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

Lucia Rugeri 1 | Annie Harroche 2 | Yohan Repessé 3 | Dominique Desprez 4 | Brigitte Pan Petesch 5 | Pierre Chamouni 3 | Christine Biron 6 | Birgit Frotscher 7 | Hasan Catovic 8 | Diane Bracquart 8 | Cédric Martin 8 | Marc Trossaërt 9 | Sandrine Meunier 1 | Roseline d’Oiron 10

1Unité Hémostase Clinique, Hospices Civils de Lyon, Bron, France
2Hemophilia Care Centre, Hematology unit, Hôpital Universitaire Necker enfants malades, Paris, France
3Unité Hémostase et Centre Régional de Traitemet des maladies Hémorragiques, Institut de Biologie Clinique, Hôpital Charles Nicolle, Rouen, France
4Centre de Traitement de l’Hémophilie, CHU Strasbourg, Strasbourg, France
5Unité Hémostase Service hématologie, CHU Brest, Brest, France
6Département d’Hématologie biologique, CHU de Montpellier, Montpellier, France
7CRTH - Service d’hématologie biologique, CHU de Nancy, Nancy, France
8CSL Behring, Paris, France
9CRTH, CHU de Nancy, Nancy, France
10CRTH, AP-HP- Hôpital de Bicêtre, Le Kremlin-Bicêtre, France

Correspondence
Lucia Rugeri, Service de Gynécologie Obstétrique, Hôpital de la Croix Rousse, Hospices Civils de Lyon, France.
Email: lucia.rugeri@chu-lyon.fr

Funding information
Hospices Civils de Lyon

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®
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%). 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. 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. 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. Most patients (60 to 80%) require treatment only to prevent bleedings from occurring after surgery or tooth extractions. 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. 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.

Yet, this panel of experts cannot provide recommendations regarding prophylaxis regimen specific to various bleeding episodes such as recurrent epistaxis, joint bleed, 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. 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.

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. 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.

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.

METHODS

Patients

The OPALE (Observatoire des patients présentant une Maladie de Wil-lebrand 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.

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. 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. 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 by the activated protein C system.
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.

### 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, 16 (12%) type 3, and 4 OD patients.

#### TABLE 1  Demographic characteristics of patients with VWD receiving LTP

|                      | Total n = 23 | Type 2A n = 1 | Type 2B n = 6 | Type 3 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)** | 16 (1–85) | 0 (0)         | 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.

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

|                      | Total n = 23 | Type 2A n = 1 | Type 2B n = 6 | Type 3 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, ×10^9/L | 161 (9–433) | 161           | 20 (9–37)     | 190 (83–433) |
| **LTP patients**     |              |               |               |              |
| **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, ×10^9/L** | 161 (9–363) | 161           | 29 (9–37)     | 180 (83–363) |
| **OD patients**      |              |               |               |              |
| **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, ×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®.
Joint bleeding

Recurrent hematoma

ENT bleeding: epistaxis, tonsillar bleeding
Ruptured ovarian cyst
Life-threatening hemorrhage: extradural hematoma
Recurrent hematoma + ENT bleeding
Joint bleeding + HMB
Joint bleeding + HMB + ENT bleeding

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 |
|----------------------|--------------|---------------|---------------|--------------|
| Dose IU/kg pdVWF*    | 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®**

|                      | Total n = 19 | Type 2A n = 1 | Type 2B n = 4 | Type 3 n = 14 |
|----------------------|--------------|---------------|---------------|--------------|
| 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.
*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) × 10^9/L. For the 6 patients with type 2B patients, the median (range) platelet count was 20 (9–37) × 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 = 0.3).

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.

**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).

Most patients included in the study were type 3 patients, reflecting the severity of the clinical forms leading the clinicians to...
| 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, 2010 Prospective       | Biostate® | 4/23                                      | 12 (6–12)                   | 5/2–6–1/6                          | NA                             | 23.4 (14–29.1) | NA              | 1 (1–17)        | 100               |
| Castaman, 2013 Prospective      | Haemate® P | 31/121                                    | 24                          | 9/1–5–0/16                         | GI = 34AB Joint = 41AB HMB = 17AB | 20                | 2–3             | 3 (1–11)        | 92.9              |
| Abshire, 2015 Prospective       | Haemate® Alphanate® Fandhi® | 11 NA                                      | NA                          | 0/6–0–0/5                          | GI = 3 (27) Joint = 2 (18) Epistaxis = 6 (54) | 50                | 1, 2.3          | 4 (0–27.7)      |                   |
| Holm, 2015 Retrospective and Prospective | Haemate® Alphanate® Fandhi® | 95–10/105                                 | 60                          | 13/25–9–3/54                        | GI (23.2) Joint (23) Epiptaxis (32.7) HBM (4.1) | 38–73AB | 3.8 (0.2–16.8) | Significant reduction of joint bleed, epistaxis, GI |
| Goudemand, 2020 Prospective     | Wilfactin® | 32/155                                    | 36                          | 1/13/18                            | GI (40.6) Joint (43.8) Others (15) | 45.2 (22–55) | 1.1 (0–11)     | 6.0 (3–6.7)     | 97.9              |
| Lisitchkov, 2021 Prospective    | Voncento® | 10/19                                     | 41                          | 1/2/7                              | NA                             | 42.8 (28.5–85.8) | 1 (90%)         | 4.37 (0–25.9)   | 99                |
| Sholzberg, 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)    |                   |
| Berntorp, 2005 Retrospective    | Humate-P® Haemate®P | 35 12                                      | 1/2–4.0/28                  | GI = 3 (8) Joint = 13 (37) ENT = 16 (45.7) HBM =3 (8) | 24 (12–50) | 1 to 3 | NA | 87%               |
| Federici, 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, 2011 Retrospective     | Humate® P Wilate® | 32 12                                      | 4/15/13                     | Joint GI Relevant anemia           | 40 (20–47) | 2 to 4 | Significant reduced BS |
| Howman, 2011 Retrospective      | Biostate® | 2/43                                      | 60                          | 0/0/2                              | Joint Epistaxis                 | NA | NA |               |
| Abshire, 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) | 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) |
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 QoL 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 × 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.\textsuperscript{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; 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.

ACKNOWLEDGMENTS

We thank Hélène Boyer (Hospices Civils de Lyon) for her help in manuscript preparation.

FUNDING INFORMATION

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.

FINANCIAL DISCLOSURE

The authors declare that this study was funded by CSL Behring.

DATA AVAILABILITY STATEMENT

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

ORCID

Lucia Rugeri ID https://orcid.org/0000-0002-3103-1737
Pierre Chamouni ID https://orcid.org/0000-0001-6269-2098
Christine Biron ID https://orcid.org/0000-0002-7549-8718
Birgit Frotscher ID https://orcid.org/0000-0002-8110-9555

REFERENCES

1. Bowman M, Hopman WM, Rapson D, Lillicrap D, James P. The prevalence of symptomatic von Willebrand disease in primary care practice. J Thromb Haemost. 2010;8(1):213-216.
2. Leebeek FWG, Eikendoom JCJ. Von Willebrand’s disease. N Engl J Med. 2017;376(7):701-702.
3. Sadler JE, Budde U, Elkenboom JCJ, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand factor. J Thromb Haemost. 2006;4(10):2103-2114.
4. de Wee EM, Sanders YV, Mauser-Bunschoten EP, et al. Determinants of bleeding phenotype in adult patients with moderate or severe von Willebrand disease. Thromb Haemost. 2012;108(4):683-692.
5. Holm E, Abshire TC, Bowen J, et al. Changes in bleeding patterns in von Willebrand disease after institution of long-term replacement therapy: results from the von Willebrand disease prophylaxis network. Blood Coagul Fibrinolysis. 2015;26(4):383-388.
6. Holm E, Carlsson KS, Lövdahl S, Lail AE, Abshire TC, Berntorp E. Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: results from national registers in Sweden compared with normal controls and participants in the von Willebrand disease prophylaxis network. Haemophilia. 2018;24(4):628-633.
7. Saccullo G, Makris M. Prophylaxis in von Willebrand disease: coming of age? Semin Thromb Hemost. 2016;42(5):498-506.
8. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-325.
9. https://www.ema.europa.eu/en/medicines/human/EPAR/voncento.
10. Favaloro EJ, Lloyd J, Rowell J, et al. Comparison of the pharmacokinetics of two von Willebrand factor concentrates (biostate and AHF [high purity]) in people with von Willebrand disorder. A randomised cross-over, multi-Centre study. Thromb Haemost. 2007;97(6):922-930.
11. Rugeri L, d’Oiron R, Harroche A, et al. Effectiveness and safety of hFVIII/VWF concentrate (Voncento™) in patients with inherited von Willebrand disease requiring surgical procedures: the OPAL multicentre observational study. Blood Transfus. 2021;19(2):152-157.
12. Liisitchkov T, Klukowska A, Buevich E, et al. An open-label extension study to assess the long-term efficacy and safety of a plasma-derived von Willebrand factor (VWF)/factor VIII (FVIII) concentrate in patients with von Willebrand disease (SWIFT-VWDext study). J Blood Med. 2020;11:345-356.
13. Auerswald G, Djambas Khayat C, Stasyshyn O, et al. Pharmacokinetics, efficacy and safety of a plasma-derived VWF/FVIII concentrate (formulation V) in pediatric patients with von Willebrand disease (SWIFTLY-VWD study). J Blood Med. 2020;11:213-225.
14. Dunkley S, Baker RI, Pidcock M, et al. Clinical efficacy and safety of the factor VIII/von Willebrand factor concentrate BIOSTATE in patients with von Willebrand’s disease: a prospective multi-Centre study. Haemophilia. 2010;16(4):615-624.
15. Castaman G, Coppola A, Zanon E, et al. Efficacy and safety during formulation switch of a pasteurized VWF/FVIII concentrate: results from an Italian prospective observational study in patients with von Willebrand disease. Haemophilia. 2013;19(1):82-88.
16. Abshire T, Cox-Gill J, Kempston CL, et al. Prophylaxis escalation in severe von Willebrand disease: a prospective study from the von Willebrand disease prophylaxis network. J Thromb Haemost. 2015;13(9):1585-1589.
17. Goudemand J, Bridey F, Claeyssens S, et al. Management of von Willebrand disease with a factor VIII-poor von Willebrand factor concentrate: results from a prospective observational post-marketing study. J Thromb Haemost. 2020;18(8):1922-1933.
18. Sholzberg M, Khair K, Yaish H, et al. Real-world data on the effectiveness and safety of wilate for the treatment of von Willebrand disease. TH Open. 2021;5(3):e264-e272.
19. Berntorp E, Pettrini P. Long-term prophylaxis in von Willebrand disease. Blood Coagul Fibrinolysis. 2005;16(Suppl 1):S23-S26.
20. Federici AB, Barillari G, Zanon E, et al. Efficacy and safety of highly purified, doubly virus-inactivated VWF/FVIII concentrates in inherited von Willebrand’s disease: results of an Italian cohort study on 120 patients characterized by bleeding severity score. *Haemophilia*. 2010;16(1):101-110.

21. Halimeh S, Krümpel A, Rott H, et al. Long-term secondary prophylaxis in children, adolescents and young adults with von Willebrand disease. Results of a cohort study. *Thromb Haemost*. 2011;105(4):597-604.

22. Howman R, Barnes C, Curtin J, et al. The clinical efficacy and safety of the FVIII/VWF concentrate, BIOSTATE®, in children with von Willebrand disorder: a multi-Centre retrospective review. *Haemophilia*. 2011;17(3):463-469.

23. Abshire TC, Federici AB, Álvarez MT, et al. Prophylaxis in severe forms of von Willebrand’s disease: results from the von Willebrand disease prophylaxis network (VWD PN). *Haemophilia*. 2013;19(1):76-81.

24. Miesbach W, Krekeler S, Wolf Z, Seifried E. Clinical use of Haemate® P in von Willebrand disease: a 25-year retrospective observational study. *Thromb Res*. 2015;135(3):479-484.

25. Federici AB, Mannucci PM, Castaman G, et al. Clinical and molecular predictors of thrombocytopenia and risk of bleeding in patients with von Willebrand disease type 2B: a cohort study of 67 patients. *Blood*. 2009;113(3):526-534.

26. Berntorp E, Abshire T, von Willebrand Disease Prophylaxis Network Steering Committee. The von Willebrand disease prophylaxis network: exploring a treatment concept. *J Thromb Haemost*. 2006;4(11):2511-2512.

27. Doncarli A, Demiguel V, Guseva Canu I, et al. FranceCoag: a 22-year prospective follow-up of the national French cohort of patients with inherited bleeding disorders. *Eur J Epidemiol*. 2019;34(5):521-532.

28. Miesbach W, Berntorp E. Translating the success of prophylaxis in haemophilia to von Willebrand disease. *Thromb Res*. 2021;199:67-74.

29. Peyvandi F, Castaman G, Gresele P, et al. A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease. *Blood Transfus Transfus Sangue*. 2019;17(5):391-398.

30. Mannucci PM, Franchini M. Laboratory monitoring of replacement therapy for major surgery in von Willebrand disease. *Haemophilia*. 2017;23(2):182-187.

31. Phua CW, Berntorp E. A personalized approach to the management of VWD. *Transfus Apher Sci*. 2019;58(5):590-595.

32. Hazendonk HCAM, Heijdra JM, de Jager NCB, et al. Analysis of current perioperative management with Haemate® P/Humate P® in von Willebrand disease: identifying the need for personalized treatment. *Haemophilia*. 2018;24(3):460-470.