2: VWF/FVIII concentrate prophylaxis	FVIII increase	31
Tamoxifen	2 (type 3 VWD)	Not reported (possibly 20 mg/day)	Pt 1: control of GI bleeding, follow-up 14 months Pt 2: control of GI bleeding, follow-up 10 months (therapy stopped after 4 months)	Pt 1: VWF/FVIII concentrate prophylaxis, thalidomide, propranolol and isosorbide mononitrate, atorvastatin Pt 2: VWF/FVIII concentrate prophylaxis, statins	Antiangiogenic effect	32

Therapy	Patient number	Dose	Outcome and follow-up	Previous unsuccessful therapies	Possible mechanism	reference
Recombinant activated FVII	1 (type 1)	80 µg/kg once daily during acute bleeding, associated to VWF/FVIII concentrate prophylaxis	Control of GI bleeding, follow-up 2 years	Estrogen, DDAVP, tranexamic acid, VWF/FVIII concentrate prophylaxis, surgery	Activation of alternative haemostatic pathway	33
High dose atorvastatin	1 (severe type 1 VWF)	40 mg/day	Control of GI bleeding follow-up 12 months	VWF/FVIII concentrate prophylaxis, thalidomide 100mg/day discontinued for side effects, octreotide 20mg/month discontinued for lack of efficacy	Antiangiogenic effect at high dose	34
	1 (type 2A VWD)	80 mg/day	Control of GI bleeding follow-up 14 months	Ethinilestradiol, thalidomide	Antiangiogenic effect at high dose	35
Octreotide	2 (type 1, type 2A)	Intravenous 500 µg for 2 days, 250 µg thrice daily (subcutaneous), then tapered to lower dose	Pt 1: control of GI bleeding, follow-up 13 months Pt 2: control of GI bleeding, follow-up 6 months	Pt 1: VWF/FVIII concentrate prophylaxis, tranexamic acid, desmopressin, high-dose oestrogens Pt 2: VWF/FVIII concentrate	Reduction of splanchnic and portal blood flow	36
	1 (type 1 VWD)	20 mg intramuscolar every month	Control of GI bleeding (in association with propranolol 20mg/3 times per day) follow-up 8 months	Desmopressin prophylaxis	Reduction of splanchnic and portal blood flow	37

Therapy	Patient number	Dose	Outcome and follow-up	Previous unsuccessful therapies	Possible mechanism	reference
Thalidomide	1 (type 2B VWD)	150 mg/day	Control of GI bleeding, follow-up 5 months	Octreotide, discontinued for diarrhea	Antiangiogenic effect	38
	1 (type 2A)	100 mg/day, increased to 150 mg/day for bleeding	Initial control of GI bleeding for 1 year, subsequent recurrence, follow-up 22 months	Desmopressin, tranexamic acid, VWF/FVIII concentrate	Antiangiogenic effect	39
	1 (type 2B)	100 mg/day, decreased to 50 mg/day for fatigue	Control of GI bleeding (in association with oestradiol/norethisterone, tranexamic acid), follow-up	VWF concentrate prophylaxis, recombinant activated FVII	Antiangiogenic effect	40
	1 (AVWS associated to IgG monoclonal gammopathy)	50 mg/day	Control of GI bleeding, follow-up 3 years	Desmopressin, VWF/FVIII concentrate, IV immunoglobulins, tranexamic acid, propranolol	Antiangiogenic effect	41
Lenalinomide	5 (3 type 3 VWD, 1 type 1 VWD, 1 type 2A VWD)	5 mg/day for 3 weeks on and 1 week off, uptitrated to 10 and 15 mg/day if necessary (tapering to 2 weeks on and 2 off when GI bleeding was obtained)	Control of GI bleeding, follow-up 4-24 months	Not reported	Antiangiogenic effect	42

Therapy	Patient number	Dose	Outcome and follow-up	Previous unsuccessful therapies	Possible mechanism	reference
Lenalinomide	1 (AVWS associated to IgM monoclonal gammopathy)	25 mg/day for 3 weeks on and 1 week off (decreased to 20 mg/day for 3 weeks on and 1 week off)	Control of GI bleeding, follow-up 11 months	Tranexamic acid, VWF/FVIII concentrate prophylaxis, plasma exchange, IV immunoglobulins, atorvastatin, octreotide, rituximab and bendamustine	Antiangiogenic effect	43
Rituximab	2 (AVWS associated to monoclonal gammopathy)	Pt 1: 350 mg/m^2 for 2 administrations Pt 2: 350 mg/m^2 for 4 administrations	Not efficacious	Successfull treatment with IV immunoglobulins	Anti-CD20, immunosuppressive effect	44
	1 (AVWS associated to systemic lupus erithematosus)	375 mg/m^2 biweekly in 2 doses	Control of GI bleeding and normalization of VWF levels	Steroid and cyclophosphamide	Anti-CD20, immunosuppressive effect	45
	1 (AVWS, characteristics not specified)	375 mg/m^2 weekly for 4 weeks	Control of GI bleeding, follow-up 5 months	VWF concentrate, thalidomide, successfull treatment with IV immunoglobulins	Anti-CD20, immunosuppressive effect	46

which was not associated with a decrease of VWF levels (as we can see in cases of AVWS).
The role of prophylaxis with VWF concentrates in these patients is debatable and a different therapeutic approach may be more effective. For example, in our patient the use of tamoxifen (driven by the presence of breast cancer) was rapidly effective in the control of GI bleeding. In the Netherlands, a trial is currently ongoing to evaluate the use of long-acting octreotide in the treatment of refractory anemia due to angiodysplasia in patients not affected by VWD (www.clinicaltrials.gov, NCT02384122, accessed 9th April 2020).

AVWS associated to monoclonal gammopathy

Case 4

A 72 years-old man presented with repeated bleeding after tooth extractions. For this symptom he was screened for a bleeding disorder and an AVWS associated to monoclonal gammopathy (IgG kappa, 1,5 g/dL) was diagnosed (FVIII:C 27 IU/dL, VWF:Ag 23 IU/dL, VWF:RCo <6 IU/dL, loss of HMWM). In the next 7 years he had 5 episodes of GI bleeding. Because desmopressin and a VWF/FVIII concentrate failed to achieve a sustained response, he received high dose IV immunoglobulins (1g/kg for 2 days, split in 400 mg/kg/day for 5 days for feasibility reasons), reaching normal levels of FVIII and VWF after 3 days. However, FVIII and VWF returned to low baseline levels after 4 weeks.
At age 79, he was admitted into the hospital 5 times in 7 months with melena and anemia, requiring red blood cell transfusion and treatment with IV immunoglobulins. Video-capsule endoscopy revealed angiodysplasia in the jejunum. As rescue therapy he was given lenalinomide 25 mg/day for 21 days every 28 days for 6 cycles with no significant change in the GI bleeding (5 episodes in 6 months). Lenalinomide was therefore stopped and a reduced dose of IV immunoglobulins (400 mg/kg/day for 3 days every 4 weeks) was started, with no more acute episodes of GI bleeding. After 6 months the dose was reduced to 400 mg/kg/day for 2 days every 4 weeks for another 6 months (no GI bleeding during this period) and eventually stopped. The patient is actually in follow-up, with normal hemoglobin levels but positive occult blood in the stools.

Discussion

Patients with AVWS may present with life-threatening GI bleeding that can be difficult to tackle because the use of VWF/FVIII concentrate may be hampered by the increased clearance of VWF. We shall focus herewith on those with monoclonal gammopathy, because this group of patients may have very low levels of FVIII and VWF and recurrent GI bleeding [16]. The use of high dose IV immunoglobulins (1g/kg for 2 days), evaluated in the context of a small prospective study (10 patients with AVWS associated to monoclonal component) [17], was able to normalize FVIII and VWF levels in 8 of 10 patients (all with IgG monoclonal component). However, the 2 patients with an IgM component failed to show a good response [17], at variance with a recent report of 2 patients [18]. Thus, our current approach is to attempt this therapeutic approach even in patients with IgM monoclonal component in case of severe GI bleeding. The mechanism of action of this treatment is not clear: only in 1 of 2 patients did immunoglobulins dramatically reduce the VWF propetide/antigen ratio (from 10.7 to 1.6), thus indicating a post-treatment normalization of VWF clearance [18]. This therapeutic approach has no immediate effect and needs at least 24-48 hours before FVIII and VWF levels start to raise, but the effect may last along 2-4 weeks [17]. These characteristics make immunoglobulins very useful in cases of scheduled surgery but less convenient in the frame of emergencies. In cases of life-threatening GI bleeding, also associating a VWF/FVIII concentrate, with close monitoring of FVIII and VWF levels owing to their accelerated clearance, may be necessary. Treatment with immunoglobulins can increase the half-life of VWF/FVIII concentrates even in those patients who only partially correct baseline levels of VWF. The use of high dose IV immunoglobulins in the context of a prophylaxis regimen is not evidence based but was chosen in our patient because of the high number of recurrent bleeding episodes, in order to avoid hospitalization and acute GI bleeding. Despite their efficacy, high dose IV immunoglobulins are not compatible with home treatment. As in congenital VWD, several rescue therapies were also reported for AVWS and GI bleeding (table 1). The choice of a rescue therapy must carefully consider, in each patient, age, comorbidities and possible side effects.

AVWS associated to heart valve defects

Case 5

A 37 years-old woman, affected by the Cantú syndrome (a rare disorder characterized by congenital hypertrichosis, osteochondrodysplasia, cardiomegaly and dysmorphism) and by a severe mitral valve insufficiency, came to our attention after a recent episode of heart failure before mitral valvuloplasty. AVWS with a mild reduction of VWF was diagnosed (FVIII:C 84 IU/dL, VWF:Ag 68 IU/dL VWF:RCo 38 IU/dL, loss of HMWM), associated with mild anemia and iron deficiency (hemoglobin 11.5 g/dL, normal range 12-16 g/dL, ferritin 5 microg/L, normal range 15-150) and presence of occult blood in the stools. Before surgery she received IV iron supplementation and desmopressin (one dose, 0.3 micro/kg). Seven days later, levels of FVIII and VWF were within the normal range (FVIII:C 163 IU/dL, VWF:Ag 130 IU/dL VWF:RCo 107 IU/dL).

Discussion

The association between GI bleeding and aortic stenosis in 10 elderly patients, was first described by Heyde in 1958 [19]. It is now recognized that the Heyde syndrome is caused by AVWS due to increased shear stress at the level of the aortic valve. In 2003 Batur et al [20] showed an increased prevalence of aortic stenosis (32%) in patients with angiodysplasia compared to those without (14%). These data were confirmed by an epidemiological study carried out in the 2011 US Nationwide Inpatient Sample database: from a total of 32079 hospitalizations due to bleeding associated with GI telangiectasia, 7% had coexistent aortic valve disease (odds ratio 2.37, 95% CI 2.10-2.66, adjusted for age and known risk factors); an association with mitral valve disease was not demonstrated [21].

AVWS and GI bleeding also occur in patients receiving continuous flow LVADs for the management of advanced heart failure (as a bridge to transplant therapy and also as destination therapy in the last few years) [22]. AVWS associated with LVADs was first shown by Geisen et al in 2008 [23] in 7 patients with LVADs and elegantly confirmed by Kang et al [24] in paired samples before and after LVAD implantation. AVWS associated to LVADs is an interesting model in which to study the mechanism of GI bleeding when there is a loss of HMWM. Indeed, elevated levels of angiopoietin-2 were shown in patients with LVADs [25], and plasma from patients with LVADs caused abnormal neoangiogenesis in vitro (reduced tubule length and migration) [26].

The prevalence of GI bleeding associated with continuous-flow LVADs has been estimated between 15% and 61% [27], and angiodysplasia is present in 30-60% of

patients, with a significant burden of morbidity and health costs [22]. In AVWS associated with heart valve defects or LVADs, at variance with autoimmune diseases or monoclonal gammopathies, VWF:RCo levels are generally normal or only mildly decreased in plasma but there is a consistent loss of HMWMs due to increased shear stress; bleeding can be severe and exacerbated by the use of antiplatelet drugs and/or anticoagulants. The loss of HMWMs can be suspected by the presence of a low RCo/Ag ratio, even when VWF:RCo is normal.

AVWS associated with valve disease can be cured by heart surgery. No evidence-based data are available on the use of desmopressin or VWF/FVIII concentrate before surgery in these patients.

Our strategy is based upon the evaluation of the degree of HMWM loss and the presence of bleeding symptoms in deciding whether a treatment with desmopressin or VWF/FVIII concentrate is useful. In these patients, there is generally no need to repeat the treatment because surgery is able to cure the AVWS.

In patients with acute GI bleeding and AVWS associated to continuous flow LVADs, endoscopic examination is recommended together with the discontinuation of antiplatelet and anticoagulant therapy [28]. The reinstitution of anticoagulant therapy after the resolution of the acute phase must be carefully monitored but it is the currently recommended approach in consideration of the thrombotic risk. In case there is recurrent GI bleeding, the guidelines recommend evaluating a possible reduction/discontinuation of antiplatelet/anticoagulant therapy and also considering a reduction of the device speed, with the goal of increasing pulsatility and ultimately reducing angiodysplasia development [28]. In some patients with recurrent and severe GI bleeding rescue therapies (danazol, octreotide, thalidomide) have been used and demonstrated to be useful in some case-series or case-control studies [29]. A randomized controlled study with a VWF concentrate prophylaxis in the first 3 months after LVAD implantation was stopped early because of poor enrollment (Prevention of Hemorrhage After Implantation of Mechanical Circulatory Support study, www.clinicaltrials.gov NCT02488525, accessed 22nd December 2019).

General conclusions

GI bleeding may be a life-threatening condition that can arise both in congenital VWD and AVWS. Few data are available on the prevalence of this symptom, which is not common but is associated with a high morbidity and costs. No data are available on the age of onset.

It is possible to hypothesize a period of latent bleeding at younger age when angiodysplasia starts to develop, followed by more evident and severe bleeding events when angiodysplasia worsens with aging or in association with other bleeding risk factors (gastritis, antiplatelet or anticoagulants drugs). The first line therapy in congenital VWD is prophylaxis with VWF/FVIII or VWF concentrates, but the few available studies could not demonstrate its consistent efficacy, perhaps due to their relatively short follow-up. GI bleeding can be so severe and intractable that rescue therapies need to be associated in some patients, but data on their efficacy are very limited (case reports and case series with no long-term follow-up). In cases of GI bleeding and AVWS, the therapeutic choice is based on the control of the associated disease, but in cases of refractory bleeding some second-line therapies have been described (figure 1).

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Figure 1.
Flow-chart of diagnosis, follow-up and treatment of GI bleeding in congenital VWD and AVWS.