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Effectiveness of long-term prophylaxis using pdFVIII/VWF concentrate in patients with inherited von Willebrand disease

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Abstract

Background: Patients with symptomatic von Willebrand disease (VWD) should be offered long-term prophylaxis (LTP) to prevent recurrent bleedings. Our objective was to evaluate the effectiveness and safety of Voncento®, a plasma-derived FVIII/VWF concentrate (ratio 1:2.4), administrated in LTP.

Methods: We included patients from the OPALE study (May 2016 to April 2021), a French multicenter observational study following patients with inherited VWD, who received a Voncento® LTP during the study period.

Results: Among the 130 OPALE-study patients, 23 patients (12 women) received a LTP and were therefore included. The median (range) age was 16 (1–85) years; 16 patients were type 3, 1 was type 2A, 6 were type 2B. Before inclusion, 19 (83%) were under LTP and 4 (17%) received on-demand (OD) treatment. The indications for initiating prophylaxis in the overall population were joint bleeding (43%), ear, nose, and throat (ENT) bleeding including epistaxis or oral bleeding (39%), and recurrent muscle hematoma (22%). The medians (ranges) dose of Voncento® per infusion, frequency, and weekly dose were 45 (33–109) IU/kg, 2 infusions per week, and 96 (44–222) IU/kg/week, respectively. The median (range) annualized bleeding rate (ABR) was 0.8, 0.7 (0–3.5), and 0 (0–2.3) for type 2A, 2B, 3 patients, respectively. There was no difference regarding to the dose, frequency of infusion, or in terms of ABR in 9/19 patients who replaced previous concentrates with Voncento®. During the study period, no adverse event was reported.

Conclusion: These results suggest that Voncento® is effective to prevent recurrent bleedings in patients symptomatic VWD.

KEYWORDS
bleeding, FVIII/VWF concentrates, prophylaxis, von Willebrand disease, Voncento®

1 | INTRODUCTION

Von Willebrand disease (VWD) is an autosomal inherited bleeding disorder, considered as the most common bleeding disorder. Its prevalence is approximately 1% in the general population, but symptomatic patients are rarer (0.01%).[1] It is caused by a partial or total quantitative deficiency (type 1 and type 3) or by a qualitative defect (type 2) in von Willebrand factor (VWF). VWF is a large multimeric protein that is required for platelet adhesion to the subendothelium and serves as a carrier for factor VIII (FVIII), thereby protecting it from early inactivation by the activated protein C system.[2] Type 2 VWD forms can be further classified into four subgroups (2A, 2B, 2M, and 2N) that are distinguished by the nature of the VWF defect.[3] Due to a heterogeneity in the levels of VWF and FVIII, patients suffering from VWD display a varied range of bleeding symptoms from provoked after surgery to spontaneous bleeding such as joint bleed, HMB, ENT (ear, nose, and throat), or gastrointestinal bleeding (GI), and those symptoms also vary with age and sex.[2] Most patients (60 to 80%) require treatment only to prevent bleedings from occurring after surgery or tooth extractions.[4] For patients with severe or symptomatic forms of VWD, such as in haemophilia, 2 options of treatment can be proposed: on-demand (OD) or long-term prophylaxis (LTP) regimen. Previous studies have reported the benefit of LTP in VWD to prevent recurrent bleedings.[5–7] Recent guidelines from the American Society of Haematology (ASH), International Society of Thrombosis and Haemostasis (ISTH), National Federation of Hemophilia (NHF), and World Federation of Hemophilia (WFH) on the management of VWD have recommended routine prophylaxis with VWF concentrates in patients with VWD with a history of severe and frequent bleedings.[8] Yet, this panel of experts cannot provide recommendations regarding prophylaxis regimen specific to various bleeding episodes such as recurrent epistaxis, joint bleeds, or also GI bleeding. The various clinical forms of the disease do not ease the standardization of treatment, and these issues are worsened by the heterogeneity of the therapeutic molecules available, including desmopressin and various VWF concentrates containing or not FVIII. Voncento® (CSL Behring Gmbh, Marburg, Germany) is a plasma-derived FVIII/VWF concentrate (pdFVIII/VWF) registered in France since 2015 for the treatment and prevention of bleeding events in patients with inherited VWD.[9] This plasma-derived product contains preserved high molecular weight (HMW) multimers, which are important for haemostatic efficacy. In Voncento®, the ratio of FVIII to VWF activity is 1:2.4. A pharmacokinetic study comparing Biostate® and AHF factor (High Purity; CSL Behring) in patients with VWD has demonstrated favourable increments of FVIII coagulant activity (FVIII:C), VWF ristocetin cofactor activity (VWF:RCo), VWF antigen levels (VWF:Ag), and VWF HMW multimers in plasma following Biostate® (Voncento®) infusion.[10] Some authors have recently showed the effectiveness and safety of Voncento® for the perioperative management of VWD patients (all types), as well as the long-term safety and effectiveness for the treatment and prevention of bleeding events in patients with severe VWD.[11,12] In addition, a reduced incidence of major bleedings, including joint bleedings, has been reported among children with VWD treated prophylactically with Voncento® compared to patients treated OD.[13]

Because the experts agree on the lack of large prospective studies that could inform and provide recommendations on the dose and frequency of treatments to be administered depending on the subtype of VWD or on the clinical symptoms, the objective of this study was to provide data about the effectiveness and safety of a pdFVIII/VWF (Voncento®) administrated in LTP in patients with symptomatic VWD.

2 | METHODS

2.1 | Patients

The OPALE (*Observatoire des patients présentant une Maladie de Willebrand et traités par Voncento®*) study is a French multicenter observational study designed to follow patients with inherited VWD (any type) requiring treatment with Voncento®. The study was conducted from May 2016 to April 2021 in 18 French bleeding disorder centers (Nantes – Lyon – Paris-Bicêtre [2 centres] – Besançon - Paris-Necker - Le Chesnay – Strasbourg – Paris-Lariboisière – Brest – Caen – Nancy – Eaubonne – Paris-Cochin-– Montpellier – Rennes – Rouen – Bordeaux).

The present analysis focused on the patients included in the OPALE study who received a Voncento®–LTP regimen during the study period.

2.2 | Clinical data collection

At inclusion, the following patient data were recorded: age, sex, weight, blood group, VWD type. Plasma FVIII:C, VWF:RCo, VWF:Ag levels, and platelet count at diagnosis were also recorded. By convention, the results of VWF:RCo and VWF:Ag in type 3 patients were reported as 0 IU/dl. VWD was diagnosed and classified according to the clinical and laboratory criteria published by the ISTH.[3] The laboratory testing was performed in each center. The molecular analysis performed by the French national reference center for von Willebrand disease confirmed the VWD type for all patients. Before inclusion, patients benefited from 2 modalities of treatment, OD or LTP. The LTP regimen was defined as a period lasting at least 6 months during which a treatment consisting of VWF replacement was administered at least once weekly.[8] The indications for the initial LTP were collected for all patients. The indications for the replacement of the initial treatment by Voncento® during the course of prophylaxis were also recorded. The type of VWF concentrate, the dose, and the frequency of any previous treatment were collected and compared to the dose and the frequency of treatment with Voncento®. For each patient, the individual study period was defined as beginning at least 12 months prior to the initiation Voncento® treatment and finishing after follow-up at the end of the overall study period. Thus, the treatment with Voncento® was prospectively prescribed, but the analysis was retrospective for some patients,

because the inclusion was performed after the initiation of Voncento® in some cases. An annualized bleeding rate (ABR) was calculated for each patient and analysed according to the type of concentrate and treatment regimen. The ABR occurring under Voncento® treatment was calculated based on the duration of follow-up and compared to the ABR corresponding to the 12 months preceding the initiation of Voncento®. The duration of follow-up was registered as the number of months during which patients received the treatment by Voncento®. The clinical effectiveness was appreciated on a scale from none to excellent (none, poor, good, and excellent) and adverse events (AEs) were also recorded by the investigators. The safety assessment included the reporting of AEs, thrombotic events, and the development of inhibitors.

According to the French regulation, an institutional review board approved the study. Patients or the parents/legal representatives of children signed a full informed consent.

A statistical analysis was performed using the GraphPad Prism 5.0 software; a Student's *t*-test was used for comparisons of the dose per week.

3 | RESULTS

A total of 130 patients were enrolled in the OPALE study, and there were 36 (27%) type 1, 20 (15%) type 2A, 22 (17%) type 2B (including one combined type 2A and 3 combined type 2N), 17 (13%) type 2M,

TABLE 1 Demographic characteristics of patients with VWD receiving LTP

	Total	Type 2A	Type 2B	Type 3
	n = 23	*n* = 1	*n* = 6	*n* = 16
Sex, *n* (%)				
Male	11 (47.8)	0 (0)	5	6
Female	12 (52.2)	1 (100)	1	10
Blood group O, *n* (%)	11 (47.8)	0 (0)	2 (33.3)	9 (56.2)
Age, years, median (range)[a]	16 (1–85)	4	7 (1–29)	20.5 (3–85)
Body weight, kg, median (range)	58 (15–84)	17	48 (15–72)	58 (21–84)

Abbreviations: VWD, Von Willebrand disease; LTP, long-term prophylaxis.
[a]Median age at the initiation of prophylaxis by Voncento®.

TABLE 2 Baseline factor levels according to the type of VWD, and the treatment regimen

	Total	Type 2A	Type 2B	Type 3
	n = 23	*n* = 1	*n* = 6	*n* = 16
VWF:RCo, IU/dl	0 (0–12)	6	5 (4–12)	0 (0–0)
VWF:Ag, IU/dl	0 (0–42)	20	29 (18–42)	0 (0–3)
FVIII:C, IU/dl	2 (1–38)	17	24.5 (16–38)	2 (1–25)
Platelet count, $\times 10^9$/L	161 (9–433)	161	20 (9–37)	190 (83–433)
LTP patients	Total *n* = 19	Type 2A *n* = 1	Type 2B *n* = 4	Type 3 *n* = 14
Age, years	18 (1–85)	1	12 (6–29)	20 (7–85)
VWF:RCo, IU/dl	0 (0–12)	6	8 (4–12)	0 (0–0)
VWF:Ag, IU/dl	0 (0–12)	20	29 (18–42)	0 (0–0)
FVIII:C, IU/dl	2 (1–38)	17	26 (24–38)	2 (1–25)
Platelet count, $\times 10^9$/L	161 (9–363)	161	29 (9–37)	180 (83–363)
	Total	Type 2A	Type 2B	Type 3
OD patients	*n* = 4	*n* = 0	*n* = 2	*n* = 2
Age, years (range)	4 (1–15)		8 (1–15)	4 (4–4)
VWF:RCo, IU/dl	2 (0–6)		5 (4–6)	0 (0–0)
VWF:Ag, IU/dl	14 (0–36)		32 (28–36)	0 (0–0)
FVIII:C, IU/dl	9 (1–23)		19 (16–25)	1.5 (1–2)
Platelet counts, $\times 10^9$/L	113 (9–433)		13 (9–17)	321 (210–433)

Note: Results are expressed as median (range). Factor levels and platelet count were recorded at diagnosis and age was recorded at the initiation of prophylaxis by Voncento®.

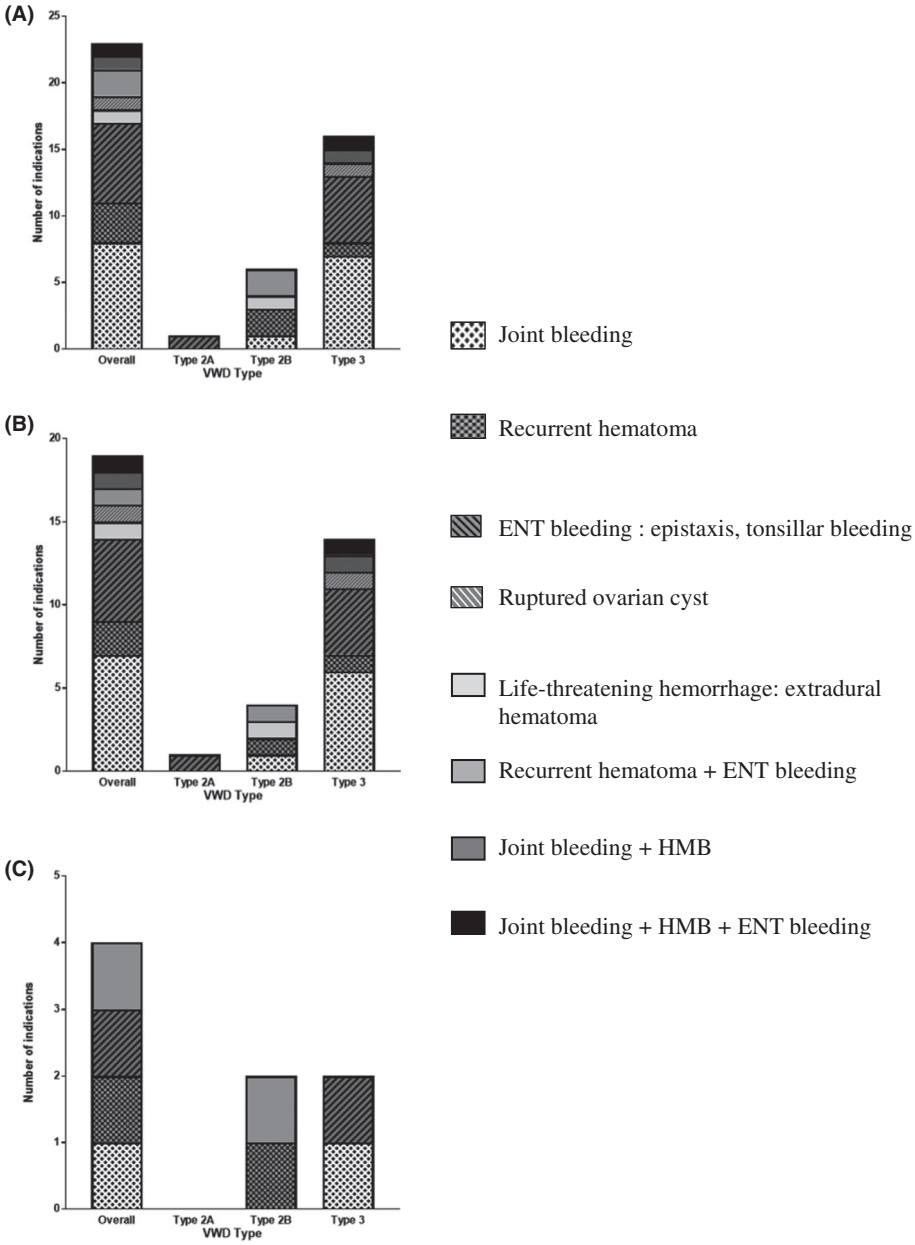

FIGURE 1 Indication of long-term prophylaxis: (A) In the overall population (B) In patients under prophylaxis (C) In on-demand patients

TABLE 3 Dose, frequency, duration of follow-up, and bleeding episodes in all patients receiving LTP with Voncento®

	Total $n = 23$	Type 2A $n = 1$	Type 2B $n = 6$	Type 3 $n = 16$
Dose, IU/kg	45 (33–109)	109	54.5 (33–100)	44 (35–62)
Weekly dose, IU/kg/week	96 (44–222)	109	100.5 (67–200)	90 (44–222)
Number of infusions per week	2 (1–3)	1	2 (1–3)	2 (1–3)
Duration of follow-up, months[a]	19 (5–48)	48	21 (17–27)	17.5 (5–46)
ABR	0.5 (0–7.2)	0.8	0.7 (0–2.9)	0 (0–7.2)
Effectiveness (Excellent/Good)[b]	9/10	0/1	3/3	6/6

Note: Results are expressed as median (range).
Abbreviations: ABR, annualized bleeding rate; LTP; long-term prophylaxis.
[a]One patient remained only for 5 months under LTP.
[b]Effectiveness was not available for 4 patients.

TABLE 4 Comparison in terms of dose and bleeding episodes between the initial prophylaxis and the prophylaxis by Voncento® (LTP group)

	Total $n = 19$	Type 2A $n = 1$	Type 2B $n = 4$	Type 3 $n = 14$
pdVWF[a]				
Dose IU/kg	42.5 (35–62)	46	44.5 (42–60)	40 (35–62)
Number of infusions per week	2 (1–3)	1	2 (2–3)	2 (1–3)
ABR	1 (0–6)	5	0 (0–6)	1 (0–4)
Voncento®				
Dose, IU/kg	43.5 (33–109)	109	38.5 (33–50)	44 (33–96)
Number of infusions per week	2 (1–3)	1	2.5 (1.5–3)	2 (1–3)
ABR	0.3 (0–2)	0.8	0.6 (0–1.9)	0 (0–2)

Note: Results are expressed as median (range).
Abbreviation: ABR, annualized bleeding rate.
[a]Two patients (one type 2B and one type 3) received pdVWF + FVIII concentrates before inclusion in the study.

7 (5%) type 2N, 22 (17%) type 3, and 6 (4%) with other types of VWD.

Among these 130 patients, 23 patients (including 12 women) received a LTP and were, therefore, included in the present study. The median (range) age at initiation of prophylaxis by Voncento® was 16 (1–85) years. Among the included patients, 16 were type 3, 1 was type 2A, 6 were type 2B (including one patient who was both type 2B and 2N; Table 1), and 8 were less than 10 years old (4 type 3, 3 type 2B, and 1 type 2A).

At diagnosis, the median (range) VWF:RCo level was 0 (0–12) IU/dl, it was 0 (0–42) IU/dl for VWF:Ag, 2 (1–38) IU/dl for FVIII:C, and the median (range) platelet count was 161 (9–433) $\times$ 10^9/L. For the 6 patients with type 2B patients, the median (range) platelet count was 20 (9–37) $\times$ 10^9/L. Among the included patients, 19 (83%) received previous LTP (i.e., classified in the LTP group) and 4 (17%) received OD treatment (Table 2).

For the patients previously treated with other VWF concentrates, the most common reasons for initiating the LTP were joint bleeding (43%), ENT bleeding including epistaxis or oral bleeding (39%), and recurrent muscle hematoma (22%). The prophylaxis was mainly introduced for a single bleeding indication (82% of patients), but in 4 patients combined indications were encountered: mainly ENT bleeds and joint bleeding or hematoma (Figure 1A,B), and among 8 women with menstruations, 2 (25%) presented Heavy Menstrual Bleeding (HMB) in association with other bleedings. Among the 19 LTP patients, 17 patients received prophylaxis with FVIII-poor VWF concentrate (Wilfactin®, LFB, France) alone (12 patients with type 3, 5 with type 2B) and 4 patients received both pure VWF and FVIII concentrates (one patient with type 2A, one with type 2B and 2 with type 3). In these 19 patients, the reported reasons for change from FVIII-poor VWF concentrate to Voncento® were the lower volume of injection with Voncento for 9 patients and a lack of effectiveness for 8 patients and one allergic symptom. For the 4 patients previously treated on demand who switch to a LTP with Voncento, the most common reason reported for initiating the LTP was the recurrent hematoma (Figure 1C).

The median (range) duration of follow-up was 19 (5–48) months. One patient was included despite being on LTP for 5 months. Among the 23 patients receiving prophylaxis with Voncento®, the median (range) dose of Voncento® per infusion was 45 (33–109) IU/kg, the median (range) frequency was 2 (1–3) infusions per week, and the median (range) dose in IU/kg/week of Voncento® was 96 (44–222) (see Table 3 for the data according to the VWD type). Additionally, no significant difference in terms of median dose per week was observed between type 2B patients (100.5 IU/kg/week) and type 3 patients (90 IU/kg/week; $p = .3$).

Regarding the effectiveness of the treatment, the median (range) ABR for all patients was 0.5 (0–7.2) and 0.7, 0.7 (0–2.9), and 0 (0–7.2) for patients with type 2A, 2B, and type 3, respectively. When available ($n = 19$), the effectiveness was reported as good/excellent in 100% of patients independently of the VWD subtype. Among the 19 patients who received previous LTP, no difference between both concentrates regarding the median dose and the median frequency of infusion (Table 4). However, the median (range) ABR decreased in patients receiving Voncento®: 0.3 (0–3) vs. 1 (0–6). As well as, for the 4 patients who changed treatment regimen: 0.5 (0–2) under OD regimen and 0 (0–2) under LTP. Ten patients with ABR >1, mainly ENT (epistaxis), $n = 6$, and joint bleeding $n = 2$, had improved ABR after introduction of LTP with Voncento® (median; range = 3; 1–6 vs. 0.6; 0–1.9). Regarding safety, Voncento® was well tolerated. During the study period, there was no case of allergic reaction, clinical development of inhibitor, or thromboembolic event reported.

4 | DISCUSSION

The present study is one of the largest prospective studies showing the effectiveness and safety of LTP using pdFVIII/VWF concentrate. A search in the medical literature has revealed that among the 13 studies showing a benefit of the prophylaxis regimen, only 7 are prospectively designed, and they all suffer from a large heterogeneity in study design, study population, VWD subtypes, and use of type of concentrate (Table 5).[5,12,14–24]

Most patients included in the study were type 3 patients, reflecting the severity of the clinical forms leading the clinicians to

TABLE 5 Summary of reports on the use of long-term prophylaxis in VWD

First author, year, study design	Products	Number of prophylaxis/ overall population	Duration of follow-up, months	VWD Type Type 1/Type 2A-2B-2M/ Type 3	Primary bleeding Indication *N* (%)	Dose FVIII:C or VWF:Rco (IU/kg) Median (range)	Frequency *N* time/week	ABR Median (range)	Outcome Excellent/good (%)
Dunkley,[14] 2010 Prospective	Biostate®	4/23	12 (6–12)	5/2–6-1/6[a]	NA	23.4 (14–29.1)	NA	1 (1–17)	100
Castaman,[15]2013 Prospective	Haemate® P	31/121	24	9/1–5-0/16	GI = 34[b] Joint = 41[b] HMB = 17[b]	20	2–3	3 (1–11)	92.9
Abshire,[16] 2015 Prospective	Haemate® Alphanate® Fandhi®	11	NA	0/6–0-0/5	GI = 3 (27) Joint = 2 (18) Epistaxis = 6 (54)	50	1, 2,3	4 (0–27.7)	
Holm,[5] 2015 Retrospective and Prospective	Haemate® Alphanate® Fandhi®	95–10/105	60	13/25–9-3/54[a]	GI (23.2) Joint (23) Epistaxis (32.7) HBM (4.1)	38–73[c]		3.8 (0.2–16.8) 6.0 (3–6-7.1) 0.8 (0–3.2) 0 (0–0.4)	Significant reduction of joint bleed, epistaxis, GI
Goudemand,[17] 2020 Prospective	Wilfactin®	32/155	36	1/13/18	GI (40.6) Joint (43.8) Others (15)[d]	45.2 (22–55) 42.2 (26–76) 46.6 (27–53)		1.1 (0–11) 0.8 (0–5.4) 1.0	
Lissitchkov,[12] 2021 Prospective	Voncento®	10/19	41	1/2/7	NA	42.8 (28.5–85.8)	1 (90%)	4.37 (0–25.9)	97.9
Sholzberg,[18] 2021 Prospective	Wilate®	91/25	24	3/5–1–0-1/14	NA	55.4 (8.3–1441.4)	1 to (85%)	1.9 (0–27.0)	99
Berntorp,[19] 2005 Retrospective	Humate-P® Haemate®P	35	12	1/2–4-0/28	GI = 3 (8) Joint = 13 (37) ENT = 16 (45.7) HMB =3 (8)	24 (12–50)	1 to 3	Joint =0.3 ENT = 0.4	
Federici,[20] 2010 Retrospective	Alphanate® Fandhi®	15/120	60	7/3–2-0/3	GI = 9 (61) Joint = 2 (13) CNS = 2 (13)	42 (17–74)	1 to 2	NA	87%
Halimey,[21] 2011 Retrospective	Humate® P Wilate®	32	12	4/15/13	Joint GI Relevant anemia	40 (20–47)	2 to 4		Significant reduced BS
Howman,[22] 2011 Retrospective	Biostate®	2/43	60	0/0/2	Joint Epistaxis	NA	NA		
Abshire,[23] 2013 Retrospective	Haemate® P Alphanate® Fandhi®	59	12	5/10–8-2–/34	GI = 13 (23.6) Joint = 12 (21.8) Epistaxis = 13 (23.6) HMB = 4 (7.3) Combined = 5 (9.1)	60 (47–60) 40 (30–50) 48 (40–60) 39 (38–40) 42 (33–49)	1.5 to 3	6 (3–6) 1.3 (0.3–3.2) 6 (2.9–12) 4 (1–9) 6 (1.2–12)	

TABLE 5 (Continued)

First author, year, study design	Products	Number of prophylaxis/ overall population	Duration of follow-up, months	VWD Type Type 1/Type 2A-2B-2M/ Type 3	Primary bleeding Indication N (%)	Dose FVIII:C or VWF:Rco (IU/kg) Median (range)	Frequency N time/week	ABR Median (range)	Outcome Excellent/good (%)
Miesbach,[24] 2015 Retrospective	Haemate® P	3		0/1–0-0/2	GI = 3 (100)	50 to 74 18 to 20	2, 2 to 6		100

Abbreviations: BS, bleeding score; GI, gastro intestinal; CNS, central nervous system; ENT, ear, nose, throat; VWD, Von Willebrand disease; NA, not available.

[a]Type of VWD given for the overall population.

[b]Number of bleeding events.

[c]Means, expressed according to the frequency and type of bleeding.

[d]Others: included epistaxis, Heavy Menstrual Bleeding (HMB), hematoma.

broadly initiate a prophylaxis regimen. The number of type 2B patients requiring prophylaxis was also high, due to their low baseline platelet count. Indeed, as previously described by Federici et al, type 2B patients with low baseline platelet count have a higher bleeding risk.[25] In type 3 patients joint and ENT bleeding were the main indications for LTP, and in type 2B patients the prevention of hematoma and epistaxis were the main indications. These results are similar to those reported by the first Prophylaxis Network Steering Committee, which has found joint bleeding, epistaxis/oral bleeding, GI bleeding, and HMB as main indications.[26] However, because of the prospective design of the study and the rarity of VWD, neither GI bleeding episode nor HMB alone were an indication of LTP in our study. In France, the FranceCoag Network, a national prospective cohort of patients with inherited coagulation factor deficiencies, has reported that among 1800 patients with symptomatic forms of VWD (VWF:RCo <15 IU/dl or type 2) only 3.1% of patients received LTP.[27]

The overall median dose and number of infusions reported herein were similar to those reported in smallest studies and did not differ according to the type of VWD, even if the type of bleeding differed.[12,14] Thus, no significant difference in terms of dose was observed between type 2B and type 3 patients.

Because the clinical presentation in VWD is often variable, the evaluation of the effectiveness of the modalities of the prophylaxis regimen remains difficult. Some authors have recommended the use of LTP in patients with severe forms of VWD, as recommended in the context of haemophilia, but they have also argued that ABR seems to be less pertinent than the individual assessment of bleeding symptoms.[28] In type 3 as well as in type 2B patients, Voncento® was effective to prevent joint bleeds, epistaxis, and recurrent hematoma with low ABR. And as reported in the first randomized study comparing OD versus prophylaxis regimen, the ABR was reduced in the 4 patients for whom the prophylaxis was introduced during the study period.[29] Thus, our results showed also that the effectiveness was excellent or good for all patients despite a large range of dose and frequency of infusion. Another way to compare the efficacy of concentrates could be the use a QoI assessment. But this assessment have not be used in this studies because not available.

The literature could not provide data in order to guide the modalities of treatment according to the type of VWD. Our results showed that in type 2B patients, despite their very low platelet count (median, range: 20, 9–37 $\times$ 10^9/L), a prophylactic regimen based on standard doses and standard frequencies of injections was effective.

The present study provided for the first time a comparison in terms of dose and bleeding episodes between 2 concentrates (for LTP patients, previous treatment vs. Voncento®). Among the 19 patients who received previous LTP, no difference between both concentrates regarding the median dose and the median frequency of infusion but a decreased of ABR was observed.

Despite the use of a pdVWF/FVIII, no thrombotic event was reported, supporting the observations previously made on the safety of this type of concentrates, which are similar to those reported in series using FVIII-poor VWF concentrates.[12,14,17]

Some limits in our study warrant discussion. Some types of bleeding episodes such as GI bleeding were not reported because of the

limited period of inclusion. Thus, the absence of GI bleeding, described as an indication of prophylaxis, could explain the low rate of ABR recorded, but cannot allow to conclude about the modalities of treatment with Voncento® in this context. The absence of VWF or FVIII activity level monitoring could constitute another limitation of this study, even if the minimal factor levels required to prevent bleedings remains controversial, especially during surgery[30]; additionally, these data are not available in studies reporting prophylaxis regimen (Table 5). This laboratory monitoring could be helpful to guide a personalized approach of prophylaxis as proposed by Phua et al.[31] Some authors have proposed to use an individualized dosing based on a pharmacokinetic study of each patient who undergo surgery.[32] These models could also be developed in order to manage the dose and frequency of infusion in LTP.

5 | CONCLUSIONS

The present study suggests that Voncento®, a plasma-derived FVIII/VWF concentrate (ratio 1:2.4), is an effective and well-tolerated therapy used to prevent recurrent joint, hematoma, and ENT bleedings in patients with severe and symptomatic VWD.

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LR, AH, MT, and R d'O performed the research, designed the research study, analyzed the data, and wrote the manuscript. YP, DD, BP-P, PC, CB, and SM performed the research and reviewed the manuscript. HC, DB, and CM analyzed the data and wrote the manuscript. All authors read and approved the final version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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