Management of rare acquired bleeding disorders

Marzia Menegatti,[1] Eugenia Biguzzi,[1] and Flora Peyvandi[1,2]

[1]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy; and [2]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Autoantibodies toward clotting factors may develop in people suffering from autoimmune or neoplastic diseases, after drug intake or even in subjects without apparent conditions. They are more commonly directed against factor VIII (FVIII) or von Willebrand factor leading to acquired hemophilia A or acquired von Willebrand syndrome, respectively. Rarely, autoantibodies develop against other clotting factors, such as fibrinogen, FII, FV, FVII, FX, FXI, and FXIII. The clinical picture of an acquired bleeding disorder includes a wide spectrum of clinical manifestations ranging from minimal or no bleeding to life-threatening events. Patients with no previous personal or family history of bleeding may have sudden-onset hemorrhagic manifestations, sometimes fatal, especially if an early diagnosis is not made. On the other hand, some patients may not have hemorrhagic symptoms at onset, and their diagnosis can therefore be delayed. The laboratory diagnostic assessment is performed by screening coagulation tests followed by specific factor-level measurement and inhibitor-titrating assays. An early diagnosis of acquired coagulopathies is mandatory for starting the appropriate treatment aimed at both controlling the acute bleeding episode mainly using the bypassing agents, and eradicating the anticlotting factor autoantibody, using immunosuppressive treatment. Therefore, prompt intervention by an expert and a specialized center is needed for immediate recognition and treatment of the disease.

Learning Objectives

- Understand that if a patient presents with bleeding and a negative hemorrhagic history, an underlying coagulation factor autoantibody should be suspected
- Recognize that treatment consists of stop-or-prevent bleeding events and eradicate the disease
- Understand that, in cases of underlying diseases, treatment can resolve the acquired bleeding disorder

Clinical case

A 62-year-old male patient was referred to the emergency room with large ecchymoses in both legs. The patient showed severe anemia (hemoglobin, 5 g/dL) with a prolonged activated partial thromboplastin time (APTT; ratio, 3.81) and a large hematoma of the left side of the chest and thigh, caused by an accidental fall that occurred 2 weeks before his arrival to the hospital. The computed tomography scan revealed hematomas of the external and internal oblique muscles, the transversus abdominis muscle, and the iliopsoas, as well as retroperitoneal bleeding. During the first 48 hours, the patient received 8 U of red blood cells and 5 U of fresh frozen plasma. In the presence of severe bleeding and persistent prolonged APTT, without a previous personal or family history of bleeding, an acquired bleeding disorder was suspected. Blood samples were sent to the hemostasis laboratory of our Center (Angelo Bianchi Bonomi Hemophilia and Thrombosis Center), where a mixing test showed a persistence of prolonged APTT (ratio, 2.6) with no correction. Factor IX (FIX), FXI, and FXII results were normal, and FVIII coagulant activity (FVIII:C) was <1 IU/dL. The anti-FVIII inhibitor was tested and a high titer of 200 Bethesda units (BU) was reported. Therefore, diagnosis of acquired hemophilia A (AHA) with high titer of inhibitor was made; the patient was transferred to the Internal Medicine department at our hospital 5 days after symptom onset, and treatment with prednisone (1 mg/day) and activated prothrombin complex concentrate (APCC; 80 U/kg twice daily) was started.

In the first 10 days after diagnosis, the patient received an additional 4 U of red blood cells due to a drop of hemoglobin levels, despite the treatment with APCC and prednisone. During this time interval, D-dimer and fibrinogen were evaluated every other day: D-dimer increased to 4325 ng/mL and the lowest level of fibrinogen was 280 mg/dL. The clinical and laboratory evaluation did not suggest any autoimmune diseases and the total-body computed tomography scan at admission excluded the presence of solid tumors. After 10 days of treatment, APCC was stopped; FVIII and inhibitor were reevaluated (3 IU/dL; inhibitor, 156 BU). During hospitalization, the patient developed bacterial pneumonia (positive for methicillin-resistant *Staphylococcus aureus*), which was treated with imipenem and vancomycin. After 21 days of treatment, FVIII increased to 8 IU/dL with a drop in inhibitor level to 37 BU. In the presence of bacterial infection and renal failure, it was decided that a second immunosuppressive therapy should not be started and that treatment should continue with only prednisone for an additional 20 days. Complete remission with an FVIII:C of 60 IU/dL was achieved after 6 weeks of corticosteroid therapy. Prednisone tapering was carried out over 2 months with normalization of FVIII levels.

Conflict-of-interest disclosure: M.M. has received travel support from Pfizer. F.P. is member of the advisory boards of Bioverativ, Roche, Sanofi, and Takeda. E.B. declares no competing financial interests.

Off-label drug use: None disclosed.

Introduction

Coagulation factors work coordinately to prevent blood loss when there is vessel damage through a complex series of cascade reactions.[1] Deficiency of coagulation factors may result in a coagulopathy leading to a bleeding diathesis with either spontaneous or posttrauma and postsurgery hemorrhages.[2] In rare cases, acquired coagulopathies, caused by the consumption of coagulation factors or by the presence of autoantibodies against coagulation factors, lead to a partial or complete neutralization of their function, promoting their rapid clearance from the blood.[3,4] The clinical picture of acquired bleeding disorders usually differs with regard to congenital cases and includes a wide spectrum of clinical manifestations ranging from minimal or no bleeding to life-threatening events.[5]

Autoantibodies usually develop not only in patients with autoimmune disorders, malignancies, pregnancy, and advanced age, but they can also be developed in subjects without apparent underlying conditions.[6] The presence of an acquired bleeding disorder is usually characterized by spontaneous bleeding or by bleeding induced by surgery, trauma, or any invasive procedures in patients with no previous family or personal history of bleeding.[7] However, the presence of autoantibodies is not the only cause of acquired coagulopathy. Disseminated intravascular coagulation (DIC), liver disease, vitamin K– and vitamin C–deficiency, and oral anticoagulant therapy may provoke a similar situation.[8-10] In this review, we will focus mainly on acquired bleeding disorders caused by the presence of autoantibodies against coagulation factors, such as FVIII and von Willebrand factor (VWF), leading to AHA, acquired von Willebrand syndrome, and other very rare acquired disorders (fibrinogen, FII, FV, FVII, FX, FIX, FXI and FXIII). To this aim, we searched Medline and PubMed for previously published original papers and reviews (within the last 10 years) in English with the following search terms: "acquired bleeding disorders" or "acquired hemophilia" or "autoantibodies and bleeding" or "acquired bleeding disorders and guidelines." In addition, we performed a separate search with the following terms: "disseminated intravascular coagulation," "liver disease and bleeding," "vitamin C defect," vitamin K defect," "treatment and acquired bleeding disorders," and "eradication and inhibitor." Articles were excluded on the basis of their titles and/or abstracts.

Autoantibodies

Autoantibodies against clotting factors are usually immunoglobulin G (IgG; mainly IgG4) polyclonal immunoglobulins (rarely IgM or IgA) targeting several functional epitopes of the clotting factors.[11] Autoantibodies directed to single coagulation factors are prevalently against FVIII or VWF, leading to AHA or acquired von Willebrand syndrome (AVWS), respectively,[6,12] but autoantibodies directed against other clotting factors causing extremely rare acquired coagulopathies are described in both children and adults, with or without associated disorders.[13]

AHA

AHA is a rare bleeding disorder, with an estimated incidence in the general population of ~1.5 case per million per year.[14] In approximately one-half of patients with AHA, autoimmune disorders, hematologic malignancies (leukemias, lymphomas, or monoclonal gammopathies), solid tumors (breast cancer), and pregnancy have been registered as causing conditions for the disease, whereas in the other half of patients, FVIII autoantibodies occur in patients lacking any relevant concomitant disease (idiopathic disorder), although in some cases an underlying disorder may be diagnosed long after the onset of the coagulation abnormality.[15] FVIII inhibitors are classified based on the kinetics and the extent of inactivation of FVIII. Type I inhibitors follow second-order kinetics and inactivate FVIII completely, whereas type II inactivate FVIII incompletely and display more complex kinetics of inhibition. The 2 different kinetics can be explained by (i) different binding affinities toward the FVIII molecule, resulting in stronger (type I) and weaker (type II) binding at their epitope and (ii) the target epitope that is crucial for type I inhibitors.[16] Patients with AHA tend to have type II inhibitors.[16] The incidence of AHA is very uncommon in children,[17] in fact, the median age of patients at diagnosis was 74 and 78 years in the 2 largest available cohorts, the European Acquired Hemophilia (EACH2) Registry and a prospective study carried out in the United Kingdom, respectively.[5,18] The incidence in male and female patients is similar, with the exception being in the age group from 20 to 40 years, due to pregnancy-related cases.[19] In this case, AHA occurs more frequently in primiparae, with a median interval between delivery and diagnosis of ~3 months reported in the EACH2 Registry.[5] The same registry reported that: the presenting clinical symptoms of the 501 patients registered were mainly spontaneous (77%) and severe (70%); bleeding sites were predominantly subcutaneous (53.2%) and deep muscle or retroperitoneal bleedings (50.2%); and intracerebral bleeding events were rare (1%) as well as joint bleeding episodes (4.9%), at variance with congenital hemophilia A.[5]

AVWS

Since the description of the first patient, >300 cases have been reported; however, the number of patients with AVWSs could be underestimated because most patients do not bleed until they are exposed to major trauma or major invasive procedures.[20] The pathophysiology of AVWS is more complex compared with other acquired bleeding disorders due to different underlying causing mechanisms. Lymphoproliferative diseases (multiple myeloma, chronic lymphocytic leukemia, monoclonal gammopathy of undetermined significance, and Waldenström macroglobulinemia) alone have been described to cause from 47% to 63% of AVWS cases,[20,21] whereas myeloproliferative diseases (essential thrombocythemia, polycythemia vera, and chronic myeloid leukemia) and solid tumors accounted for 15% and 5% of cases,[21] respectively. Lymphoproliferative disorders, tumors, and immunological disorders increase the VWF clearance from the circulation through specific or nonspecific autoantibodies generating immune complexes with VWF, whereas myeloproliferative disorders provoke VWF adsorption onto cell membranes of tumor cells or other surfaces.[7] Hypothyroidism could reduce VWF synthesis whereas myeloproliferative disorders, uremia, and the use of ciprofloxacin could increase VWF proteolysis by specific proteases.[7,21] In addition, the results of retrospective study by Tiede et al found a relatively high association between AVWS and cardiovascular disorders (46%) such as congenital heart disease, aortic stenosis, endocarditis, and severe atherosclerosis, which cause VWF degradation by increased shear stress.[7,22] AVWS is most commonly diagnosed in the elderly population with a median age at diagnosis of 60 years, with bleeding symptoms that are either spontaneous mucocutaneous bleeding (ecchymosis, epistaxis, menorrhagia, gastrointestinal tract [GI] bleeding, or hematuria) or excessive bleeding posttrauma/postsurgery.[12] There are very few deaths related to bleeding in patients with AVWS.

Autoantibodies against other coagulation factors

The incidence of acquired deficiency of fibrinogen, prothrombin, and FV, FVII, FIX, FX, FXI, and FXIII is much less known because only sporadic cases have been described in the literature. These diseases

may be associated with a wide spectrum of clinical manifestations ranging from minimal or no bleeding to life-threatening conditions.[13] Although inhibitors directed against FV causing acquired FV deficiency (AFVD) occur rarely (~150 cases have been described so far), they are the most frequent among the inhibitors against clotting factors other than FVIII or VWF.[7] These inhibitors could be developed at any age, in association with a readily identifiable risk factor, such as a surgical intervention, antibiotics (particularly β lactams and aminoglycosides), blood transfusions, malignancies, and autoimmune diseases.[23] The majority of the cases previously described occurred after exposure to bovine thrombin contained in preparations frequently used as topical hemostatic agents in vascular, orthopedic, and neurosurgical procedures. Bovine thrombin preparations often contained additional contaminating bovine proteins, such as FV, which may act as an immunological stimulus for development of anti-bovine FV inhibitors, which might then cross-react against human FV. Recombinant thrombins are now available[24]; therefore, the risk of developing FV inhibitors after thrombin exposure has become relatively low in developed countries. As reported in the systematic review by Franchini and Lippi[23] on 74 case reports, bleeding symptoms at presentation often involved multiple sites (32%).[23] Mucosal bleedings (genitourinary and airway tracts) are the most frequent (62%) with one-half of the cases presenting hematuria (often severe). Another frequent site of bleeding reported is the GI tract (19%). Retroperitoneal and intracranial hemorrhage were present less frequently (5% and 8%, respectively), and, most importantly, cerebral hemorrhage was associated with the highest mortality rate (50%). Because only a few case reports are available on AFVD, further studies are needed to elucidate the inhibitory mechanisms of FV autoantibodies.

At variance with AFVD, acquired deficiencies of other clotting factors due to autoantibodies are extremely rare. Acquired fibrinogen deficiency has been reported in a few cases associated with peripartum women, malignancies, or autoimmune diseases.[16,25-27] In 1998, Kondera-Anasz reported high concentrations of autoantibodies in the serum of pregnant in comparison with nonpregnant women, in particular in those who were Rh immunized and in absence of bleeding symptoms. The author suggested that the fibrinogen turnover occurring during the peripartum period leads to the expression of neoantigens on fibrinogen fragments that predispose to the development of autoantibodies against fibrinogen.[25] More recently, a case of the inhibition of fibrin polymerization caused by a single immunoglobulin λ light chain, rather than by a whole antibody molecule, in a patient with no history of bleeding but abnormal coagulation profile identified before surgery was also reported .[26]

Antibodies against prothrombin are usually associated with autoimmune diseases (systemic lupus erythematosus and rheumatoid disease) and malignancies,[28,29] but a high proportion of antibodies develop after exposure to bovine thrombin-fibrin glue during surgery.[13] In both cases, their presence is associated with severe bleeding. In contrast, a prothrombotic state is typical of the antiphospholipid antibody syndrome whose prothrombin is believed to be the main antigenic target.[16] In vitro, the majority of antiprothrombin detected by solid-phase immunoenzymatic assays present an anticoagulant activity, which could be explained by an increased affinity of prothrombin for negatively charged phospholipid surfaces, which consequently are less available for the other clotting factors.[16] In some cases of acquired hypoprothrombinemia associated with diffuse bleeding, a clear cause could not be identified.[30]

Acquired FVII deficiency is very rarely reported, mainly in association with severe systemic sepsis, malignancies, and hematological stem cell transplantation. Bleeding occurred in 48% of cases (20 of 42) and rarely was bleeding were severe.[31] It was suggested that antibodies recognize the calcium-dependent conformation in or near the Gla domain having the ability to inhibit the interaction between FVIIa and tissue factor (TF) or phospholipid membranes.[32]

Data on acquired FIX deficiency is scarce due to its rarity. It is reported to be associated with autoimmune diseases (systemic lupus erythematosus) and viral pneumonia, with a clinical presentation including bruising and spontaneous hematomas.[33,34]

Acquired FX deficiency (AFXD) due to the presence of autoantibodies is also rarely reported and is associated mainly with malignancies, autoimmune disorders, and drugs[16,35]; the clinical picture presents with bleeding complications including extensive bleeding.[35] However, most AFXD deficiency cases are not due to autoantibodies but are associated with amyloidosis, a plasma cell dyscrasias characterized by formation of aberrant monoclonal immunoglobulin light chains that aggregate and deposit as amyloid fibrils.[36] Infusion studies with radioactive labeled FX demonstrated that the FX is removed at a rapid rate due to the absorption of FX by the amyloid fibrils, which increases its clearance.[37] The clearance may happen in the spleen because it was shown after splenectomy FX levels had been normalized in 1 patient.[38] Bleeding in patients with amyloidosis and AFXD can be severe, and a review of 30 clinical cases showed no association between bleeding severity and FX levels.[39]

Acquired FXI deficiency is occasional and often associated with systemic lupus erythematosus with various clinical presentations including severe life-threatening hemorrhage, fetal loss, and thrombosis.[40]

Acquired FXIII deficiency (AFXIIID) is also a rare clinical condition, although a recent paper by Ichinose et al, reporting on the diagnosis of 32 patients with AFXIIID, significantly increased the number of patients with the disorder.[41] Even though >50% of AFXIIID cases are spontaneous, they may be linked to a variety of factors, including drug treatment (isoniazid, penicillin, phenytoin, amiodarone), autoimmune and hematological diseases, and treatment with anti–interleukin 6 receptor for rheumatoid arthritis,[16,41] most commonly occuring in the elderly with severe subcutaneous muscle hematomas or soft tissue bleeding,[42] but possibly also presenting with catastrophic bleeding events associated with significant mortality.[16] Other conditions and possible clinical pictures associated with antibody-independent acquired bleeding disorders are listed in Table 1.

Diagnosis

Diagnosing acquired coagulopathies remains a difficult task for practicing hematologists. The presence of these disorders should be suspected when a patient presents sudden-onset bleeding with a negative personal and family history for hemorrhagic diathesis. The laboratory diagnostic tests confirming the diagnosis of an acquired disorder are prolonged APTT and/or prothrombin time (PT), not corrected by the addition of normal plasma using the mixing test (Figure 1). To confirm an acquired coagulopathy, other inhibiting factors such as the commonly occurring lupus anticoagulants, as well as anticoagulants such as heparin, which may resemble characteristics of factor inhibitors have to be excluded.[7] The presence of heparin as a cause of a prolonged APTT and thrombin time (TT) can be excluded by a normal reptilase time. Another important distinction to be made is with DIC presenting with prolonged PT and

Table 1. Other acquired conditions

Defect	Associated conditions	Clinical picture	Reference
Lupus anticoagulant hypoprothrombinemia syndrome (LA-HS)	Lupus anticoagulant associated with prolonged PT and low levels of FII (due to the accelerated clearance of the prothrombin-antiprothrombin antibody complexes)	Mild or severe bleeding; more frequent in the pediatric age	43,44
Heparin-like syndrome	Associated with multiple myeloma, mastocytosis, acute monoblastic anemia, solid tumors, HIV infection Diagnosis is based on prolonged APTT, normalized by protamine sulphate in the absence of heparin therapy	Mild or severe bleeding	45-47
Vitamin C deficiency (scurvy)	Malabsorption, alcoholism, or malnutrition, and elderly Normal coagulation test Multifactorial normocytic nonregenerative anemia with iron, vitamin B9, and B12 deficiencies associated with systemic inflammation	Diffuse superficial hematomas without vascular or coagulation disorders	48
Vitamin K	Intestinal malabsorption, fasting, alcoholism, and drugs (warfarin, high dose of vitamin E, cephalosporins, anticonvulsants) Diagnosis is suggested after an international normalized ratio $\geq$4 or a prolonged PT with normal platelet count and fibrinogen level	The classic form occurs between 24 hours to 7 days of life and is more often idiopathic; the late form occurs between the second week and the sixth month of life The hemorrhagic manifestations mainly involve not only GI tract and skin, but also the central nervous system in the late forms	49
DIC	Generalized activation of the hemostatic system triggered by various conditions and leading to an excessive deposition of fibrin in the microcirculation followed by the lysis by plasmin Associated with an extremely high number of clinical conditions: bacterial and viral infection, neoplasms, obstetric complication, vascular abnormalities, liver disease, pancreatitis, hypothermia	May be acute with a predominantly hemorrhagic diathesis or chronic with a predominantly microthrombotic picture	10
Liver disease	Decreased synthesis of coagulation factors, deficiency of vitamin K, dysfibrinogemias, hyperfibrinolysis due to decreased synthesis of inhibitors such as antiplasmines and thrombocytopenia	Most of the hemorrhages observed in advanced hepatopathies are caused by esophageal varices, GI tract bleeding, and surgery	50

APTT, both of which should be corrected upon mixing test.[51] In the case of acquired FXIII disorder, screening PT and APTT tests are normal; therefore, measuring FXIII in the patient's sample by specific assays followed by mixing tests is the only option to identify an inhibitor. With regard to acquired fibrinogen disorder, PT, APTT, and TT are prolonged, and the fibrinogen coagulant level assayed with the Clauss functional method is reduced; in the presence of an inhibitor, the TT is not corrected using the mixing test.[7] Finally, coagulation factor inhibitor studies are then undertaken to measure inhibitor titer using the Nijmegen modification of the classical Bethesda assay, introduced to resolve the weak false-positive results given in the range of 0.5 to 1.0 BU/mL. This method can be applied to all acquired deficiencies due to the presence of inhibitors by using the specific factor-deficient plasma in both the control tube and test plasma dilutions.[51]

Treatment of acquired coagulopathies

The mainstream treatment of acquired coagulopathies is based on the treatment of acute bleeding events and on the eradication of the antibodies. Where possible, the removal or treatment of the condition associated with the development of the inhibitor (eg, cancers, drugs) should be considered, as it may lead to the disappearance or significant reduction of the inhibitor.

Treatment of acute bleeding events

AFVIIID: AHA. In patients with AHA, FVIII concentrates are usually not effective because of the high-titer inhibitor. In such circumstances, bypassing agents as recombinant activated FVII (rFVIIa) and APCC are recommended. Instead of replacing the missing factor, they bypass the clotting system and improve thrombin generation by bolstering the levels of procoagulant factors.

The usual dosage of rFVIIa at frontline is 90 to 120 μg/kg every 2 to 3 hours and it can be associated with antifibrinolytic drugs such as tranexamic acid. For APCC, the dose is 50 to 100 IU/kg every 6 to 12 hours (with a maximum dose of 200 IU/kg per day).[7,52] Because

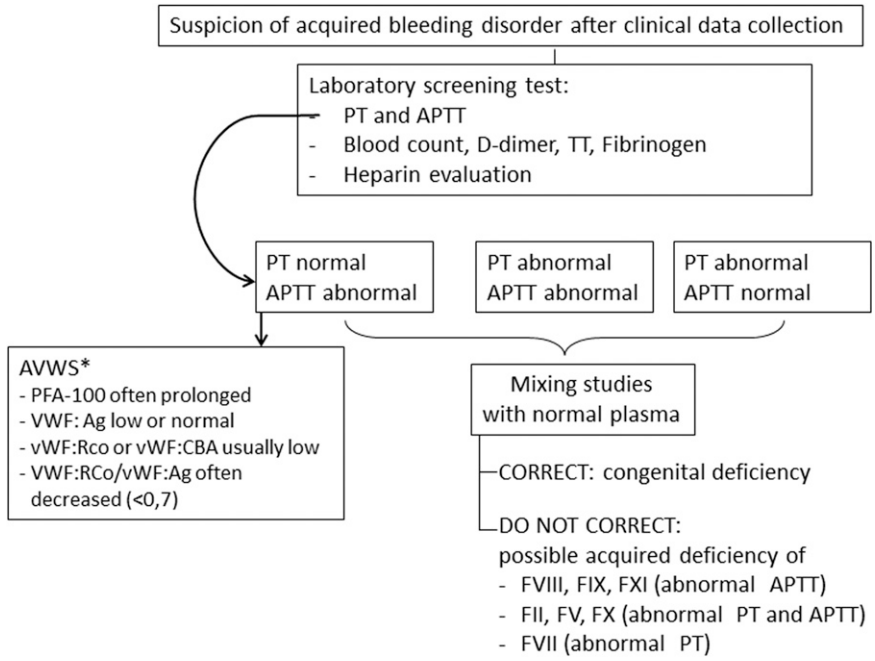

Figure 1. Approach to laboratory tests for inhibitor diagnosis. *Studies of VWF multimers may be useful to demonstrate a decrease in heavy-molecular-weight multimers or differentiate between AVWS and von Willebrand disease. PFA-100, occlusion time; VWF:Ag, VWF antigen assay; VWF:CBA, collagen-binding assay; VWF:Rco, ristocetin cofactor assay.

patients affected by AHA are generally elderly, the thrombotic risk needs to be evaluated and balanced against the bleeding diathesis, and high doses of bypassing agents should be avoided. Treatment with bypassing agents should always be monitored, evaluating platelet number, fibrinogen, and D-dimer, particularly after 48 hours of treatment.

In the EACH2 study, a Web-based registry with 501 patients enrolled, control of bleeding events did not differ using the 2 mentioned bypassing agents (93%). Also, the thrombotic complications were similar using rFVIIa and APCC (2.9% and 4.8%, respectively).[52] In some patients with a low titer of anti-FVIII neutralizing antibody (<5 BU) and residual FVIII, treatment with FVIII concentrates or DDAVP can be attempted, but because the response cannot be predicted based on the inhibitor titer, monitoring of FVIII levels is recommended.[53]

A recombinant porcine FVIII (rpFVIII; susoctocog alfa) is also currently available for the treatment of AHA. A phase 2/3 trial treated 28 patients with a first fixed dose of 200 U/kg, achieving resolution of the bleeding event in 24 of 28 patients.[54] A lower dose of 100 U/kg was reported outside of the trial in 6 patients, with control of the bleeding in 4 of them.[55]

The major limitation of this approach is the cross-reactivity of the inhibitor to rpFVIII, especially in patients with a high-titer inhibitor. Physical removal of the antibodies, using a sepharose column with recombinant protein A, has also been considered as an alternative strategy in case of surgery or ineffective treatment with bypassing agents, but this technology is now available only in a few centers.[56]

Possible future treatments in AHA and other acquired deficiencies. In the last 5 years, new drugs for congenital hemophilia A (with and without inhibitor) and B provided a new landscape for the treatment of these clinical conditions, targeting the whole hemostatic balance instead of just supplementing FVIII or FIX. Conceptually, it is possible to conceive of the use of these new drugs in patients with acquired bleeding disorders in the future. Emicizumab (Hemlibra) is a humanized monoclonal antibody that mimics the cofactor activity of FVIII, by binding both activated FIX and FX. In this manner, the coagulation cascade is chronically activated at a low level. This drug was used in different trials including in both adults and children with congenital hemophilia A with and without inhibitors, with substantial reduction of bleeding rates and improvement of health-related quality of life.[57] Single subcutaneous weekly or every-2-week administration of the drug was able to prevent most spontaneous bleeding events in the trials. The main problem was the possible thrombotic microangiopathy associated with the use of repeated high doses of APCC in instances of breakthrough bleeding and the need of a specific chromogenic test with bovine reagents to evaluate FVIII inhibitors. The use of this drug in AHA requires proper clinical studies to ensure its safety and efficacy.

Other novel alternative approaches target the whole hemostatic system by inhibiting the natural anticoagulant proteins, such as antithrombin, TF-pathway inhibitor (TFPI), and the protein C pathway. Fitusiran is a small interfering RNA that binds antithrombin messenger RNA and inhibits its synthesis. A phase 1 study demonstrated that fitusiran is able to reduce almost 80% of antithrombin activity[58]; phase 3 studies are currently ongoing in hemophilia patients with or without inhibitor (clinicaltrials.gov: NCT03549871, NCT03754790, and NCT03417245). Several molecules interfering with TFPI were developed and are currently under evaluation. Concizumab is a humanized anti-TFPI monoclonal antibody that prevents FXa binding and inhibition of the TF-FVIIa complex. A phase 1 study demonstrated reduction of TFPI plasma concentration and TFPI plasma activity.[59] Phase 2 trials are also currently ongoing in patients affected by hemophilia A and B with or without inhibitor (clinicaltrials.gov: NCT03196284 and NCT03196297). Other anti-TFPI monoclonal antibodies (PF-06741086 and BAY1093884) are currently

evaluated in phase 2 studies (clinicaltrials.gov: NCT03363321 and NCT03597022).[60] Other interesting approaches (still in the preclinical phase) tackle the inhibition of the protein C and protein S pathway. Currently under evaluation are SerpinPC, designed to inhibit the anticoagulant function of activated protein C while preserving its anti-inflammatory properties,[61] and a small-interfering RNA against protein S.[62]

Once the safety and efficacy of these new drugs has been approved for patients with congenital hemophilia, they may also be further investigated in patients with AHA and other acquired deficiencies.

AVWS. With regard to AVWS, severe bleeding episodes can be treated off-label using bypassing agents, but moderate bleeds and minor surgeries can also be treated with DDAVP or FVIII/VWF concentrates associated with tranexamic acid.[63] With regard to AVWS associated with IgG monoclonal gammopathy, treatment could be performed using off-label high-dose IV immunoglobulins (0.4 g/kg for 5 days or 1 g/kg for 2 days).[22] Normal levels of FVIII and VWF obtained by high-dose immunoglobulins can last 3 to 5 weeks, ensuring effectual hemostasis. The same therapy was also recently described as effective in a few patients with IgM monoclonal gammopathy.[64] Albeit using the described therapies, some patients with AVWS present life-threatening, recurrent GI bleeding, which is particularly difficult to solve and can have a bad impact on their quality of life. Antiangiogenic drugs (such as thalidomide and lenalidomide) were effective in GI bleeding in a few patients with AVWS.[63] In such patients, tamoxifen,[65]octreotide,[66] and atorvastatin,[67,68] described as useful in case reports of patients with congenital von Willebrand disease, could also be considered. However, data are very limited and it is difficult to make a strong recommendation.

Other rare acquired bleeding disorders. The treatment of acute bleeding events, in patients with rare acquired disorders, depends on the inhibitor titer and levels of residual clotting factor. For low inhibitor levels (<5 BU), an attempt at treatment using specific factor concentrates (when available) must be monitored clinically and with specific laboratory tests. For high inhibitor levels (>5 BU) or lack of response to concentrates, patients can be treated off-label with bypassing agents (rFVIIa or APCC). For the FV inhibitor specifically, platelet transfusion can also be an effective adjunctive treatment because platelets contain FV, which is absorbed from the plasma.[23]

In acquired FXD amyloidosis, response to treatment with the off-label prothrombin complex or the FX plasma–derived concentrates (both FIX-FX and the single FX product) is impaired by increased FX clearance; it is not predictable and needs close laboratory monitoring.[69] Use of off-label bypassing agents (rFVIIa 30-90 μg/kg) is also described in this type of deficiency,[70] particularly when the inhibitor level is high.

AFXIIID is a challenge for the physicians because there is no generally accepted guideline for its treatment and the mortality rate is high (20% to 30%).[71] Replacement therapy with high doses of FXIII concentrates (50-150 U/kg) were proven to overcome the inhibitor activity and give adequate hemostasis, whereas the safety of the recombinant FXIII-A, very successful in the congenital form of FXIII-A deficiency, must yet be proven. The use of rituximab in 3 patients was described and reported as successful in all of them.[71]

Eradication of the inhibitor

For acquired deficiencies associated with an underlying factor (ie, drugs, cancer, autoimmune diseases, aortic stenosis, and other heart defects), the first-line therapy is the removal or management of the associated condition, with possible rapid disappearance of the acquired deficiency.[72] Regarding pregnancy-associated AHA, spontaneous remission was described after some months.[20] The immunosuppressive treatment of AHA and other acquired coagulation defects is based on corticosteroid (prednisone 1 mg/kg orally daily) alone or in association with cyclophosphamide (1-2 mg/kg orally daily) or rituximab (375 mg/m^2 IV weekly for 4 weeks) off-label as an alternative to cyclophosphamide.

The European registry EACH2 showed a shorter time to inhibitor negativization in patients using corticosteroid and cyclophosphamide compared with corticosteroid alone (hazard ratio, 2.11; 95% confidence interval, 1.38-3.21).[72] Nevertheless, the proportion of patients alive and free from inhibitor at 1 year was not different in the 2 groups (62% and 67%, respectively). The overall survival was related to the presenting etiology: 100% survivors in women with pregnancy-related acquired hemophilia, 71% in patients with autoimmune diseases, 58% in idiopathic acquired hemophilia, and 32% in patients with malignancy. In the same study, a rituximab-based regimen (rituximab alone or associated with other immunosuppressive treatment) was used in 51 patients and complete remission was obtained in 61%. A recent report by Tiede et al[73] used a predefined consensus protocol in a large group of patients (n = 101) who received corticosteroids for 3 weeks. For cases with no remission, cyclophosphamide was added (weeks 4-6, n = 35). Rituximab was the third-line therapy (weeks 7-10, n = 12). Complete remission was obtained in 61% of patients and time to complete remission was 79 days (interquartile range, 48-102).

Immunosuppressive therapy is associated with a high risk of infections that can be fatal in this elderly population (4.2% deaths in the EACH2 study,[72] 16% in the GTH-AH study[73]). Possible side effects of corticosteroids (such as hyperglycemia, hypertension, GI ulcers, and psychiatric disorders) and risk of infections should be carefully evaluated in patients before the initiation of combined immunosuppressive therapy. IV immunoglobulins provided no benefit in association with first-line therapy in both the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) surveillance study and in the EACH2 study.[18,73]

With regard to AVWS associated with monoclonal gammopathy of undetermined significance, antibody eradication is not a feasible strategy. In this case, there is follow-up for these patients and bleeding must be prevented in instances of surgery or treated when there are spontaneous events. For refractory bleeding, an alternative strategy might be necessary. Recently, 2 patients affected by AVWS (associated with monoclonal component) and refractory transfusion-dependent bleeding were treated with lenalidomide and good bleeding control was obtained.[74] Lenalidomide is an immunomodulatory drug used together with dexamethasone in multiple myeloma; it is also effective at reducing GI bleeding in a small group of patients with congenital von Willebrand disease.[75]

Conclusion

Diagnosis and treatment of patients with acquired coagulopathies are challenging. Expert and specialized centers are necessary to assure correct diagnosis and management of acute bleeding episodes as well

as eradication of the antibodies or of the associated condition. With the increasing age of the general population, an increased number of patients with acquired coagulopathies is expected; therefore, educational programs for better diagnosis and management of these patients are required.

Correspondence

Flora Peyvandi, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Via Pace, 9-20122 Milan, Italy; e-mail: flora.peyvandi@unimi.it.

References

1. Furie B, Furie BC. Molecular and cellular biology of blood coagulation. *N Engl J Med*. 1992;326(12):800-806.
2. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015;125(13):2052-2061.
3. Ahmed AE. Autoantibodies to coagulation factors and bleeding disorders. *Clin Rev Allergy Immunol*. 1998;16(3):313-319.
4. Miller CH. Laboratory testing for factor VIII and IX inhibitors in haemophilia: a review. *Haemophilia*. 2018;24(2):186-197.
5. Knoebl P, Marco P, Baudo F, et al; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. 2012;10(4):622-631.
6. Franchini M, Vaglio S, Marano G, et al. Acquired hemophilia A: a review of recent data and new therapeutic options. *Hematology*. 2017;22(9):514-520.
7. Franchini M, Castaman G, Coppola A, et al; AICE Working Group. Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management. *Blood Transfus*. 2015;13(3):498-513.
8. Paddock M, Chapin J. Bleeding diatheses: approach to the patient who bleeds or has abnormal coagulation. *Prim Care*. 2016;43(4):637-650.
9. Lisman T, Porte RJ. Pathogenesis, prevention, and management of bleeding and thrombosis in patients with liver diseases. *Res Pract Thromb Haemost*. 2017;1(2):150-161.
10. Levi M, Sivapalaratnam S. Disseminated intravascular coagulation: an update on pathogenesis and diagnosis. *Expert Rev Hematol*. 2018;11(8):663-672.
11. Matsumoto T, Shima M, Fukuda K, et al. Immunological characterization of factor VIII autoantibodies in patients with acquired hemophilia A in the presence or absence of underlying disease. *Thromb Res*. 2001;104(6):381-388.
12. Charlebois J, Rivard GÉ, St-Louis J. Management of acquired von Willebrand syndrome. *Transfus Apheresis Sci*. 2018;57(6):721-723.
13. Franchini M, Lippi G, Favaloro EJ. Acquired inhibitors of coagulation factors: part II. *Semin Thromb Hemost*. 2012;38(5):447-453.
14. Collins P, Baudo F, Huth-Kühne A, et al. Consensus recommendations for the diagnosis and treatment of acquired hemophilia A. *BMC Res Notes*. 2010;3:161.
15. Coppola A, Favaloro EJ, Tufano A, Di Minno MN, Cerbone AM, Franchini M. Acquired inhibitors of coagulation factors: part I-acquired hemophilia A. *Semin Thromb Hemost*. 2012;38(5):433-446.
16. Cugno M, Gualtierotti R, Tedeschi A, Meroni PL. Autoantibodies to coagulation factors: from pathophysiology to diagnosis and therapy [published correction appears in *Autoimmun Rev*. 2015;14(7):650]. *Autoimmun Rev*. 2014;13(1):40-48.
17. Franchini M, Zaffanello M, Lippi G. Acquired hemophilia in pediatrics: a systematic review. *Pediatr Blood Cancer*. 2010;55(4):606-611.
18. Collins PW, Hirsch S, Baglin TP, et al; UK Haemophilia Centre Doctors' Organisation. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877.
19. Tengborn L, Baudo F, Huth-Kühne A, et al; EACH2 registry contributors. Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. *BJOG*. 2012;119(12):1529-1537.
20. Collins P, Budde U, Rand JH, Federici AB, Kessler CM. Epidemiology and general guidelines of the management of acquired haemophilia and von Willebrand syndrome. *Haemophilia*. 2008;14(suppl 3):49-55.
21. Federici AB, Rand JH, Bucciarelli P, et al; Subcommittee on von Willebrand Factor. Acquired von Willebrand syndrome: data from an international registry [published correction appears in *Thromb Haemost*. 2000;84(4):739]. *Thromb Haemost*. 2000;84(2):345-349.
22. Tiede A, Priesack J, Werwitzke S, et al. Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. *J Thromb Haemost*. 2008;6(4):569-576.
23. Franchini M, Lippi G. Acquired factor V inhibitors: a systematic review. *J Thromb Thrombolysis*. 2011;31(4):449-457.
24. Bowman LJ, Anderson CD, Chapman WC. Topical recombinant human thrombin in surgical hemostasis. *Semin Thromb Hemost*. 2010;36(5):477-484.
25. Kondera-Anasz Z. Antibodies against fibrinogen in pregnant women, in post delivery women and in the newborns. *Thromb Haemost*. 1998;79(5):963-968.
26. Dear A, Brennan SO, Sheat MJ, Faed JM, George PM. Acquired dysfibrinogenemia caused by monoclonal production of immunoglobulin lambda light chain. *Haematologica*. 2007;92(11):e111-e117.
27. Lee N, Kim JE, Yoo HJ, et al. Acquired dysfibrinogenemia caused by autoantibody inhibiting fibrin polymerization in a patient with MELAS syndrome and bleeding tendency. *Ann Clin Lab Sci*. 2016;46(6):696-700.
28. Bänninger H, Hardegger T, Tobler A, et al. Fibrin glue in surgery: frequent development of inhibitors of bovine thrombin and human factor V. *Br J Haematol*. 1993;85(3):528-532.
29. Ortel TL, Mercer MC, Thames EH, Moore KD, Lawson JH. Immunologic impact and clinical outcomes after surgical exposure to bovine thrombin. *Ann Surg*. 2001;233(1):88-96.
30. Huang LW, Anand S, Hassan S, Onwuemene O. Bruised black and blue: acquired hypoprothrombinemia. *Am J Med*. 2015;128(11):e7-e11.
31. Mulliez SM, Devreese KM. Isolated acquired factor VII deficiency: review of the literature. *Acta Clin Belg*. 2016;71(2):63-70.
32. Kamikubo Y, Miyamoto S, Iwasa A, Ishii M, Okajima K. Purification and characterization of factor VII inhibitor found in a patient with life threatening bleeding. *Thromb Haemost*. 2000;83(1):60-64.
33. Mazzucconi MG, Peraino M, Bizzoni L, Bernasconi S, Luciani M, Rossi GD. Acquired inhibitor against factor IX in a child: successful treatment with high-dose immunoglobulin and dexamethasone. *Haemophilia*. 1999;5(2):132-134.
34. Krishnamurthy P, Hawche C, Evans G, Winter M. A rare case of an acquired inhibitor to factor IX. *Haemophilia*. 2011;17(4):712-713.
35. Chan IS, Ogunsile FJ. An acquired factor X inhibitor: the importance of understanding coagulation. *Am J Med*. 2017;130(7):e307-e308.
36. Patel G, Hari P, Szabo A, et al. Acquired factor X deficiency in light-chain (AL) amyloidosis is rare and associated with advanced disease. *Hematol Oncol Stem Cell Ther*. 2019;12(1):10-14.
37. Furie B, Greene E, Furie BC. Syndrome of acquired factor X deficiency and systemic amyloidosis in vivo studies of the metabolic fate of factor X. *N Engl J Med*. 1977;297(2):81-85.
38. Rosenstein ED, Itzkowitz SH, Penziner AS, Cohen JI, Mornaghi RA. Resolution of factor X deficiency in primary amyloidosis following splenectomy. *Arch Intern Med*. 1983;143(3):597-599.
39. Greipp PR, Kyle RA, Bowie EJ. Factor-X deficiency in amyloidosis: a critical review. *Am J Hematol*. 1981;11(4):443-450.
40. Bortoli R, Monticielo OA, Chakr RM, et al. Acquired factor XI inhibitor in systemic lupus erythematosus--case report and literature review. *Semin Arthritis Rheum*. 2009;39(1):61-65.
41. Ichinose A, Osaki T, Souri M; Japanese Collaborative Research Group (JCRG) on AH13 (supported by the Japanese Ministry of Health, Labor, and Welfare). Clinical features of 32 new Japanese cases with autoimmune haemorrha-philia due to anti-factor XIII antibodies. *Haemophilia*. 2015;21(5):653-658.
42. Yan MTS, Rydz N, Goodyear D, Sholzberg M. Acquired factor XIII deficiency: a review. *Transfus Apheresis Sci*. 2018;57(6):724-730.
43. Bajaj SP, Rapaport SI, Barclay S, Herbst KD. Acquired hypoprothrombinemia due to non-neutralizing antibodies to prothrombin: mechanism and management. *Blood*. 1985;65(6):1538-1543.

44. Mulliez SM, De Keyser F, Verbist C, et al. Lupus anticoagulant-hypoprothrombinemia syndrome: report of two cases and review of the literature. *Lupus*. 2015;24(7):736-745.
45. Tefferi A, Nichols WL, Bowie EJ. Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med*. 1990;88(2):184-188.
46. Rodgers GM, Corash L. Acquired heparinlike anticoagulant in a patient with metastatic breast carcinoma. *West J Med*. 1985;143(5):672-675.
47. de Prost D, Katlama C, Pialoux G, Karsenty-Mathonnet F, Wolff M. Heparin-like anticoagulant associated with AIDS. *Thromb Haemost*. 1987;57(2):239.
48. Dufrost V, Risse J, Malgras A, et al. Unexpected cause of bleeding. *Am J Med*. 2017;130(9):e387-e388.
49. Marchili MR, Santoro E, Marchesi A, Bianchi S, Rotondi Aufiero L, Villani A. Vitamin K deficiency: a case report and review of current guidelines. *Ital J Pediatr*. 2018;44(1):36.
50. Forkin KT, Colquhoun DA, Nemergut EC, Huffmyer JL. The coagulation profile of end-stage liver disease and considerations for intraoperative management. *Anesth Analg*. 2018;126(1):46-61.
51. Kershaw G, Favaloro EJ. Laboratory identification of factor inhibitors: an update. *Pathology*. 2012;44(4):293-302.
52. Collins P, Chalmers E, Hart D, et al; United Kingdom Haemophilia Centre Doctors' Organization. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. *Br J Haematol*. 2013; 162(6):758-773.
53. Baudo F, Collins P, Huth-Kühne A, et al; EACH2 registry contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood*. 2012;120(1):39-46.
54. Kruse-Jarres R, St-Louis J, Greist A, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant), porcine sequence, in subjects with acquired haemophilia A. *Haemophilia*. 2015;21(2):162-170.
55. Tarantino MD, Cuker A, Hardesty B, Roberts JC, Sholzberg M. Recombinant porcine sequence factor VIII (rpFVIII) for acquired haemophilia A: practical clinical experience of its use in seven patients. *Haemophilia*. 2017;23(1):25-32.
56. Zeitler H, Ulrich-Merzenich G, Goldmann G, Vidovic N, Brackmann HH, Oldenburg J. The relevance of the bleeding severity in the treatment of acquired haemophilia - an update of a single-centre experience with 67 patients. *Haemophilia*. 2010;16(102):95-101.
57. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
58. Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *N Engl J Med*. 2017;377(9): 819-828.
59. Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *J Thromb Haemost*. 2015;13(5):743-754.
60. Cardinal M, Kantaridis C, Zhu T, et al. A first-in-human study of the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-06741086, an anti-tissue factor pathway inhibitor mAb, in healthy volunteers. *J Thromb Haemost*. 2018;16(9):1722-1731.
61. Polderdijk SG, Adams TE, Ivanciu L, Camire RM, Baglin TP, Huntington JA. Design and characterization of an APC-specific serpin for the treatment of hemophilia. *Blood*. 2017;129(1):105-113.
62. Prince R, Bologna L, Manetti M, et al. Targeting anticoagulant protein S to improve hemostasis in hemophilia. *Blood*. 2018;131(12):1360-1371.
63. Biguzzi E, Siboni SM, Peyvandi F. Acquired Von Willebrand syndrome and response to desmopressin. *Haemophilia*. 2018;24(1):e25-e28.
64. Lavin M, Ryan K, White B, Byrne M, O'Connell NM, O'Donnell JS. A role for intravenous immunoglobulin in the treatment of acquired Von Willebrand syndrome associated with IgM gammopathy. *Haemophilia*. 2018;24(1):e22-e25.
65. Thachil J, Hay CR, Campbell S. Tamoxifen for recurrent bleeds due to angiodysplasia in von Willebrand's disease. *Haemophilia*. 2013;19(5): e313-e315.
66. Bowers M, McNulty O, Mayne E. Octreotide in the treatment of gastrointestinal bleeding caused by angiodysplasia in two patients with von Willebrand's disease. *Br J Haematol*. 2000;108(3):524-527.
67. Sohal M, Laffan M. Von Willebrand disease and angiodysplasia responding to atorvastatin. *Br J Haematol*. 2008;142(2):308-309.
68. Alikhan R, Keeling D. Von Willebrand disease, angiodysplasia and atorvastatin. *Br J Haematol*. 2010;149(1):159-160.
69. Lim MY, McCarthy T, Chen SL, Rollins-Raval MA, Ma AD. Importance of pharmacokinetic studies in the management of acquired factor X deficiency. *Eur J Haematol*. 2016;96(1):60-64.
70. Thompson CA, Kyle R, Gertz M, Heit J, Pruthi R, Pardanani A. Systemic AL amyloidosis with acquired factor X deficiency: a study of perioperative bleeding risk and treatment outcomes in 60 patients. *Am J Hematol*. 2010;85(3):171-173.
71. Franchini M, Frattini F, Crestani S, Bonfanti C. Acquired FXIII inhibitors: a systematic review. *J Thromb Thrombolysis*. 2013;36(1):109-114.
72. Collins P, Baudo F, Knoebl P, et al; EACH2 registry collaborators. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood*. 2012;120(1):47-55.
73. Tiede A, Klamroth R, Scharf RE, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. *Blood*. 2015;125(7):1091-1097.
74. Lavin M, Brophy TM, Rawley O, et al. Lenalidomide as a novel treatment for refractory acquired von Willebrand syndrome associated with monoclonal gammopathy. *J Thromb Haemost*. 2016;14(6): 1200-1205.
75. Khatri NV, Patel B, Kohli DR, Solomon SS, Bull-Henry K, Kessler CM. Lenalidomide as a novel therapy for gastrointestinal angiodysplasia in von Willebrand disease. *Haemophilia*. 2018;24(2):278-282.