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Review

Evolution of replacement therapy for von Willebrand disease: From plasma fraction to recombinant von Willebrand factor

Flora Peyvandi^{a,*}, Peter Kouides^b, Peter L. Turecek^c, Edward Dow^d, Erik Berntorp^e

^a *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*

^b *Mary M. Gooley Hemophilia Center Inc., University of Rochester School of Medicine, Rochester, NY, USA*

^c *Baxalta Innovations GmbH, a member of the Takeda group of companies, Vienna, Austria*

^d *Norfolk Center for Cancer Care & Hematology, Brockton, MA, USA*

^e *Centre for Thrombosis and Hemostasis, Lund University, Malmö, Sweden*

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ABSTRACT

The diagnosis and treatment of von Willebrand disease (VWD) are challenging, in part because patients exhibit a wide range of bleeding patterns and manifestations (e.g. epistaxis, gingival bleeding, heavy menstrual bleeding, gastrointestinal bleeds, postoperative bleeding, hemarthroses) and in part because many tests are required to make an accurate diagnosis. Factor replacement therapies for VWD are the mainstay of treatment for patients who do not respond to desmopressin. They have gradually evolved from crude preparations of plasma proteins to plasma-derived concentrates containing both von Willebrand factor (VWF) and factor VIII (FVIII). However, varying amounts and quality of VWF and varying content of FVIII have contributed to the lack of a standardized approach to replacement therapy. More recently, the treatment of VWD has undergone a slow yet significant change from plasma-derived VWF/FVIII concentrates with VWF:ristocetin cofactor (RCo)/FVIII ratios ≤ 1 , to those with VWF:RCo/FVIII ratios > 10 , to a recombinant VWF. This article reviews the evolution of factor replacement therapy for patients with VWD that has occurred over the last several decades. The availability of a greater variety of factor replacement therapies poses a challenge in terms of a standard algorithm of care but may help overcome the limitations of earlier treatments and allow treatment personalization according to individual patient needs.

1. Introduction

Since its initial description in 1926, von Willebrand disease (VWD) has posed a diagnostic and therapeutic challenge [1]. VWD is the most common inherited bleeding disorder in the world, with an estimated prevalence of symptomatic disease of ~ 1 in 1000 individuals [2,3]. VWD results from a deficiency or a defect in von Willebrand factor (VWF), a multimeric plasma glycoprotein responsible for platelet aggregation and adhesion [3]. The three main types of VWD are type 1, a partial quantitative deficiency of VWF, which is the most common type; type 2, a qualitative VWF defect, which is less common and is divided into 4 subtypes (2A, 2B, 2M, 2N), depending on the specific functional defect; and type 3, a virtually complete deficiency of VWF, which is the least common type [4]. Assays of plasma VWF include measurements of VWF functional activity (VWF:ristocetin cofactor [RCo]), VWF level (VWF:antigen [Ag]), factor VIII coagulant activity (FVIII:C), collagen

binding (VWF:CB), and characterization of the VWF multimeric profile (VWF multimers) [2,5]. Although all of these assays are used to establish a correct diagnosis of VWD, it is primarily the FVIII:C assay, and sometimes the VWF:RCo assay, that is used to evaluate and monitor replacement therapy.

The numerous VWF phenotypic presentations may require the use of different treatments, depending on the particular clinical situation [4,5]. Consequently, there is a need for optimal treatment based on personalized, comprehensive, lifelong care [5].

1.1. Overview of the use of desmopressin in VWD

For many patients with VWD, endogenous recruitment of VWF and factor VIII (FVIII) with desmopressin is a frequent treatment choice [6]; however, desmopressin is effective only if adequate and functionally normal cellular VWF is present [5]. Thus, the overall clinical response

* Corresponding author at: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, University of Milan, Department of Pathophysiology and Transplantation, Via Pace 9, Milan 20122, Italy.

E-mail address: info@florapeyvandi.eu (F. Peyvandi).

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to desmopressin is poor or absent in patients with type 3 VWD or variants of type 2 VWD (e.g. patients with altered VWF-dependent platelet adhesion [types 2B and 2M], high-molecular-weight VWF multimer deficiencies or abnormalities [type 2A], or decreased binding affinity for FVIII [type 2N]) [5], and patients with more severe type 1 VWD (VWF:RCO activity < 10 IU/dL or FVIII activity < 20 IU/dL) [7,8]. In addition, the treatment response to desmopressin in the subset of patients with type 1 VWD with markedly decreased VWF survival in plasma may be inadequate or transient [9], although desmopressin can be recommended as first-line therapy for minor surgery and bleeding in most patients with type 1 VWD [5]. However, desmopressin is limited by tachyphylaxis [2], and prospective data correlating the biologic response to desmopressin with efficacy are lacking. Concerns about adverse events (e.g. hyponatremia) may also deter the use of desmopressin [6]. Hematologists may prefer VWF replacement over desmopressin in certain clinical situations (e.g. childbirth, major surgery, children < 2 years of age, elderly patients with a history of heart disease, and patients with extensive comorbidities) [4]. Most plasma-derived concentrates for the treatment of VWD contain both VWF and FVIII in varying proportions; this has implications for the dosing of each product, which must consider both VWF:RCO units as well as FVIII units [4,5]. Recombinant VWF (rVWF) does not contain FVIII and it is only necessary to coadminister FVIII with the initial infusion of rVWF in patients where the baseline plasma FVIII:C level is < 40% (or unknown) or in situations where a rapid correction of hemostasis is needed (such as acute hemorrhage, severe trauma, or emergency surgery) [10].

1.2. Evolution of factor replacement therapies for VWD

Replacement therapies for VWD have evolved slowly over the past several decades (Fig. 1 [1,11,12]) compared with those for less common inherited bleeding disorders, such as hemophilia [1]. The earliest factor replacement therapies for VWD were crude plasma protein preparations, such as plasma fraction I-O, developed in 1956, which restored bleeding time and FVIII levels and was characterized by giving an early rise in endogenous FVIII levels caused by the decreased FVIII clearance associated with the infusion of VWF [1]. In 1964, it was found that crude preparations derived from plasma cryoprecipitate were effective and easy to produce, and plasma cryoprecipitate was widely used for many years thereafter [1]. However, as with fraction I-O, its use carried a risk of transmission of blood-borne infections owing to the fact that it was not possible at that time to apply virucidal methods to cryoprecipitate production [1,13].

The need to circumvent this limitation led to the development of more purified plasma-derived concentrates produced using various methods of viral inactivation, starting with pasteurized FVIII/VWF concentrate in 1981 [1]. These concentrates contain varying ratios of VWF to FVIII, specific activities, and half-lives. They also contain

varying proportions of high-molecular-weight VWF multimers (but none contain ultra-large multimers [ULMs]) because of differences in purification and production methods. In vitro data suggest that higher-molecular-weight multimers are physiologically more similar to endothelial cell and platelet VWF [14], have a greater FVIII binding capacity, and are more effective in restoring hemostasis than smaller multimers [15,16]. In addition, ULMs bind glycoprotein Ib (GpIb) of platelets, an interaction that has an important role in hemostasis in the gastrointestinal (GI) tract [17]. Variations in FVIII content and multimer profiles among concentrates may translate to potential differences in efficacy and/or risk of FVIII accumulation along with the potential risk of thrombosis in certain situations [18]. Such differences among concentrates contributed to the lack of a standardized approach to factor replacement in patients with VWD.

More recently, a plasma-derived concentrate with a VWF:RCO/FVIII ratio ≥ 10 (Willfactin/Willfact) was approved in countries outside of the United States, and a human recombinant form of VWF (rVWF) was approved in the United States and Europe for the treatment of VWD. Products that limit a patient's exposure to FVIII allow physicians to treat the primary dysfunction of VWD and to individualize therapy based on the bleed phenotype. This allows for more frequent dosing of VWF if needed, without the risk of accumulation to supranormal levels of FVIII.

In this article, we discuss the evolution of these therapies with assay evaluation, together with the clinical efficacy and safety of the currently available types of factor replacement therapies for VWD, to help clinicians develop a more personalized approach to therapy for the individual patient's needs.

2. Methods

2.1. Classification of therapies for VWD

For our discussion, we have categorized factor replacement therapies for VWD into the following three groups: (1) cryoprecipitate, (2) plasma-derived products with VWF:RCO/FVIII content ratios < 10 and ≥ 10 , and (3) recombinant VWF. For groups 2 and 3, we carried out a systematic literature search of clinical trials in patients with VWD, as described below.

2.2. Search strategy

A PubMed database search (January 2000–March 2017) for clinical trials of factor replacement therapies approved for VWD was performed. Each of the search terms—“Alphanate,” “Fanhdi,” “Humate-P” OR “Haemate-P,” “Voncento” OR “Biostate,” “Wilate,” “Wilfactin” OR “Willfact,” and “rVWF” OR “Vonvendi”—was used in combination (AND) with the term “von Willebrand Disease” OR “VWD.” Retrospective/prospective studies evaluating hemostatic efficacy and safety in diverse VWD patient types were included. Case reports and

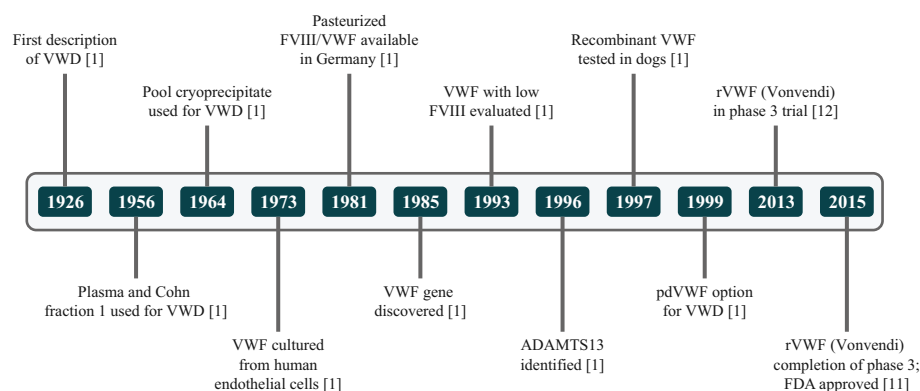


Fig. 1. Developmental progression of therapies available for VWD. Thirty years after VWD was described by Erik von Willebrand, the first plasma fraction replacement therapy was introduced, followed several years later by use of a plasma cryoprecipitate. Subsequent efforts were directed at developing virus-inactivated preparations to deliver VWF to decrease the risk of transmission of infection. The first pdVWF- and FVIII-containing concentrate, a pasteurized preparation, became available in the United States almost 20 years ago [1]. An rVWF became available in late 2015 [11], following completion of its phase 3 trial [12]. FDA, US Food and Drug Administration; FVIII, factor VIII; pdVWF, plasma-derived VWF; rVWF, recombinant VWF; VWD, von Willebrand disease; VWF, von Willebrand factor.

Table 1
Classes of available factor replacement therapies for VWF [5,11,18–28].

Commercial name Generic name	Plasma-derived				Recombinant VWF	
	VWF:RCo/FVIII ratio ≤ 1		VWF:RCo/FVIII ratio > 1 to < 10		VWF:RCo/FVIII ratio ≥ 10	
	Wilate von Willebrand factor/ coagulation factor VIII complex	Alphanate Antihemophilic factor/von Willebrand factor complex (human)	Fanhdi Human coagulation factor VIII/von Willebrand factor complex	Voncento/Biostate Human coagulation factor VIII/human von Willebrand factor	Humate-P/Haemate-P Antihemophilic factor/von Willebrand factor complex (human)	Wilfactin/Wilfact Human von Willebrand factor
Approval VWF:RCo/FVIII:C High-molecular- weight VWF, % NHP	Global 0.8–1.0 N/A	Global 0.82–1.2 29.3	Ex-US 1.29–1.6 31.7	Global 2.04–2.88 93.6	Ex-US > 10 N/A	US and EU Negligible FVIII > 100
ULM Indication in VWD ^a	Absent US: Adults and pediatric patients for on-demand treatment and control of bleeding episodes and for perioperative management of bleeding	Absent US and EU: Adult and pediatric patients in whom desmopressin is ineffective or contraindicated, for prevention and treatment of hemorrhage (EU only) or surgical and/or invasive procedures (US and EU)	Absent EU: Treatment of bleeding and prophylaxis and treatment of hemorrhage or surgical bleeding when desmopressin is ineffective or contraindicated	Absent US: Adults and pediatric patients for treatment of spontaneous and trauma- induced bleeding episodes and prevention of excessive bleeding during and after surgery	Absent EU: Prophylaxis and treatment of hemorrhage or surgical bleeding when desmopressin is ineffective or contraindicated	Present US: In adults with VWD, for on-demand treatment and control of bleeding episodes and perioperative management of bleeding
	EU: Prophylaxis and treatment of hemorrhage or surgical bleeding when desmopressin is ineffective or contraindicated	US: Not indicated for patients with severe VWD (type 3) undergoing major surgery	EU: Prophylaxis and treatment of hemorrhage or surgical bleeding when desmopressin is ineffective or contraindicated	EU: Prophylaxis and treatment of hemorrhage or surgical bleeding when desmopressin is ineffective or contraindicated	EU: Treatment of hemorrhage and surgical bleeding and prevention of surgical bleeding when desmopressin treatment alone is ineffective or not indicated	EU: Treatment of hemorrhage and surgical bleeding and prevention of surgical bleeding when desmopressin treatment alone is ineffective or not indicated

FVIII, factor VIII; FVIII:C, factor VIII coagulant activity; N/A, not available; NHP, normal human plasma; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, VWF ristocetin cofactor; ULM, ultra-large multimers.

^a Specific indications may vary by country; please see individual country prescribing information for specific recommendations.

Table 2
Clinical profiles of factor replacement therapies for VWD.^a

Commercial name t _{1/2} (VWF:RCO), h [11,19,24-26,31,39] Clinical study: efficacy population/VWD types ^b	Plasma-derived					Recombinant VWF	
	VWF:RCO/FVIII ratio ≤ 1	VWF:RCO/FVIII ratio > 1 to < 10	VWF:RCO/FVIII ratio ≥ 10	Humate-P/Haemate-P	Willfactin/Willfact	Humate-P/Haemate-P	Willfactin/Willfact
Wilate 15.8	Alphanate 7.67	Fanhdi 14.4	Voncento/Biostate 13.7	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Bertorp 2009 [32] (N = 44): 1, 2A, 2B, 2 N, 3 Windyga 2011 [50] (N = 32): 1, 2, 3 Batty 2014 [30] (N = 54): 1, 2A, 2B, 2 M, 2 N, 3, acquired	Mannucci 2002 [46] (N = 53): 1, 2A, 2B, 3 Rivard 2008 [47] (N = 39): 1, 2, 3 Federici 2010 [35] (N = 155): 1, 2A, 2B, 2 M, 3	Federici 2002 [36] (N = 22): 1, 2B, 3 Hernandez-Navarro 2008 [40] (N = 60): 1, 2A, 2B, 2 N, 3	Shortt 2007 [48] (N = 43): 1, 2A, 2B, 3 Dunkley 2010 [34] (N = 23): 1, 2A, 2 M, 2 (subtype unknown), 3 Howman 2011 [41] (N = 43): 1, 2A, 2B, 2 M, 2 N Lisitschkov 2017 [45] (N = 21): 1, 2A, 3	Lillicrap 2002 [44] (N = 97): 1, 2A, 2B, 2 N, 2 M, 3, acquired Federici 2007 [37] (N = 100): 1, 2A, 2B, 2 M, 3 Lethagen 2007 [43] (N = 27): 1A, 2A, 2 M, 3 Gill 2011 [38] (N = 35): 1, 2A, 2B, 2 M, 3	Goudemand 2005 [39] (N = 25): 3 or severe Borel-Derlon 2007 [33] (N = 50): 1, 2A, 2B, 2 M, 2 N, 3	Voncento/Biostate 13.7	Willfactin/Willfact 12.4
Khair 2015 [42] (N = 47): 1, 2, 3, acquired Srivastava 2017 [49] (N = 28): 1, 2, 3	Federici 2002 [36]: 92% excellent/good (hemostasis similar to normal/mildly abnormal)	Federici 2002 [36]: 92% excellent/good (hemostasis similar to normal/mildly abnormal)	Lillicrap 2002 [44]: 97% excellent/good (hemostasis achieved/cessation of bleeding)	Federici 2007 [37]: 95% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Bertorp 2009 [32]: 96% excellent/good Batty 2014 [30] 97.9% excellent/good (number of estimated infusions ≤ number required and no additional VWF concentrate required, or ≤ 2 [minor] or ≤ 1.5 × [major] infusions required than estimated and no additional VWF concentrate required)	Mannucci 2002 [46]: 74.7% episodes controlled with 1 infusion; 11.5% controlled with 2 infusions Federici 2010 [35]: 97% excellent/good (hemostasis similar to normal/mildly abnormal)	Federici 2002 [36]: 92% excellent/good (hemostasis similar to normal/mildly abnormal)	Lillicrap 2002 [44]: 97% excellent/good (hemostasis achieved/cessation of bleeding)	Federici 2007 [37]: 95% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Khair 2015 [42]: 97.7% excellent/good (number of estimated infusions vs. number required and no additional VWF concentrate required, or ≤ 2 [minor] or ≤ 1.5 × [major] infusions required than estimated and no additional VWF required)	Federici 2010 [35]: 87% complete prevention	Federici 2010 [35]: 87% complete prevention	Lillicrap 2002 [44]: 100% excellent/good (effective reduction in number of bleeds)	Federici 2007 [37]: 100% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Bertorp 2009 [32]: Significantly reduced bleeding frequency in 16/19 patients; mean bleeding frequency/month decreased from 4.5 (before study entry) to 1.4 with prophylaxis	Federici 2010 [35]: 87% complete prevention	Federici 2010 [35]: 87% complete prevention	Lillicrap 2002 [44]: 100% excellent/good (effective reduction in number of bleeds)	Federici 2007 [37]: 100% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Batty 2014 [30]: Demonstrated similar efficacy to alternative pdVWF/FVIII concentrate after switching	Federici 2010 [35]: 87% complete prevention	Federici 2010 [35]: 87% complete prevention	Lillicrap 2002 [44]: 100% excellent/good (effective reduction in number of bleeds)	Federici 2007 [37]: 100% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4
Khair 2015 [42]: 3 of 4 with type 3 VWD had no	Federici 2010 [35]: 87% complete prevention	Federici 2010 [35]: 87% complete prevention	Lillicrap 2002 [44]: 100% excellent/good (effective reduction in number of bleeds)	Federici 2007 [37]: 100% excellent/good (not different from normal or mildly abnormal hemostasis/partial or delayed control of bleeding)	Goudemand 2005 [39]: - Part 1 (BT): fully/partially corrected (BT ≤ 10 min/shortened between 11 and 15 min) in 86% of patients - Part 2 (BT): transient shortening in 71% of patients	Humate-P/Haemate-P 11	Willfactin/Willfact 12.4

(continued on next page)

Table 2 (continued)

	Plasma-derived		Recombinant VWF		
	VWF:RCo/FVIII ratio ≤ 1	VWF:RCo/FVIII ratio > 1 to < 10	VWF:RCo/FVIII ratio ≥ 10		
Efficacy in surgery ^f	breakthrough bleeding; 1 patient had rash and wheeze following treatment and was switched to original pdVWF/FVII concentrate	Windya 2011 [50]: 96% excellent/good (hemostasis achieved, adequate control)	Mannucci 2002 [46]: 39.7% fully and partially corrected prolonged BT	Median rate of bleeding episodes reduced from 12 in the year before prophylaxis to 3.6 during prophylaxis (77% of patients received Humate-P)	
	Windya 2011 [50]: 96% excellent/good (hemostasis achieved, adequate control)	Batty 2014 [30]: 94.2% excellent/good (blood loss/transfusion similar to normal and no additional doses needed, or slight, not clinically significant, increase in bleeding than expected with no additional doses needed and transfusion requirements similar to normal)	Federici 2002 [36]: 93% excellent/good (hemostasis similar to normal/mildly abnormal)	Lillicrap 2002 [44]: 99% excellent/good (hemostasis achieved/cessation of bleeding)	Borel-Derlon 2007 [33]: 100% excellent/good (in patients with type 3 VWD only, not reported overall)
	Khair 2015 [42]: 95.1% excellent/good (blood loss/transfusion similar to normal and no additional doses needed, or slight, not clinically significant, increase in bleeding than expected with no additional doses needed and transfusion requirements similar to normal)	Rivard 2008 [47]: 95.1% excellent/good on day 0; 91.8% excellent/good on day 1	Hernandez-Navarro 2008 [40]: 94% excellent; 5% good	Federici 2007 [37]: 97% excellent/good (not different from normal or slight transient oozing from surgical wounds)	Peyvandi 2019 [63]: 100% excellent/good for overall and intraoperative hemostatic efficacy (in all patients studied and in patients with type 3 VWD)
	Strivastava 2017 [49]: 96.5% success overall (determined based on a composite assessment algorithm incorporating intraoperative and postoperative assessments)	Federici 2010 [35]: 99% excellent/good (hemostasis similar to normal/mildly abnormal)	Dunkley 2010 [34]:	Lethagen 2007 [43]: 96.3% excellent/good day of surgery (clinical hemostasis within normal limits/slight oozing); 100% excellent/good 1 day after and 14 days after surgery	
	– Major surgery: 95.2% success		– Major surgery: excellent/good in 75% and 25%	Gill 2011 [38]: 91.4% excellent/good (hemostasis similar to normal/mildly abnormal)	
	– Minor surgery: 100% success		– Minor surgery: 93% excellent	Howman 2011 [41]: 90% excellent/good for surgical procedures; 94% excellent/good for NSBs (normal hemostasis, blood loss equivalent to normal or partial but adequate control with no additional product or unplanned treatment required)	
				Lissitchkov 2017 [45]: 100% excellent (during prophylaxis phase)	

BT, bleeding time; FVIII, factor VIII; N/A, not assessed; NSB, nonsurgical bleed; pdVWF, plasma-derived VWF; t_{1/2}, half-life; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:RCo, VWF ristocetin cofactor.

^a Excludes factor replacement therapies with low VWF activity and/or clinical studies in limited number of patients with VWD.

^b VWD types generally classified as type 1 (partial quantitative deficiency of VWF); type 2A (decreased VWF-dependent platelet adhesion and selective deficiency of high-molecular-weight VWF multimers), type 2B (increased affinity of VWF for platelet glycoprotein 1b), type 2M (decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight VWF multimers), type 2N (markedly decreased binding affinity for FVIII), type 3 (virtually complete deficiency of VWF).

^c Definitions of efficacy (excellent/good) included if provided in publication.

studies with < 20 patients (Immunate, Dried Factor VIII Fraction Type 8Y) were excluded.

2.3. Literature search results

The available factor replacement therapies for patients with VWF are outlined in Table 1 [5,11,18–28]. The literature search strategy identified 274 studies (Wilate® [n = 15], Alphanate® [n = 36], Fanhdi® [n = 9], Voncento/Biostate® [n = 9], Humate-P/Haemate-P® [n = 152], Wilfactin/Willfact® [n = 2], rVWF or Vonvendi® [n = 51]). Of these, 21 publications met the inclusion criteria. Results are organized by class and summarized in Table 2 [11,12,19,24–26,29–50].

3. Results

3.1. Cryoprecipitate

Cryoprecipitate was the earliest (1964) commonly used form of replacement therapy for VWD and was used to treat bleeding in patients with VWD as late as 1995 [1]. Cryoprecipitate use is no longer recommended in Europe or the United States [51]; however, it remains in use in countries where specific concentrates are not available [1]. Advantages were that it could be prepared rapidly from cold fractions of fresh-frozen plasma and that it corrected hemostatic defects to restore normal bleeding times [52]. However, a key disadvantage was that virucidal methods were not available at that time to be applied in the production of cryoprecipitate, which resulted in risk of transmission of blood-borne infections [13]. Now, virus-inactivated cryoprecipitate is also available in a limited number of countries.

3.2. Plasma-derived factor concentrates

Plasma-derived concentrates, the first of which became available in Germany in 1981, were able to undergo viral inactivation, resulting in a much lower risk of blood-borne infection compared with cryoprecipitate. Initial FVIII concentrates prepared by chromatography and subjected to virus-inactivation procedures were used for the treatment of hemophilia; however, their low content of VWF rendered them ineffective for the treatment of VWD [1]. Since 1981, several plasma-derived VWF/FVIII concentrates have become available worldwide to treat individuals with VWD (Table 1) [19–28]. They vary in method of purification, method of viral inactivation, ratio of VWF to FVIII, and VWF activity. Drawbacks to the use of these plasma-derived concentrates include a small risk of unknown pathogen transmission and the inability to administer VWF separately from FVIII [5]. The summary of product characteristics for one plasma-derived VWF/FVIII concentrate notes that, for products prepared from human blood, the possibility of transmitting infective agents cannot be totally excluded [25]. In a recent study investigating the US hemophilia treatment centers, the US Centers for Disease Control and Prevention found that all patients treated for VWD were using plasma-derived products owing to the lack of a recombinant alternative [53]. The inability to completely remove parvovirus B19 by conventional virus inactivation and reduction procedures is a limitation of these products. Good evidence exists to suggest that the adhesive activity of VWF depends upon the size of its multimers; those of high molecular weight (HMW) 5000 to 10,000 kDa and ULMs of > 10,000 kDa are the most hemostatically active, being more effective at binding collagen and platelet receptors to facilitate platelet aggregation and wound healing [54]. Plasma-derived VWF concentrates do not have an intact multimeric structure, being deficient in the larger, more hemostatically active multimers because of their exposure to the VWF-cleaving protease ADAMTS13 during manufacture [5,14,55]. rVWF is not exposed to ADAMTS13 and, therefore, contains a full multimeric profile [14], including the HMW multimers and ULMs typically seen only in platelets and endothelial cells [56].

3.2.1. Products with VWF:RCo/FVIII ratio ≤ 1

In patients requiring a greater increase in FVIII:C level, products with a VWF:RCo/FVIII ratio ≤ 1 could be beneficial in potentially enabling the correction of both the primary VWF defect and, in some patients, a low FVIII level. The von Willebrand factor/coagulation FVIII complex (Wilate), a plasma-derived concentrate with a VWF:RCo/FVIII ratio of 0.8 to 1.0, was approved for the treatment of VWF in 2009 [5,18]. In the production of this concentrate, the mixture of VWF and FVIII is purified from plasma via ion exchange and size-exclusion chromatography. Viral inactivation is achieved by subjecting the sample to solvent/detergent plus dry heat [57]. As summarized in Table 2, results of clinical trials in patients with all three types of VWD showed excellent or good hemostatic efficacy in > 95% of patients treated for spontaneous or trauma-induced bleeds and patients undergoing surgery [30,32,42,50,58]. The concentrate was also effective in patients requiring prophylaxis [30,32,42]. In these trials, no marked FVIII accumulation or thromboembolic events were observed [30,32,42,49,50] and no patient developed alloantibodies [30,32,42,49,50] or transfusion-related infections [30,32,49,50]. In a pooled analysis of four prospective clinical trials in 44 patients with VWD of all types, efficacy was rated as excellent or good in 96% of all treated bleeding episodes [32]. Bleeding was stopped in a mean of 1.93 treatment days, with a mean dose per treatment day of 29 IU/kg. However, the number of infusions required to achieve hemostasis and mean dose varied by bleed site (range 1.35 treatment days for menorrhagia to 4.23 treatment days for GI bleeds; 23 IU/kg/d for muscle/soft tissue bleeds to 44 IU/kg/d for GI bleeds) and VWD type (range 1.24 treatment days for type 1 VWD to 3.97 treatment days for type 2 VWD; 28 IU/kg/d for type 1 VWD to 36 IU/kg/d for type 2 VWD).

3.2.2. Products with VWF:RCo/FVIII ratio > 1 to < 10

Four plasma-derived products with a VWF:RCo/FVIII ratio > 1 to < 10 are available for the treatment of VWD [5,18,59]. Two are purified with heparin ligand chromatography (Alphanate and Fanhdi), one with size-exclusion chromatography (Voncento/Biostate), and one with multiple precipitation steps (Humate-P/Haemate-P) [21,57]. For viral inactivation, three are treated with solvent/detergent plus dry heat (Alphanate, Fanhdi, and Voncento/Biostate) and one is pasteurized (Humate-P/Haemate-P) [21,57]. In patients with each of the three types of VWD, all of these concentrates have achieved high rates of excellent or good hemostatic efficacy as an on-demand treatment of bleeding episodes (range 67–97%) as well as for patients undergoing surgery (range 90–100% overall; Table 2). In addition, three concentrates (Alphanate, Voncento/Biostate, and Humate-P/Haemate-P) have been investigated for their efficacy as prophylaxis and have demonstrated high rates of success (range 87–100%; Table 2). In a clinical trial of antihemophilic factor/von Willebrand factor complex (human) (Humate-P/Haemate-P) for the treatment of emergency bleeding episodes in patients with VWD (n = 33), hemostatic efficacy was rated as excellent/good for 52 of 53 events [60]. In total, 45 loading doses (median [range] 67.0 [25.7–143.2] IU/kg) were administered, and 30 patients continued treatment for 1 to 3 days (mean 1.13 infusions/d), 22 patients for 4 to 7 days (mean 1.04 infusions/d), and 7 patients for > 7 days (mean 0.78 infusions/d). The median number of infusions per patient ranged from 1 in patients with type 3 VWD to 10 in patients with type 1 VWD. Patients with orthopedic or neurologic events were treated the longest (median 6 and 5 days, respectively). Overall, the median (range) daily maintenance dose per infusion was 74.0 (16.4–182.9) IU/kg, with a median (range) of 2 (1–36) infusions per event and a median (range) treatment duration of 3 (1–67) days. In the clinical studies reviewed in Table 2, all four concentrates were well tolerated. Thrombotic complications occurred in two patients treated with Alphanate in one study and were managed medically, without compromising treatment [46]; no other thrombotic complications were reported in any of the other studies. One case of B19 parvovirus infection occurred in a study of Alphanate [46]; no other treatment-related infections were reported in any of the other studies. Reported mild adverse events possibly related to treatment were eye edema and

infusion-site pruritus in a study of Voncento [45], and nausea in a study of Biostate [41].

3.2.3. Products with VWF:RCo/FVIII ratio ≥ 10

Currently, human von Willebrand factor (Wilfactin/Willfact) is the only plasma-derived VWF concentrate that is almost devoid of FVIII (VWF:RCo/FVIII ratio $10:\leq 1$) and may be administered without additional FVIII concentrate in the appropriate clinical setting [28,33,39]. It is purified by ion exchange and affinity chromatography, and viral inactivation is accomplished using solvent/detergent treatment, 35-nm filtration, and dry heating [57]. It has demonstrated high rates of hemostatic efficacy for on-demand treatment of bleeding in patients with all types of VWD (89% rated excellent/good) [33,39], and for prophylaxis of bleeding (100% success in preventing bleeds associated with sporting activities or ovulation period) [33] and during surgical or invasive procedures (100% rated excellent/good) in patients with type 3 VWD [33] (Table 2). For spontaneous bleeding, median infused dosage was 41.8 IU/kg, with a median of 3 infusions per episode [33]. In most cases (62%), treatment of spontaneous bleeding episodes did not require concomitant FVIII administration. For surgical prophylaxis, median infused dosage was 45.5 IU/kg, with a median (range) of 3 (1–46) infusions across procedures and a median (range) exposure of 3 (1–37) days. No patient experienced clinically overt thrombosis, displayed evidence of FVIII accumulation, developed a transfusion-related infection, or had detectable levels of anti-VWF:RCo antibodies [33].

3.3. Recombinant VWF

The first rVWF, vonicog alfa, is approved for on-demand treatment and control of bleeding episodes and perioperative management of bleeding in the United States [11], and for the treatment of hemorrhage and surgical bleeding and prevention of surgical bleeding in Europe [10] (Table 1). Unlike the plasma-derived products containing VWF and FVIII at predefined ratios $< 10:1$, vonicog alfa, which has a VWF:RCo/FVIII ratio of $100:\leq 1$, may be administered independently if an immediate rise in FVIII:C is not necessary or if baseline FVIII:C is sufficient to ensure hemostasis ($\geq 40\%$). In the elective surgical setting, rVWF can be given alone to raise endogenous FVIII:C when baseline FVIII:C is $< 40\%$ [10,11]. In contrast to the plasma-derived VWF replacement therapies, which do not contain any ULMs, vonicog alfa is not exposed to ADAMTS13 during manufacturing and thus contains hemostatically effective ULMs during initial infusion. In vitro and clinical data indicate that the ULMs in rVWF may help stabilize FVIII via platelet GpIb binding [14,61,62], which could promote sustained VWF and FVIII activity without the administration of additional FVIII. Following infusion, the ULMs undergo rapid proteolysis, indicating the appropriate susceptibility of vonicog alfa to physiologic regulation by ADAMTS13 [61] (Fig. 2). Given the rapid proteolysis, the risk for thrombosis seems quite low, but does necessitate further study, particularly in high-risk prothrombotic situations like pregnancy and orthopedic surgery.

Vonicog alfa has been evaluated in patients with severe VWD [12,61,63]. In patients given a single dose of vonicog alfa + FVIII at a fixed ratio of 1.3:1 or plasma-derived VWF/FVIII (Humate-P/Haemate-P), outcomes indicated a higher specific activity (VWF:RCo/VWF:Ag) and significantly enhanced FVIII stabilization for vonicog alfa + FVIII compared with plasma-derived VWF/FVIII ($P < 0.01$). Improved stabilization suggests the potential to achieve sustained FVIII activity, and in comparing the two treatment groups, vonicog alfa + FVIII was associated with a greater secondary rise in endogenous FVIII (Fig. 3), with FVIII:C being significantly higher 72 h after administration ($P < 0.01$). Co-administration of vonicog alfa and FVIII was not associated with the development of clinically significant inhibitors or thrombosis [61]. The half-life of VWF:RCo was 21.9 h with vonicog alfa alone and 19.6 h when vonicog alfa was coadministered with FVIII (Fig. 4). A pharmacokinetic assessment of VWF:RCo analyzed from data combined from the phase 1 and phase 3 on-demand studies, indicated a significantly longer terminal

half-life with vonicog alfa (50 IU/kg VWF:RCo) with or without FVIII (38.5 IU/kg) ($P < 0.05$) than after administration of plasma-derived (pd) pdVWF and pdFVIII (50 IU/kg pdVWF:RCo and 38.5 IU/kg pdFVIII) [10].

The hemostatic efficacy of on-demand treatment with vonicog alfa (\pm FVIII) was rated as excellent (96.9%) or good (3.1%) for all bleeding episodes in the phase 3 study [12]. In 81.8% of bleeds, a single infusion was effective; the median number of infusions per bleed was 1 across all VWF types, bleed severities, bleed sites, and known bleed causes, with the exception of major or severe bleeds ($n = 7$ [3 joint, 3 GI, and 1 nasopharyngeal tract]; median 2 infusions/bleed) and 1 bleed of unknown cause (3 infusions). The median dose administered per bleed was 46.5 IU/kg. Treatment was not associated with the development of neutralizing antibodies or thrombotic events, and there were no serious infusion-related events [12].

The use of vonicog alfa in the surgical setting has also been evaluated in a phase 3 trial (Table 2) [63] and the safety profile was consistent with that seen in the phase 3 on-demand study [12]. Ongoing phase 3 clinical trials are studying the use of vonicog alfa as prophylaxis (NCT02973087) and in pediatric patients (NCT02932618).

4. Discussion and conclusion

Factor replacement therapies for VWD are the mainstay of treatment for patients who do not respond to or are intolerant of desmopressin or other pharmacologic therapies [5,51]. Although the lack of prospective head-to-head studies prohibits efficacy comparisons between agents, we have described the beneficial effects of innovations in factor replacement therapy for VWF over the past several decades. Our analysis shows that plasma-derived VWF/FVIII concentrates, which evolved from cryoprecipitate to reduce the risk of transmission of infection, have varying degrees of reported efficacy when used for on-demand treatment, prophylaxis, and surgical hemostasis in patients with VWD. In the studies reviewed here, investigators rated treatment efficacy as excellent or good in most cases (67–100%), but comparative data are lacking, and comparisons of additional endpoints, such as levels of FVIII:C, VWF:RCo, high-molecular-weight multimers, and ULMs are of interest. Plasma-derived products with high ratios of VWF:RCo to FVIII provide good options for patients but also present challenges, owing to the fact that they vary in VWF to FVIII ratios and activity, pharmacokinetic profile, FVIII accumulation potential, and regional availability [5]. Although thrombotic complications are rare with these agents, a recent 33-year safety review of one such product indicated a potentially higher risk in patients with VWD compared with patients with hemophilia A [64]. Overall, 33 thrombotic complications were identified corresponding to one case per every 78,787 standard doses administered. Twenty-four of the 33 cases were in patients with VWD. Hypersensitivity reactions (identified by the terms anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, hypersensitivity, angioedema, and related terms) occurred in 110 cases overall, corresponding to one case per every 23,636 standard doses administered, and 64% occurred in patients with VWD [64]. These reactions may be related to the plasma-derived nature of the product [64].

Furthermore, there is ongoing debate regarding which assay(s) (and which biologic and pharmacologic functions of VWF) should be used to monitor treatment of VWD [65]. Clarification of the appropriate assay could help further individualize and advance lifelong VWF replacement therapy via more informed treatment decisions. As new products evolve, it will be important that corresponding progress is made with laboratory measurements so that the most appropriate assay is used to understand the beneficial effects of treatment, FVIII level, and VWF activity. The traditional tests for monitoring VWD therapy are FVIII:C and VWF:RCo [66]. These assays must be used in combination to determine the VWD phenotype, but they are time consuming, difficult to standardize, and limited to specialized laboratories [67]. These and other limitations (e.g. high coefficient of variation and high limit of detection with VWF:RCo assay) underscore the need to develop novel

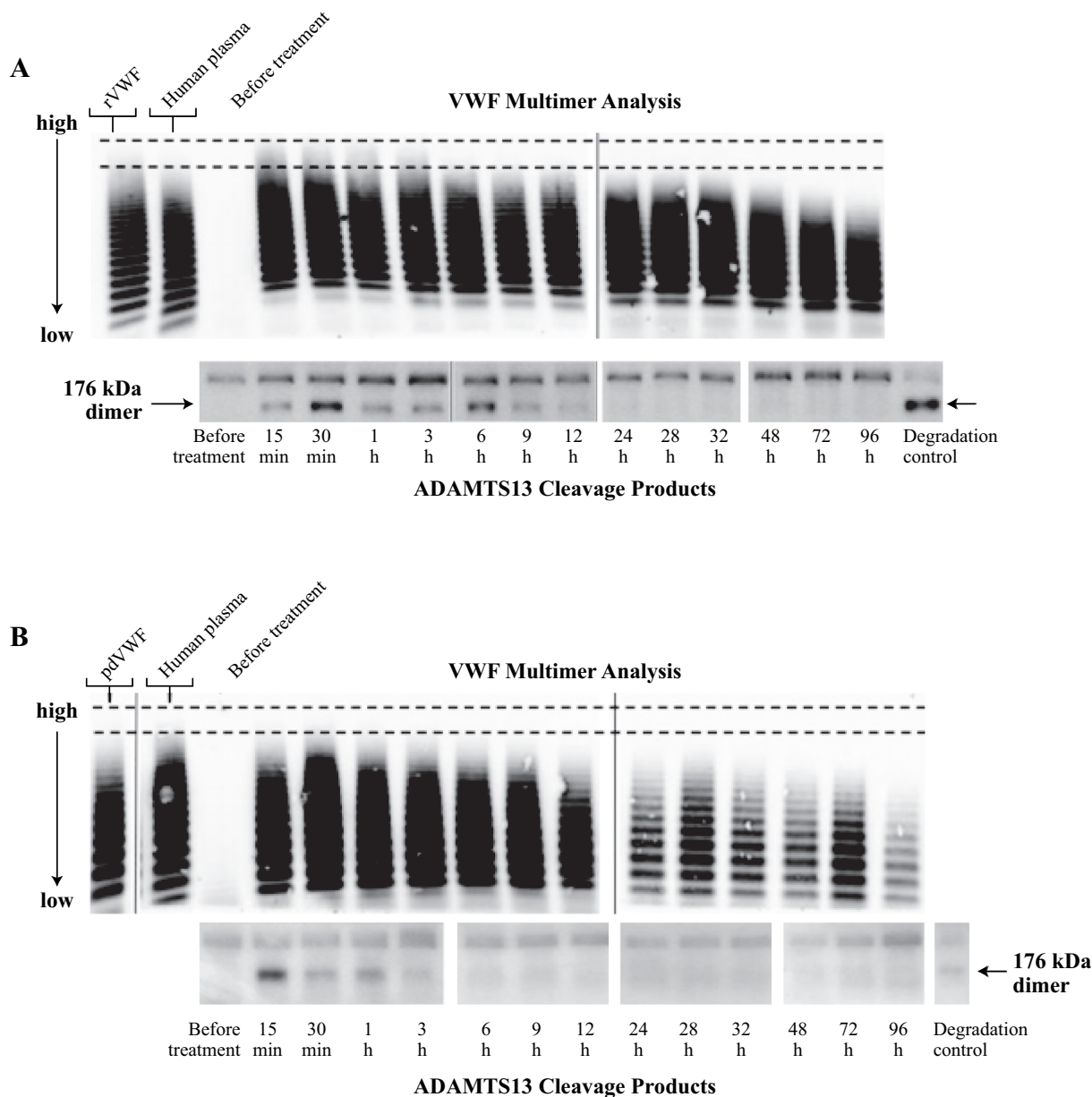
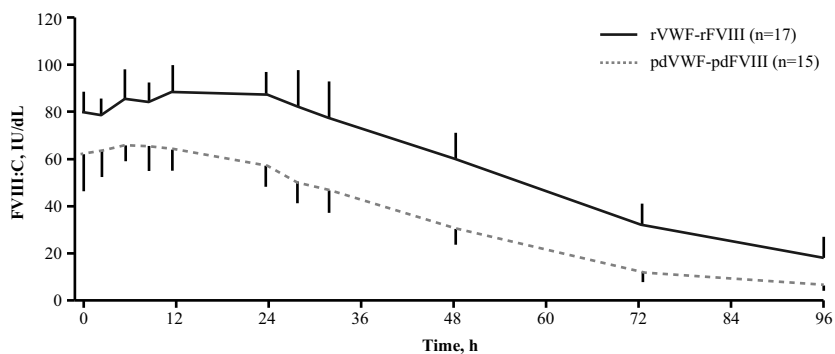


Fig. 2. Increase in the proportion of ULM after rVWF infusion, followed by rapid degradation (A). Lack of ULM after Humate-P infusion (B). pdVWF, plasma-derived VWF; rVWF, recombinant VWF; ULM, ultra-large multimers; VWF, von Willebrand factor. (Reproduced with permission from P.M. Mannucci, C. Kempton, C. Millar, E. Romond, A. Shapiro, I. Birschmann, et al., Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. *Blood* 122 (2013) 648–657 [61].)



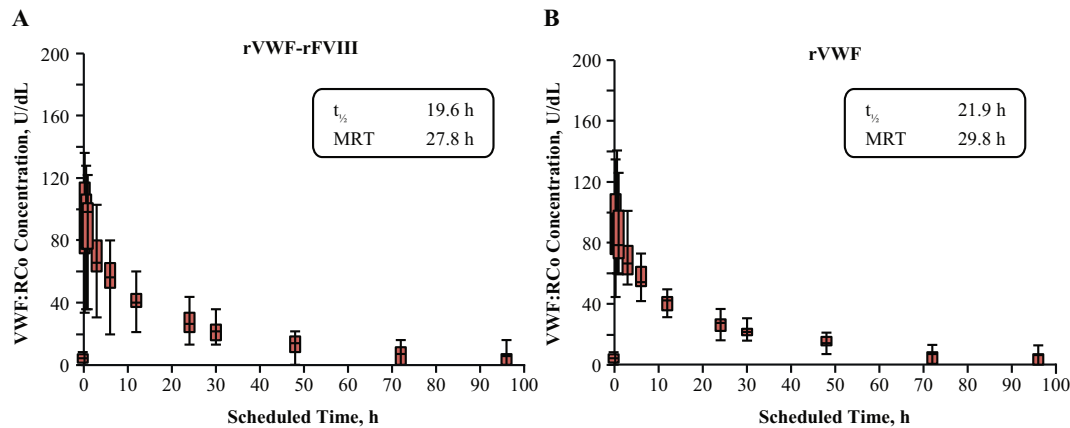


Fig. 4. VWF:RCo level after administration of rVWF with rFVIII (A) and without rFVIII (B). FVIII, factor VIII; MRT, mean residence time; $t_{1/2}$, half-life; rFVIII, recombinant FVIII; rVWF, recombinant VWF; VWF, von Willebrand factor; VWF:RCo, VWF ristocetin cofactor. (Reproduced and adapted with permission from J.C. Gill, G. Castaman, J. Windyga, P. Kouides, M. Ragni, F.W. Leebeek, et al., Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood* 126 (2015) 2038–2046 [12].)

assays that are simple and have greater accuracy, specificity, and sensitivity [67–69]. Repeat assay testing is now necessary in the majority of cases, which delays the diagnosis and treatment of patients with VWD [67]. In vitro evidence suggests that the Platelet Function Analyzer-200, which is sensitive in detecting ULMs, could prove to be a step forward in the monitoring of rVWF activity [70]. rVWF was shown to normalize platelet function analyzer closure times in whole-blood samples obtained from patients with VWD, whereas plasma-derived VWF concentrates were not. Evidence-based treatment guidelines should provide recommendations on the type of assays to be used with the different VWF products available for the treatment of patients with VWD [4,71]. The International Society on Thrombosis and Haemostasis, American Society of Hematology, National Hemophilia Foundation, and World Federation of Hemophilia are to develop clinical practice guidelines on the diagnosis and management of VWD, due for publication in 2020 [72].

Although the treatment of VWD has progressed, it remains a challenge, particularly with regard to accurately diagnosing and treating major bleeds. There is also a need for treatment options that support an effective, individualized approach in accordance with a patient's type and clinical scenario. Replacement of deficient or dysfunctional VWF and correction of reduced levels of FVIII are both important in restoring hemostasis in patients with VWD [3]. Plasma-derived products with VWF:RCo/FVIII ratios ≥ 10 (Wilfactin/Willfact) and rVWF products can successfully treat bleeding episodes without concomitant FVIII administration in the majority of patients, particularly in situations not needing an immediate attainment of hemostatic levels of FVIII. This affords increased flexibility with regard to the amount of FVIII administered, repeat dosing, and treatment individualization. FVIII accumulation is a concern, particularly when repeated dosing is necessary (e.g. surgery, prophylaxis, postpartum, GI bleeding) and in the elderly, and plasma-derived products with low or equal VWF content relative to FVIII may increase the potential risk for thrombotic events in these

patients [73]. Independent administration of rVWF or purified pdVWF and FVIII enables independent optimization of plasma FVIII and VWF. This could improve efficacy and safety by allowing clinicians to address and optimize the primary deficiency in VWF without the concern of FVIII overaccumulation. Many patients with VWD have specific needs and would benefit from a more personalized treatment approach and advanced replacement therapy, particularly tailoring coadministration of FVIII. Examples include surgical (specifically major surgeries that may require frequent postoperative doses), obstetrical, gynecological (heavy menstrual bleeding), and elderly patients, populations at risk for thrombosis and for whom clinicians must balance the desire for optimal efficacy with the concern for FVIII overaccumulation; patients with bleeding associated with loss of ULMs (e.g. GI bleeding) for whom restoration theoretically could enhance bleed resolution; and patients receiving prophylaxis and desiring a longer VWF half-life in hopes of reducing the frequency of infusions. Patients who experience anaphylactic or allergic reactions to plasma-derived products, patients not responding to plasma-derived high-VWF-content products, patients with relatively high levels of FVIII who do not require any additional FVIII (e.g. patients with type 1, 2A, or 2B VWD), and patients living in remote locations where storage and reconstitution of plasma-derived products are either cumbersome or not possible might also benefit from such an approach. Additional data regarding vonicog alfa are needed. In particular, there is a need to investigate the mechanisms underlying the extended half-life and FVIII stabilizing properties of vonicog alfa [10] and the role of ULMs. Whether these properties will translate to benefits for particular patient populations and improved hemostatic efficacy for specific types of bleeds is an important area of ongoing clinical research (Table 3). Although some evidence on the use of vonicog alfa for menorrhagia and epistaxis is documented in the phase 3 on-demand study [12], as well as a subanalysis on the treatment of GI bleeding [74], the hemostatic efficacy of vonicog alfa in challenging clinical scenarios is an important area for future clinical research. Extra-

Table 3

Potential areas for future clinical study of rVWF in patients with VWD.

Clinical setting	Rationale for rVWF
AVM-related GI bleeding	ULMs may inhibit angiogenesis
Pediatrics	Multicenter, phase 3 study in patients < 18 years of age is ongoing (NCT02932618)
Prophylaxis	Multicenter, phase 3 study is ongoing (NCT02973087)

AVM, arteriovenous malformation; GI, gastrointestinal; rVWF, recombinant VWF; ULM, ultra-large multimer; VWD, von Willebrand disease; VWF, von Willebrand factor.

intestinal angiodysplasia is a big challenge in the treatment of patients with VWD, particularly in the elderly, as well as in those with refractory epistaxis [75]. Real-world data, especially in the pediatric population and the prophylaxis setting, would help to further inform the clinical use of rVWF.

The management of VWD is complex, and global standardization for biologic therapies and clear guidance for treatment are currently lacking. Although clarification is needed regarding the optimal order of factor replacement therapies in a treatment algorithm, marked technological achievements—from the development of the first plasma-derived VWF concentrates to the recent rVWF product—should allow clinicians to further individualize and control VWF replacement therapy for patients with VWD.

Practice Points

- There is currently no standardized approach to factor replacement therapy in VWD.
- The more recently available factor replacement therapies may provide flexibility to control the amount of FVIII administered along with VWF, allowing for individualization of therapy.
- It is important to understand which assays will be most appropriate for use with the new VWF replacement therapies that have become available.

Research Agenda

- Determination of the role of rVWF in prophylaxis against spontaneous bleeding episodes.
- Determination of the effects of new products on mucosal and GI bleeds.
- Development of assays to evaluate the treatment efficacy of new products.
- Development of assays to evaluate the role of ULMs in hemostasis in clinical situations.

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