



New therapies for von Willebrand disease

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The management of von Willebrand disease (VWD) is based upon the dual correction of the primary hemostasis defect, due to the inherited deficiency of von Willebrand factor (VWF), and of the secondary defect of factor VIII coagulant activity (FVIII:C), due to the loss of binding and stabilization by VWF of this intrinsic coagulation factor in flowing blood. The traditional therapeutic weapons (the synthetic derivative of the antidiuretic hormone desmopressin and plasma-derived VWF/FVIII concentrates) are able to transiently correct both the defects. With the goal of tackling the primary deficiency in the disease, that is, VWF, but at the same time exploiting the normal capacity of patients to produce FVIII, the novel approach of replacing only VWF was implemented in the last 10 years. Following the manufacturing of a concentrate fractionated from human plasma and of one obtained by recombinant DNA technology, clinical studies have shown that VWF-only products correct not only the primary VWF deficiency but also the secondary FVIII:C deficiency. The demonstrated efficacy of these products in various clinical situations and, ultimately, in such a hemostasis-challenging context as surgery testifies to the effectiveness and safety of this approach. It remains to be seen whether VWF-only products are efficacious and safe in still-unexplored situations, such as use in children; the long-term use for prophylaxis; and in recurrent gastrointestinal (GI) bleeding due to angiodysplasia, a major therapeutic problem in VWD.

Learning Objectives

- Understand the advantages and limitations of currently available therapies for VWD, that is, desmopressin and FVIII/VWF plasma-derived concentrates
- Outline why therapeutic products containing only VWF have been produced through plasma fractionation and recombinant DNA technology
- Describe the potential applications of these new products in the management of GI tract bleeding associated with angiodysplasia

Clinical case

A 76-year-old Egyptian woman was referred to us after having been evaluated on multiple occasions by hematology and gastroenterology specialists in her native country and European centers specializing in bleeding disorders. In the last 10 years, she had suffered from multiple episodes of melena that recurred with high frequency and were poorly handled with red cell transfusion and cryoprecipitate, the only treatments available in her country. Several attempts at endoscopic control of bleeding were unable to prevent recurrences, owing to the presence of multiple angiodysplasia lesions in the upper gastrointestinal (GI) tract. Previously diagnosed with inherited type 3 von Willebrand disease (VWD; she was born from a consanguineous marriage), this diagnosis was confirmed by laboratory findings of unmeasurable plasma levels of von Willebrand factor (VWF) antigen and VWF ristocetin cofactor (VWF:RCo) and a moderately severe

deficiency of factor VIII coagulant activity (FVIII:C; 5 U/dL). After excluding that her unresponsiveness to therapy was due to the development of anti-VWF alloantibodies, we started a regimen of regular prophylaxis by infusing her every other day with 50 U/kg of a pasteurized plasma-derived VWF/FVIII concentrate. Throughout an observation period of 3 months, the patient continued to have episodes of melena despite the fact that VWF:RCo plasma levels were kept at trough levels no lower than 40 to 50 U/dL. At the same time, her FVIII:C plasma levels reached very high values, sometimes in excess of 200 U/dL. With this concern and on the basis of reports on the antiangiogenic properties of high-dose statins and the successful use of atorvastatin in the context of angiodysplasia in VWD,^{1,2} we attempted to stop the formation of new GI tract lesions by administering this drug at the high dosage of 80 mg daily. The patient tolerated this treatment for 3 to 4 months with no severe side effect except moderate muscle pain in her legs, but recurrent episodes of GI bleeding continued unabated in frequency, and there was endoscopic evidence of new angiodysplasia lesions. The patient returned to Egypt after stopping atorvastatin and we recommended that she implement a prophylactic regimen with cryoprecipitate or VWF/FVIII concentrate at home if available. We were subsequently informed that she died suddenly after a myocardial infarction had occurred following an episode of GI bleeding that had caused severe anemia.

Introduction

Patients with VWD, the most frequent inherited bleeding disorder together with hemophilia A, are enjoying excellent treatment and

This article was selected by the *Blood Advances* and *Hematology* 2019 American Society of Hematology Education Program editors for concurrent submission to *Blood Advances* and *Hematology* 2019. It is reprinted from *Blood Advances* 2019, Volume 3.

Conflict-of-interest disclosure: P.M.M. has acted as principal investigator in the frame of the phase 1 study of vonicog alfa (see Mannucci et al²⁵) and contributed substantially to drafting and writing the first clinical study on the plasma-derived Wilfactin (Borel-Derlon et al²¹).

Off-label drug use: None disclosed.

a life expectancy at birth similar to that of men and women in the general population, at least in high-income countries. Quality of life is acceptable, although the most clinically severe patients must contend with an inevitable degree of medicalization and frequent hospitalizations. With this broadly optimistic background, in the last 10 years new therapeutic weapons became available, and I shall outline what can be expected from them, with particular emphasis on how and when they may help to meet still partially unfulfilled needs, such as the management of recurrent GI tract bleeding due to angiodysplasia.

Rationale of therapy in VWD and determinants of its efficacy

In VWD, the bleeding tendency is primarily due to the inherited deficiency or dysfunction of the multimeric glycoprotein VWF, which causes abnormal platelet-vessel wall interactions and the defective formation of the platelet plug (primary hemostasis).^{3,4} VWF defects are also associated with enhanced angiogenesis because the protein functions as an inhibitor of this process. A number of patients (particularly those with type 1, type 2N, and the most severe, type 3) also have a mild to moderate plasmatic deficiency of FVIII:C.^{3,4} The degree of this FVIII deficiency (which is secondary to the primary genetic deficiency of VWF, ie, the physiological binding protein that stabilizes this intrinsic coagulation protein in the blood)⁵ has implications for the clinical phenotype of these patients because it plays an important role in the occurrence of soft tissue, joint, and postoperative bleeding, which adds to the typical and more frequent bleeds from mucosal sites due to reduced or dysfunctional platelet-dependent VWF activity. In general, both VWF and FVIII must be replaced to prevent or stop bleeding,^{3,4} even though the correction of FVIII:C plasma levels is the main determinant of the control of soft tissue bleeding (hematomas, hemarthroses) and postoperative bleeding, whereas the correction of the platelet-dependent VWF activity is the main determinant of the control of mucosal bleeding (epistaxis, menorrhagia, GI bleeding).^{3,6} With these preambles, until recently, the mainstay of treatment of VWD was the replacement of both the deficiencies of VWF and FVIII, and both the traditionally available weapons (ie, desmopressin and VWF/FVIII plasma-derived concentrates) are able to achieve this dual correction.^{3,4}

Desmopressin

The administration (IV, subcutaneous, or intranasal) of this synthetic derivative of the antidiuretic hormone vasopressin acts mechanistically by releasing transiently in patient plasma VWF and FVIII from endothelial storage sites, thus being an autologous form of replacement therapy.⁷ The advantages of desmopressin are unlimited availability, relatively low cost, and the avoidance of allogeneic plasma-derived products, which, albeit seldom, may cause hypersensitivity reactions and the occurrence of anti-VWF alloantibodies.⁸ It is the treatment of choice in patients with type 1 VWD, who in ~80% of cases transiently achieve adequate posttreatment plasma levels of FVIII:C and VWF:RCo, at 30 to 40 U/dL or more.^{9,10} This notwithstanding, there is evidence that desmopressin is underused, even in type 1 patients who should be responsive to this agent. The main reason is likely to be the active promotion of the use of commercial concentrates rather than the adverse effects of this medication, because these are generally mild (facial flushing, transient tachycardia, and hyponatremia).^{11,12} Desmopressin triggers the early postinfusion release in plasma of ultra-large VWF multimers physiologically present only in platelet and endothelial VWF, but this multimeric fraction, highly active in primary hemostasis, is

Table 1. Average ratios of VWF/FVIII content in plasma-derived concentrates licensed for the therapy of VWD

	VWF:RCo/FVIII:C ratio, IU/dL
Alphanate	0.91
Biostat	2.0
Fandhi	1.04
Haemate P/Voncento	2.45
Immunate	0.90
Wilate	0.90

Data derived and modified from Castaman et al.¹⁴

rapidly cleaved from plasma. Thus, the risk of thrombosis is small but desmopressin should be used with caution in older people and in those at high risk of atherothrombosis. Limitations of desmopressin are its poor effectiveness in VWD types other than type 1 and 2N, because in type 3 no VWF nor FVIII is released in plasma from storage sites; in type 2, the drug releases and raises a functionally defective VWF. Another limitation is the development of tachyphylaxis, so that closely spaced and repeated administrations are often associated with a progressive decrease of the degree of FVIII and VWF responses, which may become a problem in patients requiring sustained high levels of these moieties at the time of surgery or severe bleeds.^{3,4} Because the increase of FVIII and VWF elicited by desmopressin is transient, to obtain a sustained effect, Ragni et al¹³ chose to evaluate recombinant interleukin 11, which increased these moieties nearly twofold in patients with VWD unresponsive to desmopressin.¹³ This was a phase 2 study and further data are needed to better focus the role of this approach to obtain a therapeutic response more sustained than that of desmopressin.

VWF/FVIII-containing products

Originally manufactured and licensed to treat FVIII-deficient patients with hemophilia A, the copurification from human plasma of VWF with FVIII can be used in VWD to replace both the deficiencies in cases unresponsive or inadequately responsive to desmopressin. Until recently, these products were the mainstay of treatment in patients with types 3, 2 (2A, 2B, 2M), and in the relatively rare type 1 cases that respond to desmopressin with insufficient plasma levels; in those who show a rapid plasma clearance of FVIII and VWF; and in those who need repeated infusions, particularly in the surgical context. The commercially available products licensed for use in VWD are generally labeled for the VWF content (measured as VWF:RCo) and that of FVIII (measured as FVIII:C); the diverse average ratios of the 2 activities are shown in Table 1.¹⁴ There are several guidelines on the dosages to be used in various clinical situations.^{3,4,14-16}

Are there limitations for these products? There is no longer a safety issue, because they are manufactured from human plasma using methods of viral inactivation that avoid posttransfusion transmission of bloodborne agents. At variance with hemophilia A, the development of neutralizing anti-VWF alloantibodies is very rare in VWD, occurring in patients with type 3 due to large gene deletions or other relatively rare null mutations.⁸ In all of the available products, the multimeric structure of VWF is abnormal because it lacks, to a variable degree, the higher-molecular-weight multimers (HMWMs)^{14,17} owing to their cleavage during plasma fractionation by the naturally occurring VWF protease ADAMTS13.¹⁸ There is some evidence that the defect of HMWMs, most active in platelet-vessel wall interactions, may render these products less effective in bleeds from mucosal sites (see "Clinical case"). Notwithstanding their

Table 2. Main comparative features of the therapeutic products containing VWF only

Characteristics	Production method	
	Plasma fractionation	Recombinant technology
Commercial name	Wilfactin/Willfact	Vonvendi/Veyvondi
Generic name	Human VWF	Vonicog alfa
Licensing	EMA	FDA and EMA
VWF HMWMs	Deficient	All present
Ultra-large VWF multimers	Absent	Present
VWF:RCo/FVIII:C, IU/dL, ratio	>60	FVIII: only traces

EMA, European Medicines Agency; FDA, US Food and Drug Administration.

defective multimeric structure, available concentrates secure an effective surgical hemostasis, because the attainment of adequate plasma levels of FVIII:C is a more crucial determinant of perioperative hemostasis than those of platelet-dependent VWF measurements.⁶ During not only surgery but also in other clinical situations needing multiple therapeutic doses, the exogenous FVIII infused adds to the endogenous FVIII normally synthesized in VWD and stabilized by VWF replacement, thereby leading to the accumulation of FVIII:C in plasma and sometimes to very high levels of this activity (see “Clinical case”).³⁻⁵ The ensuing increased risk of thrombosis (mainly venous thromboembolism)¹⁹ can be controlled by laboratory monitoring of FVIII:C levels, thus modulating replacement frequency, with the goal of avoiding values above 150 IU/dL, but at the same time attaining and maintaining plasma levels sufficient to ensure hemostasis.

All in all, these time-honored products have dramatically improved, together with desmopressin, the management of VWD. Notwithstanding this satisfactory scenario, therapeutic products containing only VWF, that is, the protein primarily deficient in VWD, have been developed. This new approach, based upon the biological plausibility that replacement therapy with exogenous VWF is followed by the endogenous correction of any clinically relevant FVIII deficiency, was first implemented through the production of a plasma-derived concentrate, and then with a product manufactured by recombinant DNA technology (Table 2).

Plasma-derived VWF-only concentrate

Licensed in several European countries for the prevention and treatment of bleeding episodes in VWD, Wilfactin/Willfact is manufactured using a purification method based upon ion exchange and affinity chromatography and a triple net of viral inactivation methods (solvent detergent, dry heating, and nanofiltration).²⁰ Practically devoid of FVIII and thus with a much higher VWF:RCo/FVIII:C ratio than plasma-derived products (Tables 1 and 2), the concentrate was first evaluated clinically in the frame of a multicenter study of 50 patients with clinically severe forms of VWD, judged unsuitable for desmopressin owing to their too low plasma levels of VWF:RCo and FVIII:C.²¹ In the frame of 139 spontaneous bleeding episodes, an 89% rate of excellent or good responses was reported and only one-third of the episodes needed the upfront addition of a FVIII-containing plasma product. The 94 scheduled surgical procedures were successfully handled using only the VWF product given 12 to 24 hours before surgery to take advantage at the time of the operation of the spontaneous postinfusion FVIII:C rise. This preoperative approach was feasible in the context of this study, but it remains to be seen how

practical it is in real-life situations. For 13 emergency surgical procedures, a priming dose of a FVIII-containing product had to be coadministered with the first VWF infusion in order to cope with baseline FVIII:C considered inadequate for surgical hemostasis, that is, lower than 40-50 IU/dL.²¹ On the whole, this pioneer clinical study on the use of the VWF-only replacement demonstrated the feasibility, efficacy, and safety of this therapeutic approach in VWD.

Recombinant VWF-only concentrate

Because VWF is a huge protein of formidable structural complexity, its large-scale manufacturing by recombinant DNA technology needed a long time to overcome several process hurdles. Baxter-Baxalta (subsequently purchased by Shire and the latter in turn by Takeda) chose for its production a genetically engineered Chinese hamster ovary cell line,²² the same used to produce a widely used recombinant FVIII (Advate). Vonicog alfa (brand name Veyvondi in Europe, Vonvendi in the United States) is a highly purified product, being manufactured in the absence of animal or human proteins in the cell culture medium and with only trace amounts of FVIII in the final formulation (Table 2).^{22,23} Because vonicog alfa is produced in absence of the VWF-cleaving protease ADAMTS13, a peculiar feature is that it contains not only all of the VWF multimers present in normal plasma, but also the ultra-large fraction^{22,23} physiologically present in endothelial cells and platelets but not in normal plasma (Table 2).^{13,17,24} These peculiarities have the potential advantage of supplying bleeding patients with the multimeric fraction most active in primary hemostasis,²³ but as for desmopressin it raised concerns that the very high activity of ultra-large VWF multimers on platelet-vessel wall interactions may enhance platelet adhesion, aggregation, and thrombus formation in vivo. This concern was dissipated first by in vitro and in vivo animal studies and ultimately by a phase 1 study in VWD patients, showing that ultra-large multimers were rapidly cleaved postinfusion by the enzymatic activity of patients' own plasma ADAMTS13.²⁵ Indeed, no thrombotic complication has been described in the early postinfusion period, at a time when these hyperactive multimers circulate for a short time period. It remains to be established whether vonicog alfa should be used with caution in older patient at high risk of atherothrombosis.

Several studies carried out in patients with VWD have shown the efficacy and safety of this product and led to its therapeutic licensing: a phase 1 first-in-human study, mainly designed to characterize the pharmacokinetic and pharmacodynamic profile of vonicog alfa in 32 patients with clinically severe disease (type 3 or severe type 1)²⁵; a phase 3 study in clinically severe cases treated on demand for several types of bleeding episodes^{26,27}; and, more recently, another phase 3 study, designed to evaluate efficacy and safety in the context of elective surgical procedures.²⁸

The main findings of the phase 1 study were attained in the frame of a crossover comparison with the widely used pasteurized, plasma-derived VWF/FVIII concentrate. The recombinant VWF-only product vonicog alfa showed a slightly longer plasma half-life for the platelet-dependent activity measured as VWF:RCo (16.3 vs 14.4 hours) and as VWF:antigen (25.5 vs 17.9).²⁵ In addition, the analysis of the area under the plasma concentration curve indicated that the concomitant administration of vonicog alfa with a recombinant FVIII produced by the same manufacturer (Advate) stabilized the endogenously produced FVIII:C to a greater extent than following the plasmatic VWF/FVIII product.²⁵ This improved stabilization helped to support the potential for vonicog alfa to achieve hemostatic levels of FVIII:C even when

this recombinant VWF is administered alone, with no concomitant source of FVIII.

The main goal of the first phase 3 study, besides that of confirming the pharmacokinetics of vonicog alfa, was to establish the efficacy of this therapeutic product to stop bleeding in 192 episodes developing in 37 patients with clinically severe forms of VWD.^{26,27} The outcome was rated by the investigators as excellent in 96% of the episodes and good in 3%, a single infusion being sufficient to stop bleeding in 82%.²⁶ The study also included a crossover design that demonstrated that the pharmacokinetic profile of recombinant VWF was not affected by the concomitant administration of a recombinant FVIII product, should the latter be needed in some clinical situations to secure adequate FVIII:C plasma levels. When vonicog alfa was infused alone, FVIII:C activity reached clinically satisfactory levels within 6 hours postinfusion, and hemostatically effective plasma levels of this coagulant activity were sustained for 72 hours.

These findings provided a robust clinical rationale for the design of another phase 3 study meant to assess the efficacy of the product in a hemostasis-challenging setting such as elective major (n = 10), minor (n = 4), and oral (n = 1) surgery.²⁸ This study was seminal to establish the efficacy and safety profile of this product in patients with clinically severe forms of VWD. Two additional phase 3 studies are ongoing to explore the currently unlicensed use of vonicog alfa for prophylaxis (NCT02973087) and in pediatric patients (NCT02932618).

Advantages and potential limitations of VWF-only products

The manufacturing by recombinant DNA technology of VWF, the largest and most complex plasma protein, is a monument of ingenuity. The aforementioned clinical trials established not only that vonicog alfa is efficacious and safe, but also that the traditional use in VWD of therapeutic products such as desmopressin and VWF/FVIII concentrates that concomitantly correct the dual VWF and FVIII deficiency is not a paradigm, and that the exogenous replacement of the primarily deficient VWF makes possible the stabilization of endogenous FVIII in plasma with modalities and timings compatible with clinical use. However, a word of caution is warranted for this as for any new drug. Vonicog alfa was efficacious and safe in the frame of ideal clinical conditions, but a large amount of data on effectiveness and safety in postmarketing, real-life situations remain to be accrued. Moreover, expensive new drugs are competitive only if proven to result in better patient outcomes than traditional drugs. Vonicog alfa, and also the plasma-derived VWF-only product, may be particularly useful in patients who need regular prophylactic replacement therapy because their choice would make it possible to skip the administration of exogenous FVIII present in VWF/FVIII products and perhaps avoid the attainment of very high plasma levels of FVIII:C. However, at present, the license of the product does not include this indication. Elective surgery is another situation in which the advantages of VWF-only products may materialize, particularly at the time of hypercoagulability-associated conditions such as pregnancy/parturition, as well as in patients undergoing cancer and orthopedic surgery, that is, all situations characterized by an increased risk of thromboembolism that would suggest avoiding high plasma levels of FVIII:C. Another potential situation is the management of recurrent bleeding due to angiodysplasia in the GI tract,²⁹ that is, one of the few situations of currently unsatisfactory management of VWD epitomized by the clinical case.

Angiodysplasia in VWD

Angiodysplasia-related GI bleeding in VWD was described by pioneer Armand Quick,³⁰ but Fressinaud and Meyer³¹ were the first to tackle this clinical problem in the context of a multicenter survey. Their most important observation was that recurrent GI bleeding occurred more frequently not only in patients with type 3 VWD but also in those with types 2A and 2B, particularly with aging. It has been longstanding clinical experience that, in VWD, the response of GI bleeding to on demand replacement therapy is generally poorer than for other clinical manifestations, and that this symptom is the most common cause of hospitalization.³² This was confirmed by the observational multicenter study of Berntorp and Windyga,³³ who showed that the average dosage of a plasma-derived VWF/FVIII concentrate needed to control GI bleeds was approximately double that needed to successfully handle other bleeding episodes (Table 3).³³ That it is more difficult to manage GI than other bleeds is also confirmed by Abshire et al,³⁴ who found that the rate of favorable outcomes in the context of regular prophylaxis was lower for GI than joint bleeding (49% vs 86%), the 2 most frequent reasons for adopting this therapeutic regimen in VWD.^{32,34} In addition, GI bleeds required more frequent prophylactic infusions.³²

Which are the putative reasons for the lower efficacy of both on-demand and prophylactic replacement therapy in GI tract bleeding due to angiodysplasia? The tortuous morphology of the vascular malformations may need a fully intact VWF multimeric structure to stop bleeding in blood vessels characterized by flow conditions of high shear rate.²⁹ The mechanistic role of the multimeric structure is indirectly supported by the observation made in natural clinical models by Castaman et al,³⁵ who observed that, at the same level of severity of VWF and FVIII plasma defects, GI bleeding was twice more frequent in patients with type 2A than in those with type M VWD, the only measurable difference between these patients being the VWF multimeric structure, normal in type 2M and deficient in HMWMs in type 2A. The role of an intact multimeric structure is also supported by the observation that GI bleeding due to angiodysplasia occurs not only in inherited VWD types characterized by the lack or defect of HMWMs, but also in the acquired forms of the disease, similarly characterized by a multimeric defect.^{36,37} Considering the uncertain therapeutic value of antiangiogenic medications such as thalidomide and lenalidomide^{38,39} and also of high-dose statins as witnessed by the clinical case,^{1,2} vonicog alfa may be evaluated as a novel option to stop bleeding, with the biological plausibility that this is the only form of replacement therapy in VWD endowed with an intact multimeric structure and even, albeit transiently, with ultra-large, highly hemostatically effective multimers.^{23,40} Perhaps a product containing ultra-large multimers may also halt the development of new angiodysplasia lesions because ultra-large VWF multimers inhibit neoangiogenesis.⁴¹ Yet, too few cases of GI bleeding were treated with apparent success in the frame of the reported phase 3

Table 3. Poor clinical efficacy of a plasma-derived VWF/FVIII concentrate in the control of GI bleeding

Daily dose needed for bleeding control, IU/kg

GI bleeds: 44
Other bleeds: 29

Treatment days needed for bleeding control

GI bleeds: 4.2
Other bleeds: 1.8

Data derived from Berntorp and Windyga.³³

study²⁷ to substantiate these views and recommend this expensive therapeutic approach for the many difficult cases similar to that described in the clinical case. A specifically designed trial is warranted, multinational and multicenter in order to accrue an adequate sample size in the context of this relatively rare complication, and based upon the randomized patient allotment to vonicog alfa or to the pasteurized VWF/FVIII concentrate, preferably chosen as a comparator because it is relatively less deficient in HMWMs than the other plasma-derived products. Even though more data on the outcome of GI bleeding treated with vonicog alfa are being currently collected in the frame of registries promoted by the manufacturer,⁴² a robust answer on the efficacy of vonicog alfa only stems from a randomized study, because data on efficacy are currently based only on the indirect comparison between plasma-derived VWF/FVIII and recombinant VWF-only products. It is difficult to envisage that such a study is going to be supported by the manufacturers of the therapeutic products; as such, this is the typical scenario for an independent trial that should be promoted and funded independently by agencies such as the National Institutes of Health and the European Union.

Future developments

The weapons currently available for the clinician to manage patients with VWD are satisfactory, at least in countries that can afford to make them available. On the whole, the health care burden of VWD is lower than that of hemophilia, and a recent estimation suggests that the number of patients who need replacement therapy is smaller by one-tenth.⁴³ As in hemophilia, the multiple therapeutic options available should allow personalized management according to the problems, needs, and lifestyle of each patient. At variance with hemophilia, pharmacokinetic-guided dosing of replacement therapy is more difficult, owing to the complexities and variability of the different types of VWD and of the dual factor deficiency.⁴³ By the same token, cure by gene therapy is much less advanced than for the hemophilias. Earlier, Wang et al⁴⁴ used a mouse model and viral gene vectors to achieve a partial correction of VWF levels in knockout mice. More recently, high and long-term expression of VWF has been achieved in a mouse model of severe VWD using an integrative transposon-mediated approach.⁴⁵ However, whether these pioneer approaches are feasible, safe, and efficacious in humans is far from being established.

Finally, all of the aforementioned therapeutic weapons are based upon factor replacement therapy, as is typical for inherited bleeding disorders. However, adjunctive therapies such as the antifibrinolytic agents aminocaproic and tranexamic are useful when given alone or in addition to replacement therapies, particularly for mucosal symptoms such as epistaxis, oral bleeding, and menorrhagia.

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