Historical, current and future treatments for von Willebrand disease

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Abstract

Von Willebrand disease (VWD) is a heterogeneous group of defects characterized by a spectrum of bleeding symptoms ranging from mild to severe, which remain difficult to identify and assess quantitatively. Despite significant advances in our understanding of the pathophysiology of the disease, diagnosis and management remain challenging. This review examines the therapeutic landscape for VWD, discussing historical treatments, recent advancements and prospects. Decades of clinical evidence supporting the efficacy of replacement therapy will be critically presented, and preclinical data for emerging options will be examined. For many years, the standard of care for VWD has involved replacement therapy with blood-derived products and desmopressin. The introduction of recombinant von Willebrand factor represents a more recent development compared to other recombinant factors, and its use in certain populations of patients is still under investigation. Despite being relatively new, innovative therapeutic options are being explored and developed to address patients' unmet needs. Some of these therapies are currently undergoing or nearing clinical evaluation, while others remain in the preclinical phase of development. After years of neglected attention, innovation in the treatment of VWD is now rapidly expanding.

Introduction

Von Willebrand disease (VWD) is the most prevalent inherited bleeding disorder, affecting up to 1% of the general population, although symptomatic disease is less common. It is caused by defects in von Willebrand factor (VWF), a multimeric glycoprotein essential for primary hemostasis and stabilization of coagulation factor VIII (FVIII).[1] VWD results from quantitative deficiencies (types 1 and 3) or qualitative defects (type 2) of VWF.[2,3]

Type 1, the most common form accounting for approximately 70-80% of cases, is characterized by a partial quantitative deficiency. Subtype 1C group defects are associated with increased clearance of VWF. Type 2 includes subtypes 2A, 2B, 2M, and 2N, each with a different qualitative defect in VWF function. Type 3 is the rarest and most severe form, marked by a near-total absence of VWF, often associated with severely reduced FVIII levels.

Symptoms range from mild mucocutaneous bleeding (e.g., epistaxis, menorrhagia) to life-threatening hemorrhages in severe forms. The diagnosis involves assessment of personal and familial bleeding history and specialized laboratory assays measuring VWF antigen (VWF:Ag) and activity (VWF:RCo or more recent activity tests), and FVIII activity (FVIII:C). For the past two decades, treatment options have primarily focused on replacement strategies with plasma-derived (pd) and recombinant (r) VWF, or with desmopressin (DDAVP), which induces the release of VWF (and FVIII) from intracellular storage granules within endothelial cells, resulting in a temporary rise of the protein concentrations in circulation. Additional approaches, not specific to VWD, include antifibrinolytics and hormonal therapies.

In contrast to these general methods, innovative strategies are being developed and tested to enhance and correct specific molecular defects in VWF functions, targeting groups of patients with similar molecular abnormalities and clinical presentations.

This review aims to discuss the history of currently available therapies, including pdVWF, rVWF and desmopressin, highlighting available clinical evidence. Innovative strategies will be described, exploring preclinical studies and a few case reports outlining their specific mechanisms of action

as potential future therapeutic approaches for VWD patients (Figure 1). A separate manuscript in this review series focuses on the management of women, girls and people with the potential to menstruate affected by VWD. Therefore, this subject will not be discussed thoroughly here.

Plasma-derived products to treat von Willebrand disease

At the time Erik von Willebrand[4] published his hallmark article on the first families with a bleeding disorder, currently known as VWD, no hemostatic treatment was available. He did however describe how patients were managed in a follow-up paper in 1931: "One must ensure the most favorable hygienic conditions possible, especially a varied mixed diet with plenty of vegetables and fruit".[5] He reported a favorable outcome and reduction of bleeding in this detailed description of a patient treated with vitamin A supplements. Direct blood transfusion also appeared to be a very effective hemostatic agent for severe and life-threatening bleeding in cases of hemorrhagic diathesis.[5] In the following decades, during the time that the exact pathogenesis of VWD was still unknown, patients were treated with blood transfusions, and later with various blood-derived products, including fresh-frozen plasma, plasma fractions and cryoprecipitate. This was initiated by the laboratory findings of Blömback in 1957, who purified fibrinogen from human plasma fractions and observed that, besides fibrinogen, anti-hemophilia globulin (AHG, now called FVIII) remained as a precipitate. Subsequently, Blömback and Nillson[6] found that AHG was recovered in Fraction I-0 and remained stable. This human plasma fraction (I-0) was used to treat patients with hemophilia, and later also patients with VWD.[7] In the 1960s, after Pool[8,9] discovered the therapeutic effect of cryoprecipitate in patients with hemophilia A, patients with VWD were also treated with this plasma-derived product. In 1971 several research groups discovered that AHG actually consisted of two proteins, a smaller fragment now known as FVIII and a larger fragment, consisting of multimers, which they designated as factor VIII-related antigen, now called VWF.[10,11] After obtaining more insight into the pathophysiology of the disease and the characteristics and functions of VWF, it became obvious that both VWF and FVIII are reduced in VWD patients. Since both proteins are needed for proper hemostasis, both deficient proteins should be replaced at the time of bleeding or before medical interventions. In the following years, several pdFVIII products containing VWF were developed for the treatment of both hemophilia A and VWD. Unfortunately, cryoprecipitate and the newly developed FVIII/VWF plasma products manufactured from large pool-blood donations were contaminated by viruses, resulting in hepatitis B, hepatitis nonA-nonB (hepatitis C)

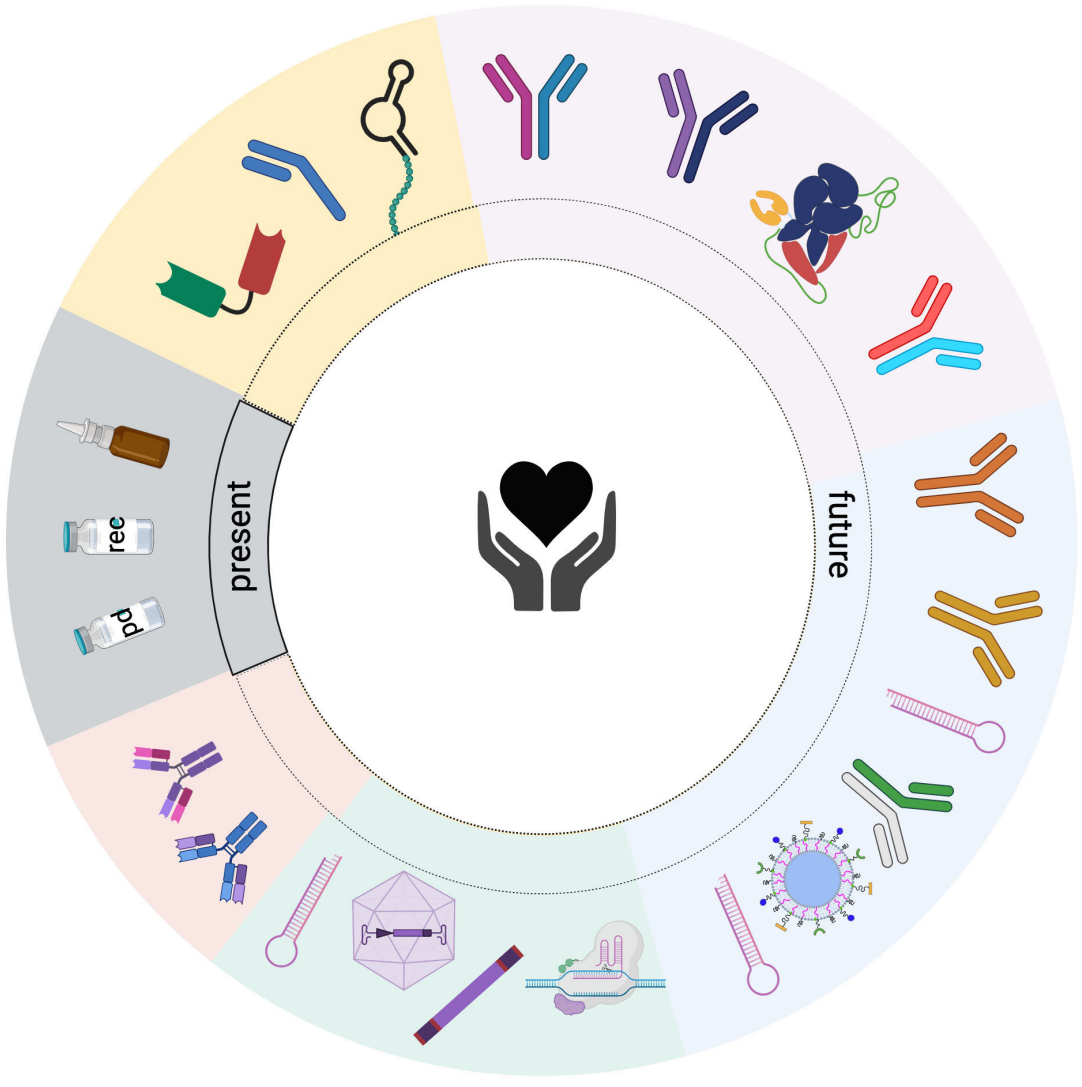

Figure 1. Overview of current and future therapies for von Willebrand disease. For the past two decades, limited treatment options have been available, essentially consisting of replacement strategies with plasma-derived and recombinant von Willebrand factor (more recently), or desmopressin. These therapies were quite efficient at arresting bleeding episodes, but were still associated with burden and low quality of life in patients. Future novel options are intended to implement personalized approaches designed for groups of patients with similar genotypic or phenotypic characteristics and for specific types and locations of bleeding. Moreover, to address the current limited use of prophylaxis, most new therapies focus on bleeding prevention (prophylactic administration) rather than acute management. Figure created in BioRender. Casari, C. (2025) https://BioRender.com/trf8ys0

and later also human immunodeficiency virus infections in many patients with hemophilia and VWD.[12-14] These devastating transmissions called for new purification methods to ensure virus safety.

VWF/FVIII concentrates are mostly purified by heparin ligand chromatography or ion-exchange chromatography.[15] This is now followed by viral inactivation steps using solvent/detergent and dry heat. Concentrates are administered once or twice daily by intravenous injections or by continuous infusion. pdVWF/FVIII concentrates are still the most used treatment for patients with severe VWD worldwide. There are several pdVWF/FVIII concentrates available (Table 1), with a large variation in VWF:RCo/VWF:Ag and VWF:RCo/FVIII:C ratios and multimer patterns. The VWF:RCo/VWF:Ag ratios vary from 0.29 to 2.4 and the VWF:RCo/FVIII:C ratios vary from 0.81 to >10.[16,17] It is, therefore, important to take into account the exact VWF and FVIII contents in the specific concentrate that is used.[18] Haemate P® (Humate P®; CSL Behring), one of the first virus-safe products, is a pasteurized FVIII/VWF product that was developed more than 40 years ago and is still in use.[19] It has the most physiological multimeric composition and a high VWF:FVIII ratio.

Dosing of VWF/FVIII concentrate was historically based only on the FVIII:C content of the product. Therefore, during treatment with VWF/FVIII concentrate the only parameter to perform dose adjustment was FVIII:C, because the VWF:RCo activity assay was time-consuming, and the results were not readily available. Nowadays, both FVIII and VWF can be measured more easily using various automated assays.[20] Therefore, monitoring of both FVIII and VWF levels during treatment with factor concentrates has become more routine.[21,22] During surgery or repeated VWF/FVIII concentrate infusions, it is recommended that both VWF activity and FVIII:C are measured daily to tailor the dose of concentrates and ensure that patients

Table 1. Comparison of plasma-derived and recombinant concentrates.

Name (Manufacturer)	Product type	VWF:RCo/FVIII	Multimer composition	Plasma provenance	Availability	Viral inactivation
Plasma-derived concentrates						
Haemate P/ Humate-P (CSL Behring)	VWF/FVIII	~2.4:1	L- M- H-MWM, HMWM 94% of NHP, abnormal triplet structure	USA, Germany, Austria, Canada	Europe, USA, Canada,	S/D and pasteurization 60°C 10 h
Voncento/ Biostate/Aleviate (CSL Behring)	VWF/FVIII	~2-2.4:1	L- M- H-MWM, HMWM 86%	Australia, New Zealand, Malaysia, Singapore, Hong Kong, USA	EU, UK, Australia, New Zealand, Asia-Pacific, Latin America	TNBP/Triton X-100 and dry heat 80°C 72 h
Wilate/Eqwilate (Octapharma)	VWF/FVIII	~1:1	L- M- H-MWM but <HMWM, intact triplet structure	Sweden, Austria, Germany, USA	EU, USA, Canada	TNBP/Triton X-100, and terminal dry heat, 100°C, 120 min, at controlled residual moisture
Immunate/ Alphanate/Fanhdi (Grifols)	VWF/FVIII	~1.2:1	L- M- H-MWM but reduced HMWM 4-32%, abnormal triplet structure	USA, Spain, Czech Republic, Slovakia	USA, EU, Latin America	TNBP/polysorbate 80 and dry heat, 80°C, 72 h
Immunate (Baxalta/Takeda)	VWF/FVIII	~0.75/1	L- M- H-MWM, normal triplet structure	USA, Austria, Czech Republic, Germany, Sweden, Switzerland, Norway	Europe, Asia	S/D; vapor-heat, 60°C, 10 h at 190 mbar
Wilfactin/Willefact (LFB)	VWF/(low FVIII)	~60:1	L- M- H-MWM, normal triplet structure	France/EU	Western Europe/ Nordic countries	S/D; dry heat, 80°C, 72 h; nanofiltration (35 nM)
Recombinant VWF						
Veyvondi/Vonvendi (vonicog alpha) (Takeda)	VWF (no FVIII)	-	UL-MWM present; L- M- H-MWM (no triplet structure)	-	EU, USA, Australia	-

Online Registry of Clotting Factor Concentrates, Third edition, 2016, WFH eLearning Platform. Multimer composition references: Gritsch H *et al.*[38] - Riddell A *et al.*[96] - Harper P *et al.*[97] - Kannicht C *et al.*[98] VWF:RCo: von Willebrand factor activity; FVIII: factor VIII; VWF: von Willebrand factor; L- M- H-MWM: low- medium- high-molecular-weight multimers (HMWM are generally considered as >10mer); NHP: normal human plasma; S/D: solvent/detergent; TNBP: tri-N-butyl phosphate (lipid solvent); UL-MWM: ultra-large molecular weight multimers (not present in normal human plasma).

reach the target levels of VWF and FVIII.[22] It is, however, still disputed whether normalization of VWF, FVIII or both is needed to achieve adequate hemostasis in VWD patients.[3,23]

In the latest guidelines on VWD from the American Society of Hematology (ASH), International Society on Thrombosis and Haemostasis (ISTH), World Federation of Hemophilia (WFH) and National Foundation of Hemophilia (NHF),[22] recommendations are given regarding the dose and duration of administration of VWF/(FVIII) concentrate. Typically, a dose of 40-80 IU VWF:RCo per kg body-weight is administered, aiming for aVWF:RCo and FVIII:C of ≥50 IU/dL for at least 3 days in individuals undergoing major surgery.

Patients with more severe VWD also have low baseline FVIII due to the fast clearance of FVIII in the absence of VWF. Therefore, correction of FVIII levels is needed in the case of emergency surgery or severe bleeding. However, since patients with VWD have normal endogenous synthesis of FVIII, FVIII levels will increase during treatment with plasma-derived products containing both VWF and FVIII, which may even lead to supraphysiological levels of FVIII. This can increase the risk of venous thrombosis in these individuals.[24,25]

Despite the wide use of pdVWF concentrates in patients with VWD, data on their efficacy during surgery, delivery and in the case of bleeding have mostly been obtained from case series, and large, randomized studies are still lacking.[26,27]

Plasma-derived pure von Willebrand factor concentrates

To reduce the risk of high levels of FVIII, pure plasma VWF concentrate can be used. Pure VWF is currently available in some countries (Wilfactin®, LFB) in Europe and may be preferred in patients who are at high risk of thrombosis, for instance, patients who have had prior thrombotic events, or patients with other predisposing factors for thrombosis. Experience with this product has been reported in several retrospective case series and it has been shown to be effective and safe.[28] Pure VWF concentrates increase VWF levels immediately to the desired target level, while FVIII levels will increase gradually over time by binding of endogenous FVIII to the administered exogenous VWF. Most patients reach FVIII levels of >60 IU/dL 6 to 8 hours after infusion of pure VWF.[28] Therefore, the first dose of pure VWF can be given the evening prior to planned surgery. If pure VWF concentrates are administered to patients with severe VWD in emergency situations or shortly before surgery, additional FVIII is given to normalize FVIII levels immediately.

Long-term prophylaxis with plasma-derived concentrates

In 2005 the first case-series from Sweden was reported on the use of long-term prophylaxis with pdVWF/FVIII concentrates in VWD patients with a severe bleeding phenotype, including severe nose bleeds, joint bleeding or gastrointestinal bleeding.[29] This study presented data of 35, mainly VWD type 3, patients with VWF and FVIII levels <10 IU/dL, who were treated with long-term prophylaxis with a pdFVIII concentrate containing VWF (Haemate-P®). In a second small, prospective study on prophylaxis in only 12 patients with severe VWD, VWF concentrate (50 VWF:RCo IU/kg 2 or 3 times per week) reduced mucosal and joint bleeds.[30] The PRO.WILL study included 19 VWD patients of whom 12 completed the study. Patients were randomized to intervention with VWF/FVIII concentrate (60 VWF:RCo units/kg every 2 or 3 days; Fanhdi®, Grifols, Spain) or on-demand treatment. Bleeding was reduced with prophylaxis (rate ratio=0.24, 95% confidence interval: 0.17-0.35), which also significantly reduced the number of spontaneous epistaxis.[31]

The current ASH-ISTH-WFH-NHF VWD guidelines acknowledge that prophylactic treatment reduces the risk of bleeding and potentially improves quality of life. The conditional recommendation was to use long-term prophylaxis rather than no prophylaxis in patients with VWD with a history of severe and frequent bleeds.[22] After the guidelines were published, the largest study to date, including 43 VWD patients, was completed and showed that long-term prophylaxis with Wilate® (Octopharma, Lachen, Switzerland), a VWF/FVIII concentrate with a ratio of 1:1, (20-40 IU VWF/kg 2 or 3 times per week) reduced the number of bleeds by 84.4%. Other recent studies on the use of prophylaxis with plasma-derived concentrates confirmed the findings that prophylaxis reduces the number of bleeds.[32]

Side-effects of plasma-derived concentrates

Several side-effects of pdVWF/FVIII products have been recorded. The main documented side-effects are mild allergic reactions, as reported earlier by the European Haemophilia Safety Surveillance system (EUHASS).[33] As mentioned above, viral transmission has occurred in the past, but has not been reported with the current products in patients with VWD.[33]

A rare but severe side-effect of treatment with plasma-derived concentrates is the development of alloantibodies against VWF. In a recent study in patients with VWD type 3, inhibitors developed in 6% of patients treated with exogenous VWF.[34] Inhibitor development is frequently associated with potentially life-threatening anaphylactic responses, which makes treatment of these patients challenging. Thrombosis is rarely reported in VWD patients receiving pdVWF/FVIII products, and this may be related to high levels of FVIII. Therefore, it is recommended to avoid the combination of extended increased VWF and FVIII levels >150 IU/dL.[22]

Desmopressin

In 1977 Mannucci *et al.*[35] reported for the first time the use of desmopressin (DDAVP) for treatment of VWD. Administration of desmopressin, a vasopressin analog, leads to transient increases of FVIII and VWF in the circulation.

FVIII and VWF levels are increased 2- to 3-fold, which makes it safe to perform dental extractions and minor surgery in VWD patients. Desmopressin can be administered intravenously, subcutaneously or intranasally. It is recommended that a test dose be given to newly diagnosed VWD patients to assess the individual response. DDAVP is administered at a dose of 0.3 μg/kg subcutaneously or infused intravenously over 30 minutes, and VWF and FVIII are measured immediately prior to and 1 and 4 hours after administration.[22] Desmopressin can also be administered intranasally at a dose of 150 μg in both nostrils. Most patients treated with desmopressin encounter mild side-effects such as flushes or tachycardia, but more serious side-effects, including acute myocardial infarction and ischemic stroke, have also been described sporadically.[36] Desmopressin is still the most frequently used treatment in patients with type 1 VWD. If the test shows a positive functional response, it can be used in individuals with type 2 VWD (2A, 2M, 2N), usually for minor bleeds, despite VWF being altered. Desmopressin is not useful in type 3 VWD because stores are virtually empty, and it is contraindicated in VWD type 2B, in which it can induce or worsen thrombocytopenia due to platelet-aggregate formation subsequent to 2B/VWF release. In most patients with severe forms of VWD or major bleeding VWF(/FVIII) concentrates are needed.[2,22]

Recombinant von Willebrand factor

Concerns about blood-borne pathogen transmission and product variability in plasma-derived concentrates have prompted the development of recombinant alternatives (Table 1).

Recombinant VWF (rVWF), known as vonicog alfa (VONVENDI® in the USA, Japan, Australia, and VEYVONDI® in Europe, UK, Switzerland) offers a purified, consistent, and pathogen-free alternative, addressing several limitations of plasma-derived products.

rVWF is produced using Chinese hamster ovary cells via recombinant DNA technology. It consists of full-length human VWF and is free of any other human or animal plasma proteins, reducing the risk of immunological reactions and transmissible infections.

Notably, rVWF contains a full spectrum of multimers, including ultra-large multimers, which are critical for effective hemostasis and are depleted in pdVWF products due to processing. Ultra-large multimers enhance platelet adhesion and aggregation, potentially translating into superior clinical outcomes.[37,38]

Recombinant von Willebrand factor to treat von Willebrand disease

rVWF was approved for on-demand treatment and control of bleeding episodes, perioperative bleeding management and routine prophylaxis in severe VWD.

Market access varies by region. It is widely available in the USA, while reimbursement for prophylactic use is still being negotiated in some European countries. As more long-term data become available, broader guideline adoption is expected.

A clinical advantage of rVWF relies is its use in patients with elevated baseline FVIII levels or underlying thrombotic risk factors. Since rVWF contains very little or no FVIII, it enables hemostatic management without the risk of accumulation of FVIII, which could otherwise predispose patients to thromboembolic events.[37,38] FVIII must be co-administered during initial bleeding episodes or emergency surgery, particularly in patients with type 3 VWD or when baseline FVIII levels are low. Pharmacokinetic studies have shown that rVWF has a biphasic elimination profile with a terminal half-life of approximately 15-20 hours for VWF: RCo activity. Following administration of rVWF, VWF activity typically increases within 30-60 minutes, while FVIII levels rise more gradually, reaching peak concentrations around 6-12 hours after infusion, as endogenous FVIII is stabilized by circulating rVWF.[39,40] Dose recommendations for acute bleeding or surgery are 40–80 IU/kg of rVWF, with or without FVIII, followed by additional doses guided by clinical response and laboratory monitoring.

rVWF has demonstrated excellent or good hemostatic efficacy in the treatment of bleeding episodes and during surgical procedures in patients with severe VWD.

In a pivotal phase III study by Gill *et al.*[40] patients with severe VWD (types 1, 2, and 3) were treated with rVWF on-demand for a total of 192 bleeding episodes. All bleeding events were controlled effectively, showing rapid cessation of bleeding. The study reported excellent (97%) or good (3%) hemostatic efficacy with 100% treatment success.

In the surgical setting, the use of rVWF provided effective hemostatic coverage during the perioperative period for VWD patients undergoing both minor and major procedures. Co-administration with a recombinant or pdFVIII concentrate may be necessary in those cases in which baseline FVIII levels are low or rapid correction is needed, especially in emergency interventions.[40,41] In a phase III study by Peyvvandi *et al.*[42] patients undergoing elective surgery received a preoperative rVWF dose of 40-60 IU/kg. If FVIII:C levels were below target (≥30 IU/dL for minor/oral surgery or ≥60 IU/dL for major surgery) 3 hours before surgery, rFVIII was (co-)administered prior to the surgery. Intra- and postoperative infusions were individualized to maintain target trough levels. Overall and intraoperative hemostatic efficacy was rated excellent (73.3% and 86.7%, respectively) or good (26.7% and 13.3%, respectively) in all patients. Most rVWF infusions (89.4%) were administered alone, resulting in hemostatically effective levels of endogenous FVIII within 6 hours, which were sustained for 72-96 hours (70%, N=7/10).[42]

Long-term prophylaxis with recombinant von Willebrand factor

Routine prophylaxis in VWD has gained traction, especially in patients with type 3 VWD and those with severe type 2 with recurrent joint or gastrointestinal bleeding. The 2021 ASH/ISTH/NHF/WFH guidelines[22] recommend considering prophylaxis with VWF concentrates in patients with a high bleeding burden or poor quality of life. In the case of rVWF, individualized regimens (e.g. 50-80 IU/kg twice weekly) are used in patients with severe disease or frequent bleeding. rVWF is suited for this role because of its reliable multimer profile and dosing flexibility. Multiple phase III trials have reinforced evidence of its clinical benefit as prophylaxis. One trial (NCT02973087) showed that long-term prophylaxis with rVWF significantly reduced the bleeding burden in patients with severe VWD, with a strong reduction in spontaneous bleeding episodes compared to on-demand treatment. A *post-hoc* analysis focused on patients with type 3 VWD, showing that switching from on-demand therapy to rVWF prophylaxis led to a 91.6% reduction in the annualized rate of treated spontaneous bleeds. Notably, 84.6% of these patients experienced no spontaneous bleeds requiring treatment during the study period.[43]

Menorrhagia is a frequent and debilitating symptom in women with VWD. rVWF can be effective for the control of menstrual bleeding and during pregnancy-related events, such as delivery and postpartum hemorrhage. However, data from the VWDMin study[44] suggested that rVWF was not superior to tranexamic acid in reducing abnormal uterine bleeding in patients with mild/moderate VWD. The predictable pharmacokinetics and lack of plasma exposure could make rVWF a preferred choice also in sensitive and challenging settings such as gastrointestinal bleeding. However, available data suggest that even rVWF is not always sufficient to control and prevent these severe and recurrent types of bleeding.[2,42]

Safety and side-effects of recombinant von Willebrand factor

The safety and effectiveness of rVWF in individuals aged 18 or younger are currently under investigation in several clinical trials.

rVWF has shown a favorable safety profile[40-43,45] with no inhibitors to VWF or FVIII reported so far. Mild hypersensitivity reactions, such as rash or pruritus, have occurred in a small percentage of patients.[40] Thrombotic events are rare but may occur, especially when rVWF is administered with FVIII in high doses. Therefore, careful monitoring of FVIII:C levels is advised in patients with risk factors for thrombosis (e.g., age >65 years, obesity, cardiovascular disease).

rVWF has represented a significant advancement in the treatment landscape of VWD and ongoing studies continue to refine its role across diverse patient populations. As with all therapies, optimal outcomes rely on individualized treatment plans, careful monitoring, and adherence to evolving clinical guidelines.

Innovative therapeutic strategies

Despite current treatment options being quite efficient in arresting and preventing bleeding episodes, VWD patients still report a high disease-associated burden, negatively impacting their social, school and working life.[46] Quality-of-life studies document increased depression and anxiety, especially in diagnosed women, and an overall low quality of life in VWD patients.[46] Limitations of current treatments include the need for frequent intravenous administrations, recurrent hospital admissions, specialized monitoring, the restricted use of prophylactic regimens and gender disparities, in terms of diagnosis and access to medical attention and appropriate care.[46-48]

Some changes are required to improve the therapeutic management of VWD, aiming at maintaining high efficacy in bleeding prevention and implementing personalized approaches tailored to the needs of the patients and the type and location of the bleeding.

In this context, innovative strategies have been proposed,[48-51] with a few being under clinical investigation and others remaining in preclinical development (Table 2). To address the current limited use of prophylaxis, most new therapies focus on bleeding prevention rather than acute management. Moreover, emerging therapies are not intended to target all VWD patients; rather, they are designed for groups of patients with similar genotypic or phenotypic characteristics and to tackle specific molecular aspects of the disease. Downsides of personalized approaches are the limited number of eligible patients, which can pose significant challenges in designing and conducting clinical trials, and the economic barrier.

New approaches for VWD are described and classified based on their mechanism of action.

Molecules increasing von Willebrand factor levels

KB-V13A12

KB-V13A12 is a bispecific single-domain antibody bridging circulating VWF to albumin. When associated with albumin, VWF is recycled through an FcRn-mediated pathway, increasing VWF half-life and plasma concentration. Importantly, the anti-VWF single-domain antibody is non-inhibitory, and KB-V13A12 did not interfere with VWF functions or ADAMTS13 proteolysis.[52] One single subcutaneous administration (5 mg/kg) of KB-V13A12 in a murine model of VWD type 1 (hVWD1 mice) was associated with a sustained 2-fold increase of VWF (and FVIII) levels for up to 10 days, an improved multimeric profile and normalization of the hemostatic defects in bleeding models.[52,53] It is important to note that in mice, a consistent albeit subnormal rise in VWF/FVIII levels was sufficient to normalize hemosta-

Table 2. Potential future therapies for von Willebrand disease.

Name	Molecule	Mechanism of action	Available studies	Administration	Potential target VWD type	References
Molecules increasing VWF levels						
KB-V13A12	Bispecific single-domain antibody anti-albumin and anti-VWF	Albumin-bridging of VWF and FcRn-mediated recycling of VWF	Murine model of VWD1	SC/prophylactic	VWD1 (VWD2)	52, 53
HMB-002 (Hemab Therapeutics)	Anti-VWF/CK monovalent antibody	FcRn-mediated recycling of VWF	WT-NHP, healthy subjects	IV/SC/ prophylactic	VWD1 (VWD2)	55
BT200/ rondoraptivon pegol (Band Therapeutics)	Pegylated RNA aptamer blocking VWF/GPIbα interaction	Decrease of VWF/FVIII clearance, increase of platelet counts (in thrombocytopenic patients)	Clinical trials/case reports in VWD2B, HA	IV/SC/ prophylactic	VWD1 VWD2B	56, 58-61
Agents enhancing the procoagulant potential						
Emicizumab (Roche/Chugai)	FVIII-mimetic. Bispecific antibody anti-FIXa & anti-FX	Increase of thrombin generation in the absence of FVIII	Case reports in VWD3 patients, murine models of VWD3, VWD2A	SC/prophylactic	VWD with low FVIII (VWD1), VWD3, VWD2N	63-69
BIVV001/ efanesoctocog alfa (Sanofi)	FVIII-mimetic. Fusion protein independent of VWF	Increase of thrombin generation in the absence of FVIII	Clinical trial in VWD3 VWD2N	IV/prophylactic	VWD with low FVIII (VWD1), VWD3, VWD2N	70
Other FVIII mimetics potentially useful for VWD: Mim8 (Novo Nordisk), NTX007 (Chugai/Roche)						
VGA039 (STAR Therapeutics)	Rebalancing-agent. Monoclonal antibody anti-protein S	Rebalance of thrombin generation in the absence of FVIII	NHP model of acquired VWD, clinical trial in VWD (various types)	SC/prophylactic	All VWD types	71-73
Platelet inspired nanoparticles (Haima Therapeutics)	Synthetic functionalized nanoparticles	Increase of platelet adhesion and aggregation	Murine models of VWD3, VWD2B	IV/on-demand	Severe VWD(3), VWD2B Other VWD	75
Other rebalancing and generalized hemostatic agents potentially useful for VWD: ETX-148 (E-Therapeutics), marstacimab (Pfizer), concizumab (Novo Nordisk), fitusiran (Sanofi), SerpinPC (Apcintex Ltd/Centessa Pharmaceuticals), HMB-001 (Hemab Therapeutics), SG-100 (SeraGene Therapeutics)						
Genetic approaches						
siRNA	siRNA targeting VWF unique or common variants	Inhibition of the expression of altered VWF multimers and correction of the dominant-negative effect	Murine models VWD2A, VWD2B	Prophylactic	All VWD genetic variants	80, 84
Gene therapy	Lentivirus	Additional VWF expression/ Increase of VWF levels	Cellular and murine model of VWD3	IV	Quantitative VWF defects	91, 92
Gene therapy	Dual-AAV	Additional VWF expression/ Increase of VWF levels	Murine model of VWD3	IV	Quantitative VWF defects	93
Molecules preventing excessive VWF degradation						
MAb508	Monoclonal antibody anti-VWF/D4	Prevention of excessive ADAMTS13-mediated VWF degradation	Mock circulatory ECMO loop	-	Acquired VWS	94
3H9/17C7	Monoclonal antibodies anti-ADAMTS13	Inhibition of ADAMTS13-mediated VWF degradation	Calf model of acquired VWS	IV	Acquired VWS	95

VWD: von Willebrand disease; VWF: von Willebrand factor; FcRn: neonatal Fc receptor; SC: subcutaneous; WT: wild-type; NHP: non-human primate; IV: intravenous; GPIbα: glycoprotein Ibα; HA: hemophilia A; FVIII: coagulation factor VIII; FIXa: activated coagulation factor IX; FX: coagulation factor X; siRNA: small interfering RNA; AAV: adeno-associated virus; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ECMO: extracorporeal membrane oxygenation device; VWS: von Willebrand syndrome.

sis in bleeding models. In patients, an inverse correlation between VWF/FVIII levels and the bleeding score was reported for patients with type 1 VWD, suggesting that even modest sustained increases in protein levels might reduce bleeding.[54] It should be noted that albumin-fusion proteins generally have a relatively shorter half-life in mice than in humans, due to the shorter half-life of murine albumin compared to that of human albumin. This suggests that the rise in VWF might be more important in humans than in mice. Therefore, KB-V13A12 is a promising prophylactic option for many VWD type 1 patients with low levels of functional VWF. While it has not been tested yet in models of VWD type 2, it could be effective in patients eligible for desmopressin. Advantages include subcutaneous administration, long half-life and unaltered VWF functions. Preclinical studies are ongoing.

HMB-002

HMB-002 is a monovalent antibody that binds to the C-terminal CK domain of endogenous VWF. The modified Fc portion can engage the FcRn-recycling pathway. *In vitro*, the antibody did not interfere with VWF functions and ADAMTS13 proteolysis. Intravenous/subcutaneous administration (10 mg/kg) in cynomolgus monkeys increased VWF/FVIII antigen levels and VWF:RCo activity while leaving multimer profiles unaffected.[55] HMB-002 could represent a prophylactic option for VWD type 1 patients. An interventional phase I study in adults with type 1 VWD (NCT06754852) was started early in 2025. Similarly to KB-V13A12, HMB-002 has not yet been evaluated in models of type 2 VWD.

BT200/rondoraptivon pegol

BT200/rondoraptivon pegol is an optimized pegylated RNA aptamer that binds to the VWF/A1 domain derived from ARC1779. It was first designed as an anti-thrombotic agent for its capacity to inhibit the VWF-GPIbα interaction, thereby decreasing platelet adhesion and aggregation.[56,57] A pilot trial in patients with VWD type 2B showed that ARC1779 could counteract desmopressin-induced thrombocytopenia, suggesting that it interferes with VWF elimination,[58] and next-generation BT200 was tested in five VWD type 2B patients. Low doses of BT200 increased VWF/FVIII levels and, in thrombocytopenic patients, also improved platelet counts and the multimeric profile. The inhibitory effects were predominant at higher doses, and only minor spontaneous bleeds and minor thrombotic complications were reported.[59,60]
BT200 is particularly interesting for its ability to increase platelet counts in complex cases of VWD type 2B. Recently, it was successfully administered peri-interventionally with or without replacement therapy to elevate platelet counts during interventions and post-procedurally.[61]
While beneficial effects are undoubted in some patients, BT200 still maintains inhibitor potential toward VWF, and close monitoring should be considered.

Agents enhancing the procoagulant potential

Procoagulant approaches, mainly developed for patients with hemophilia A, include FVIII mimetics and general hemostatic agents that enhance FVIII activity, rebalance the pro- and anti-coagulant equilibrium or improve platelet adhesion and aggregation.

Emicizumab and factor VIII mimetics

Emicizumab is a bispecific monoclonal antibody that simultaneously binds activated factor IX and factor X, thereby partially mimicking FVIII cofactor activity. Emicizumab has revolutionized the clinical management and quality of life of many people with hemophilia A.[62] In 2019, a first clinical case documented the off-label use of emicizumab in a pediatric patient with severe VWD type 3 with anti-VWF alloantibodies,[63] rekindling the question of whether restoring FVIII-like activity improves or corrects the hemostatic response in these patients. Since then, several VWD type 3 patients with or without anti-VWF antibodies and different bleeding characteristics have been treated off-label with emicizumab, with regimens similar to those applied to hemophilia patients. Importantly, emicizumab not only enhanced the hemostatic capacity of these VWD patients but also significantly improved their quality of life.[64-68] Not surprisingly, breakthrough bleeding occasionally occurred and sometimes required additional treatments with recombinant activated factor VII, rFVIII, or pdVWF/FVIII.[63–65,67] Generally, the follow-ups reported have been short (1-12 months), except for one patient with severe VWD who developed gastrointestinal bleeding and was then switched to off-label emicizumab. Only one bleeding episode was reported during 5 years of treatment, with a concomitant reduction of VWF inhibitor to undetectable levels.[69]
Ryu *et al.*[70] have reported the first successful surgical management (multiple teeth extraction) using BIVV001/efanesoctocog alfa (one preoperative dose) in a patient with VWD type 2N and coronary artery disease.
Similarly, other FVIII mimetics (Mim8, NXT007) could be interesting prophylactic options for some VWD patients. Phase I clinical studies have been initiated for emicizumab (NCT05500807) and BIVV001/efanesoctocog alfa (NCT04770935), but no results have yet been presented.
Advantages of FVIII mimetics include subcutaneous administration, except for BIVV001, long half-life, and the existence of clinical data in patients with hemophilia A.

VGA039

VGA039 is a monoclonal IgG4 antibody inhibiting the cofactor activity of protein S to activated protein C and tissue-factor pathway inhibitor. *In vitro*, VGA039 enhanced thrombin generation in plasma samples from patients with various types of VWD,[71] and, in a non-human primate with acquired VWD, it improved hemostatic response in a labial mucosa puncture assay.[72] In the early stage of the VIVID2 open-label phase I study (NCT05776069), seven adult pa-

tients with VWD (1 with VWD type 1, 1 with VWD type 2A, 2 with VWD type 2M and 3 with VWD type 3) with FVIII activity ≤50 IU/dL received a single dose of 3 or 4.5 mg/kg of the antibody. In patients receiving the higher dose, thrombin generation was enhanced to levels observed in healthy volunteers for about 4 weeks and annualized bleeding rates decreased. No grade ≥2 or drug-related adverse events were reported.[73]

Other rebalancing molecules

Other rebalancing agents with potential effects in VWD include marstacimab and concizumab, antibodies inhibiting tissue-factor pathway inhibitor; fitusiran, a short interfering (si)RNA targeting antithrombin; SerpinPC, a serin-protease inhibitor of activated protein C; and ETX-148, a siRNA targeting protein Z-dependent protease inhibitor.[51,74]

Platelet-inspired synthetic nanoparticles (SynthoPlate)

Synthetic platelet nanoparticles are transfusable lipid vesicles decorated with peptides to mimic some platelet functions. Early versions of synthetic platelets designed to improve platelet adhesion and aggregation displayed peptides binding VWF, collagen and activated αIIbβ3. In physiological conditions, synthetic platelets have no biological activity, while at sites of vascular injury, they collaborate with endogenous platelets and improve the hemostatic response. Synthetic platelets were tested *ex vivo* and *in vivo* in murine models of VWD types 3 and 2B, significantly improving hemostasis in a tail-clip assay.[75] Milder effects in VWD type 2B were probably associated with the thrombopathy in these mice.[76,77]

Synthetic platelets are potential general hemostatic agents for short-term/peri-interventional treatment (alone or in combination with other treatments) which could be beneficial for all VWD types, with or without inhibitors. Advantages include high stability, room temperature storage, lyophilized formulation and the potential to expand their functions.

Other generalized approaches

Other generalized approaches include siRNA that target plasminogen (SG-100) and suppress fibrinolysis[78] and HMB-0001, a bispecific antibody that accumulates activated factor VII and promotes factor X activation.[48]

Genetic approaches

Short interfering RNA/gene editing

siRNA are short RNA molecules inducing RISC-mediated RNA degradation based on sequence complementarity and can, theoretically, target any gene of interest. The first siRNA-based studies in VWD used variant-selective siRNA in cellular models[79] and, a few years later, in a murine model[80] mimicking heterozygous VWD. These proof-of-concept studies aimed to demonstrate that it is possible to modulate the dominant-negative effect of heterozygous VWF variants with silencing approaches. Later, allele-selective siRNA were proposed to target common variants (single nucleotide polymorphisms) present on the same allele of a heterozygous pathologic variant, with the potential to target patients with different disease-causing alterations with the same siRNA.[81] This approach was tested in cellular models,[82,83] and in an a*d-hoc* murine model of VWD type 2B administered endothelial-directed lipid nanoparticles loaded with siRNA.[84]

Despite some specific limitations of each strategy, siRNA-based approaches are rarely associated with complete inhibition of their target, failing to completely prevent the expression of altered VWF and its dominant-negative effect.

Besides siRNA, CRISPR/Cas9-based gene editing approaches also have the potential to counteract dominant-negative variants and have been tested in cellular models of VWD.[85] These are rapidly evolving personalized technologies with great potential to cure VWD but are still in early preclinical development.

Other genetic approaches/gene therapy

Early attempts at gene therapy for VWD relied on hepatocyte-mediated expression of VWF by hydrodynamic gene transfer or a “Sleeping Beauty” transposon system in murine models of VWD with the major challenge being correct multimerization.[86-90] Such techniques remain invaluable tools for research studies.

Lentiviral-mediated expression of VWF was first achieved in canine VWD type 3 endothelial colony-forming cells[91] and in VWF knock-out mice through intrahepatic administration in newborn mice,[92] but these early studies were not pursued. Adeno-associated virus-based gene therapy for VWD is limited by the large size of *VWF* cDNA, which exceeds the packaging capacity of adeno-associated virsuses. An endothelial cell-targeted dual vector strategy resulted in long-term expression of VWF in VWF knock-out mice.[93] However, expression levels were too low to be clinically relevant.

Further studies are required to improve viral-mediated VWF expression and to understand if and how gene therapy can overcome the dominant-negative effect of VWF variants, which will not be prevented by endothelial expression of the normal transgene.

Molecules preventing excessive von Willebrand factor degradation

ADAMTS13-mediated degradation is enhanced in patients carrying VWD type 2A (group II) variants and in some cases of acquired von Willebrand syndrome, secondary to aortic stenosis or to support with mechanical circulatory devices. Mab508 is a monoclonal anti-VWF/D4 antibody interfering with the docking of ADAMTS13 on VWF. This antibody prevented excessive VWF degradation without interfering with physiological degradation.[94] 3H9 and 17C7 are anti-ADAMTS13 monoclonal antibodies that entirely block ADAMTS13 activity, thereby preventing VWF degradation in *ex vivo* loops. 17C7 was tested in a preclinical calf model of acquired von Wille-

brand syndrome and partially reversed the loss of VWF high molecular weight multimers.[95]
The major difference between anti-VWF and anti-ADAMTS13 antibodies is the partial *versus* complete inhibition of ADAMTS13 activity, with potentially higher risks of thrombotic thrombocytopenic purpura-like adverse events with 3H9 or 17C7. The latter may, therefore, require closer medical surveillance.

Concluding remarks

Desmopressin remains the standard treatment for patients with mild VWD type 1 with partial quantitative deficiencies of VWF. For patients with moderate to severe VWD, plasma-derived and recombinant VWF are effective and safe options. Despite efficacy in arresting and preventing severe bleeding events, these treatments have some limitations, including their short duration of action, requiring frequent administration, and they may be less effective in certain bleeding situations, resulting in a high burden and low quality of life for the patients. To address these challenges and better meet the needs of the patients, innovative therapies tailored to groups of patients with the same molecular defect or bleeding phenotype are currently under investigation. While clinical studies in VWD patients remain challenging, some of these new options have been evaluated in clinical trials or are close to entering clinical evaluation. These advancements are paving the way for more personalized treatments for VWD.

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