

Clinical use of Haemate® P in inherited von Willebrand's disease: a cohort study on 100 Italian patients

Augusto B. Federici, Giancarlo Castaman, Massimo Franchini, Massimo Morfini, Ezio Zanon, Antonio Coppola, Annarita Tagliaferri, Elio Boeri, Maria Gabriella Mazzucconi, Gina Rossetti, Pier Mannuccio Mannucci

From the Centro Emofilia e Trombosi "Angelo Bianchi Bonomi", Fondazione IRCCS Ospedale Maggiore, Mangiagalli e Regina Elena, Milano (ABF, PMM); Dipartimento di Terapie cellulari ed Ematologia, Ospedale San Bortolo, Vicenza (GC); Immunoematologia e Trasfusione, Centro Emofilia, Azienda Ospedaliera di Verona, Verona (MF); Agenzia per l'Emofilia, Azienda Ospedaliera Universitaria Careggi, Firenze (MM); Centro Emofilia, Clinica Medica II, Azienda Ospedaliera di Padova, Padova (EZ); Centro di Riferimento Regionale per le Emocoagulopatie, Dipartimento di Medicina Clinica e Sperimentale, Università "Federico II", Napoli (AC); Centro di Riferimento Regionale per la Cura dell'Emofilia e delle Malattie Emorragiche Congenite, Azienda Ospedaliera, Universitaria di Parma, Parma (AT); Centro Emofilia, Istituto Gianna Gaslini, Genova (EB); Ematologia, Dipartimento Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", Roma (MGM); Centro Emofilia, Servizio di Immunoematologia e Trasfusione, Ospedale S. Chiara, Trento (GR).

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Correspondence:

Augusto B. Federici, MD, Centro Emofilia e Trombosi "Angelo Bianchi Bonomi", Dipartimento Medicina Interna e Specialità Mediche, Fondazione IRCCS Ospedale Maggiore, Mangiagalli e Regina Elena, Milano.
E-mail: augusto.federici@unimi.it

ABSTRACT

Background and Objectives

Plasma-derived concentrates containing von Willebrand factor and factor VIII (VWF/FVIII concentrates) are the mainstay of treatment of patients with inherited von Willebrand's disease (VWD) who are unresponsive or have a contraindication to desmopressin (DDAVP) therapy. Only a few clinical studies are available on the use of these VWF/FVIII concentrates in large numbers of cases and within the same country. The aim of our study was to collect retrospective data on the efficacy and safety of Haemate® P (CSL Behring, Marburg, Germany) in a large cohort of well-characterized VWD patients after the introduction of the guidelines for VWD management in Italy.

Design and Methods

A retrospective survey of data records was organized among ten Italian Hemophilia Centers in order to retrieve information on the clinical use of Haemate® P. Data on 100 VWD patients (44 males and 56 females, median age 41.5, range 2-87 years) were available relating to the period from January 2002 to December 2004. All patients were diagnosed according to the criteria proposed by the Italian guidelines for VWD management.

Results

Of the 100 VWD patients enrolled, 23 had type 1 VWD, 40 had type 2 (2A=7, 2B=11, 2M=9, 2M Vicenza=13) and 37 had type 3. Seventy-one percent were severely affected, as shown by VWF:RCo levels <10 IU/dL. Fifty-nine patients were treated with Haemate® P because of 280 spontaneous bleeding episodes. These patients required 1,003 infusions of Haemate® P with a median daily dose of 72 (27-135) VWF:RCo IU/kg. In 95% of patients, clinical responses were rated as excellent/good. Fifty-six patients underwent major surgery (n=17), minor surgery (n=28), invasive procedures (n=9) or dental procedures (n=19), with a total consumption of 1.97×10^6 IU of VWF:RCo through 366 infusions of Haemate® P. The median daily dose was 80 (range, 27-146) VWF:RCo IU/kg, with clinical responses rated as excellent/good in 97% of patients. Twelve patients (type 1=1, type 2B=1, type 2M Vicenza=1, type 3=9, with a median age of 34.5, range 11-71 years) also underwent 17 long-term secondary prophylaxis regimens to prevent recurrent bleeding at the same site (47% in the gastrointestinal tract, 35% in joints). During the 4,358 days of prophylaxis, the patients received 1,424 infusions of Haemate® P, given three times (53%) or twice (47%) a week, with clinical responses rated as excellent/good in 100%. No serious adverse events, including thrombosis, were reported in the 370 evaluated treatments.

Interpretation and Conclusions

Based on this retrospective study conducted in a large cohort of Italian patients (n=100) and covering a long period of observation (36 months), Haemate® P was shown to be effective and safe for the clinical management of patients with VWD, whether given on demand or as prophylaxis.

Key words: von Willebrand's disease, Haemate® P/Humate-P®, ristocetin co-factor unit, bleeding, surgery, secondary long-term prophylaxis.

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Von Willebrand's disease (VWD), the most frequent inherited bleeding disorder, is caused by quantitative (types 1 and 3) or qualitative (type 2) defects of von Willebrand factor (VWF).^{1,2} The therapy objective for VWD is to correct the dual defects of hemostasis, i.e. abnormal platelet adhesion and the abnormal coagulation due to low factor VIII (FVIII:C).³ Two main therapeutic options are available: desmopressin (DDAVP), which releases endogenous VWF from endothelial cells, and exogenous VWF contained in VWF/FVIII plasma-derived concentrates. VWF/FVIII concentrates are indicated for patients with type 3 VWD, for patients with type 2B (since DDAVP can induce transient thrombocytopenia) and, for all those patients with types 1 and 2 VWD who are unresponsive or who may have contra-indications to DDAVP.^{2,4}

Plasma-derived VWF/FVIII concentrates suitable for treatment of VWD should contain a relatively high amount of VWF activity and some FVIII:C. They should be tested before clinical use for their pharmacokinetics and clinical efficacy in retrospective and prospective clinical trials in relatively large numbers of VWD patients.¹⁻³ Among the several concentrates containing VWF, only a few have been extensively evaluated in pharmacokinetic trials as well as in retrospective or prospective efficacy studies in VWD.⁵

Haemate® P/Humate® P, a pasteurized plasma-derived VWF/FVIII concentrate widely used in VWD, is characterized by a very high content of VWF (VWF:RCo IU, 2.4 for each IU of FVIII:C) with a relatively high percentage of large molecular weight VWF multimers.⁶⁻⁸ Haemate® P has also had an excellent safety record with regards to blood-borne infections over the past 25 years of clinical use.⁹⁻¹²

Clinical efficacy data were collected for Haemate® P through a large retrospective study organized by the Canadian Hemophilia Centers.¹³ Other published studies include a retrospective analysis of the efficacy and safety of Haemate® P in preventing bleeding during surgery or invasive procedures in 26 Italian VWD patients,¹⁴ as well as two prospective, multicenter, open-label, non-randomized studies conducted in the USA on Humate®-P used in urgent bleeding and urgent surgical events.^{15,16}

In this retrospective survey of ten Italian Hemophilia Centers, we report the most updated information on the clinical use of Haemate® P as collected in 100 patients with VWD unresponsive to DDAVP who were given the study drug because of spontaneous bleeds, for prevention of bleeding during surgery, and also for secondary long-term prophylaxis. This is the largest retrospective clinical study in Italian VWD patients treated with the same VWF/FVIII concentrate after the introduction in 2002 of the guidelines on VWD management by the Italian Association of Hemophilia Centers (AICE).

Design and Methods

Study design

The study is based on a retrospective collection of clinical data from patients diagnosed with inherited VWD and treated with Haemate® P to stop bleeds when they occurred spontaneously (*bleeds*), to prevent excessive bleeding during surgical procedures (*surgery*) and to prevent the recurrence of bleeding at the same site (*secondary long-term prophylaxis*). The study involved patients with VWD followed from January 2002 to December 2004 (36 months) in ten Italian Hemophilia Centers. The attending physicians were asked to collect all the available data on the clinical situation leading to treatment. Inclusion criteria consisted in the availability of at least a minimum set of data: age, gender and body weight, diagnosis and classification of VWD, indication for treatment with VWF/FVIII concentrates (e.g. documented unresponsiveness or contra-indication to DDAVP) detailed description of the bleeding episode or surgical procedure and treatment outcome; the administered dosage of concentrate and data on any other concomitant and adjuvant treatments (e.g. DDAVP, antifibrinolytic amino acids, and other transfusion therapies).

Study product

Haemate® P (CSL Behring, Marburg, Germany) is a pasteurized plasma-derived VWF/FVIII concentrate characterized by a high VWF activity ($\geq 2,400$ IU VWF:RCo/1,000 IU FVIII:C) and by the relatively high proportion of high molecular weight VWF multimers when compared with other commercially available VWF/FVIII concentrates.⁶⁻⁸

Patients

Patients were diagnosed according to the criteria of the Scientific Standardization Committee on VWF of the International Society for Thrombosis and Haemostasis, approved by the Italian Association of Hemophilia Centers (AICE)² to which the ten Centers participating in this study are affiliated. The diagnoses of VWD types 1, 2A, 2B, 2M and 3 were made as reported elsewhere.² Patients with VWD type 2M *Vicenza* (2M VIC) were identified by the presence of the typical *supranormal* multimers in plasma shown in low resolution agarose gel electrophoresis. These patients were enrolled in three Hemophilia Centers in northern Italy and were also characterized by VWF mutations as reported elsewhere.^{17,18} Patients with VWD type 2M VIC were still classified as having VWD type 2 following previous Italian recommendations,^{1,2} even though the most updated VWD classification suggests that these particular patients should be included among the type 1 group.¹⁹

Data on 100 VWD patients (44 males and 56 females, median age 41.5, range 2-87 years) could be retrieved for the study period. All patients were aware of the nature of this retrospective survey and gave their informed consent according to the Declaration of Helsinki (1964).

Management of VWD

All patients were treated with bolus injections of VWF/FVIII concentrate in the case of bleeds, surgery or secondary long-term prophylaxis. The dosing regimens of Haemate[®] P used were decided by each investigator on the basis of the AICE's recommendations.² These are expressed in units of FVIII because in Italy all concentrates are still labeled in terms of FVIII content only. However, to allow us to compare our data with those from other studies on Haemate[®] P previously reported in the literature, we chose to express the dosage of the study concentrate as VWF:RCo units, calculated from an analysis of the batches used (average VWF:RCo/FVIII:C ratio of 2.4).

Distribution of patients enrolled by the various Centers differed, each Center contributing a median of six patients (range 2–26). As could be expected, the three largest Centers enrolled 63% of the entire VWD population.

Bleeds were defined by site, such as epistaxis, gastrointestinal tract, gums, hemarthrosis, hematomas, menorrhagia, or of traumatic nature. Cases of bleeding involving more than one site or located in unusual sites were defined, respectively, as at *multiple sites* and in *other sites*. Surgery was divided according to the potential bleeding risk of the procedures: major surgery (thoracic/abdominal surgery, obstetric/gynecological surgery, orthopedic surgery, endocrine surgery and vascular surgery), minor surgery (minor surgical interventions, ophthalmic, skin, and ear, nose and throat [ENT] surgery), oral surgery and invasive procedures. The pre-operative dose of Haemate[®] P was administered 1 hour before surgery. Twelve patients were included in a program of secondary long-term prophylaxis because of recurrent (at least three times) bleeds at the same sites, mainly in the gastrointestinal tract or in the joints.

The distribution of conditions requiring treatment among the ten Hemophilia Centers showed a median (range) numbers of bleeds, surgery and secondary long-term prophylaxis of 17 (0-114), 6.5 (0-19) and 2 (0-4) respectively.

Assessment of efficacy and safety

Bleeding episodes and adverse drug reactions possibly occurring in association with the treatment were recorded using standardized data sheets. The efficacy of the study drug in achieving hemostasis was evaluated according to the following criteria: hemostasis clinically not different from normal (excellent), mildly abnormal hemostasis partial or delayed control of spontaneous

bleeding or slight transient oozing from surgical wounds (good), moderately abnormal hemostasis bleeding not fully controlled but no need for additional therapy (moderate); and no improvement at all with continuation of bleeding and need for additional or alternative therapies (poor). Adverse events were defined as any change from baseline in the patient's health status that occurred within 24 hours of the administration of Haemate[®] P, regardless of the potential relationship to the study product. Adverse events related to surgery (post-operative nausea, vomiting, fever and/or pain) were not considered to be possibly or probably related to concentrate treatment and were not included as adverse events in this study. In the case of repeated administrations of Haemate[®] P during the post-operative period or secondary long-term prophylaxis, FVIII:C levels were measured in most patients. If FVIII:C levels were >180 IU/dL, the following injection of Haemate[®] P was postponed by 24 hours.

Statistical analysis

All study variables are summarized by descriptive statistics (i.e. mean, range and standard deviation) with various subgroup analyses (e.g. demographics, VWD types, indications for use).

Results

Demographic data of the cohort of VWD patients

Among the 100 VWD patients enrolled, 23 had type 1 VWD, 40 had type 2 (2A=7, 2B=11, 2M=9, 2M VIC= 13) and 37 had type 3. Seventy-one percent had clinically severe disease, as shown by VWF:RCo levels <10 IU/dL. Age at first exposure and number of days of exposure to VWF/FVIII concentrate were respectively lower and higher in patients with VWD type 3 than in those with other types (Table 1). The features and clinical responses of the VWD patients treated with Haemate[®] P for bleeds, surgery and secondary long-term prophylaxis are summarized in Table 2.

Bleeds

Fifty-nine patients were treated because of 280 bleeds with 1,003 infusions of Haemate[®] P (total amount infused = 5.66×10^6 IU of VWF:RCo) with a median daily dose of 72 (range, 27-135) VWF:RCo IU/kg. The clinical response was rated as excellent/good in 95% of patients. Moderate responses were mostly observed in one patient with VWD type 3 who experienced concomitant bleeds at two different sites on three occasions (Table 2). A median number of 3 bleeding episodes (range, 1-43) treated with Haemate[®] P was observed during the 3 years of follow-up. The different types of bleeds that occurred in patients with the various types of VWD are shown in Figure 1. Hemarthroses, hematomas, menorrhagia and bleeds after moderate or

Table 1. Demographic data and clinical and laboratory parameters (median and range) of the 100 VWD patients enrolled in the retrospective study.

Parameters	Type 1 (n=23)	Type 2A (n=7)	Type 2B (n=11)	Type 2M (n=9)	Type 2MVIC (n=13)	Type 3 Total (n=37)	VWD (n=100)
Sex (male/female)	8/15	5/2	3/8	6/3	7/6	15/22	44/56
Age (years)*	45(14-73)	60 (19-84)	58 (9-75)	46 (16-80)	57 (2-87)	23 (4-76)	41 (2-87)
Weight (kg)*	70 (48-97)	72 (55-78)	65 (36-87)	74 (50-107)	72 (13-90)	64 (19-120)	66 (13-120)
VWF:RCo (U/dL)*	28 (3-47)	3 (3-15)	23 (10-39)	10 (5-47)	3 (3-9)	< 3	3 (<3-47)
VWF:Ag (U/dL)*	29 (3-61)	27 (5-47)	54 (25-72)	29 (12-74)	7 (5-13)	< 3	7 (<3-74)
FVIII:C (U/dL)*	53 (7-118)	42 (12-67)	56 (28-99)	55 (35-105)	18 (9-31)	5 (1-25)	24 (1-118)
Bleeding time (min)*	12 (5-35)	20 (6-35)	18 (9-27)	20 (12-35)	10 (5-25)	27 (9-35)	15 (5-35)
N. of patients with severe VWD (%)	39	71	9	67	100	100	71
(VWF:RCo < 10 IU/dL)*							
Blood group (%)							
0	22	17	14	40	28	29	26
Non-0	78	83	86	60	72	71	74
Age at first exposure to VWF concentrates (years)*	40 (7-73)	37 (6-79)	33 (5-71)	46 (16-80)	48 (2-87)	11 (1-76)	26 (1-87)
Days of exposure to VWF concentrates (%)							
0- 4	32	14	9	23	30	3	17
5-24	46	43	55	44	54	30	42
25-50	18	14	—	—	8	6	8
51-150	—	15	18	—	8	18	11
> 150	4	14	18	33	—	43	22

*Results are expressed as median (min-max).

major trauma were observed mainly in patients with VWD type 3, characterized by low FVIII levels. On the other hand, gastrointestinal bleeds were observed in all VWD types characterized by low levels of VWF:RCo. Out of the 59 patients treated for bleeding episodes with Haemate® P, a group of 11 patients (19%) (type 3=7, type 2A=1, type 2B=1, type 2M=2) with a more severe bleeding tendency was identified. These patients were responsible for 179 (64%) events and for the use of 4.06×10^6 IU VWF:RCo of study product (72% of the total consumption for bleeds) with an average administration of 101 VWF:RCo IU/kg/day (range 38-135). With regards to the total consumption of Haemate® P in all VWD patients, 2.4×10^6 U of VWF:RCo were used for gastrointestinal bleeds and 1.2×10^6 for hemarthroses.

Surgery

Fifty-six patients underwent 73 surgical procedures. Seventeen underwent major surgery (1 vascular, 5 orthopedic, 9 thoracic-abdominal, 2 obstetric/gynecological), 28 had minor surgery (1 ENT, 1 endocrine, 3 skin, 4 eye, 3 orthopedic, 6 obstetric/gynecological, 3 abdominal, 7 others), 9 underwent invasive procedures and 19 had dental procedures, with a total consumption of 1.97×10^6 IU of VWF:RCo in 366 infusions of Haemate® P. The median daily dose was 80 (range, 27-146) VWF:RCo IU/kg, with clinical responses rated as excellent/good in 97% of patients (Table 2). The types and sites of invasive and surgical procedures are shown in Figure 2 while their number according to the VWD type together with the use of Haemate® P by type of

Table 2. Features and clinical responses of VWD patients treated with Haemate®P for bleeds, surgery, and as secondary long-term prophylaxis.

Parameters	Bleedings	Surgeries	Prophylaxis
Number of patients	59	56	12
Sex (male/female)	30/29	24/32	6/6
Age (years)*	31 (2-80)	42 (2-87)	35 (11-71)
Weight (kg)*	68 (13-120)	69 (13-120)	68 (28-90)
von Willebrand's disease			
Type 1	7 (12%)	19 (34%)	1 (8%)
Type 2A	3 (5%)	5 (9%)	—
Type 2B	6 (10%)	6 (11%)	1 (8%)
Type 2M	6 (10%)	5 (9%)	—
Type 2M VIC	5 (9%)	11 (19%)	1 (8%)
Type 3	32 (54%)	10 (18%)	9 (76%)
N. of pts with severe VWD (VWF:RCo < 10 IU/dL)	80%	64%	92%
Number of events	280	73	17
Number of infusions	1,003	366	1,424
Total VWF:RCo IU	5,665,000	1,970,000	5,601,000
VWF:RCo IU/kg/day*	72 (27-135)	80 (27-146)	72 (24-96)
Clinical response			
excellent/good	95	97	100
moderate/poor	5	3	0

*Results are expressed as median (min-max).

procedure are summarized in Table 3. Overall, patients undergoing major surgery received higher loading and maintenance doses, more infusions and were treated for more days than those exposed to minor surgery, oral surgery or other invasive procedures. Efficacy was rated as excellent/good in all but two procedures (97%)

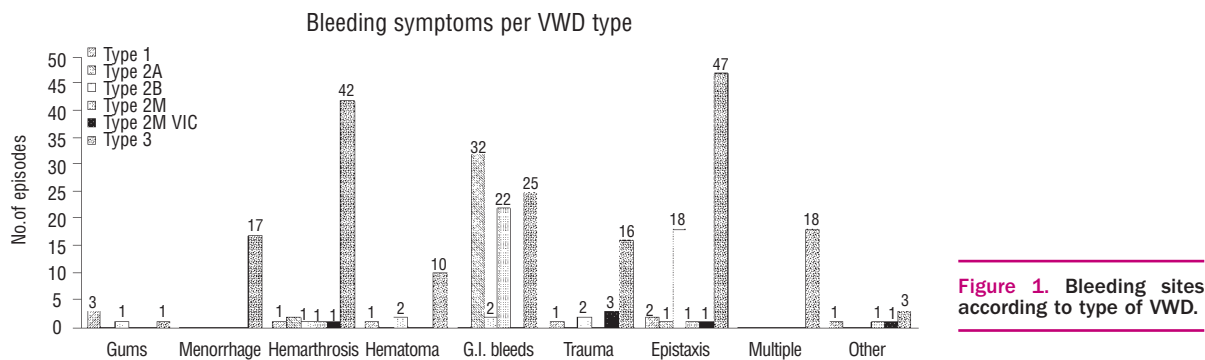


Figure 1. Bleeding sites according to type of VWD.

which were complicated by post-operative bleeding (1 pelvic hematoma and 1 episode of melena). A large amount of Haemate® P (177600 IU VWF:RCo, 146 IU/kg/day) was used during spinal surgery in one 11-year old patient. Only two patients were transfused with red blood cells and one other patient received both fresh-frozen plasma and platelet concentrates. These three patients underwent major surgical interventions. Twenty-one patients also received additional drugs affecting hemostasis: tranexamic acid in 18 cases, desmopressin in one case, and unfractionated heparin or low molecular weight heparin in two cases.

Secondary long-term prophylaxis

Twelve patients (type 1=1, type 2B=1, type 2M VIC=1, type 3=9, with a median age of 34.5 years; range 11-71) also received 17 long-term secondary prophylaxis regimens to prevent recurrent bleedings at the same site (47% in the gastrointestinal tract, 35% in joints). Patients received 5.60x10⁶ IU VWF:RCo in 1,424 infusions of Haemate® P given three times (53.0%) or twice (47.0%) a week, with clinical responses rated as excellent/good response in 100%. Among patients receiving prophylaxis, 70% had VWD type 3 and received 54% of the overall product infused (Table 4). During the 4,358 days of prophylaxis (median 201; range, 30-730) only four bleeding episodes were observed.

Safety of Haemate® P

Haemate® P was well tolerated and no adverse drug reactions or thrombotic episodes were observed following infusions. FVIII levels before and after each infusion during repeated administration of Haemate® P for surgery and secondary long-term prophylaxis were measured and were always below 180 IU/dL.

Discussion

Despite the fact that VWD is the most prevalent inherited bleeding disorder,² relatively few retrospective or prospective data are available in literature describing the efficacy and safety of plasma VWF concentrates in

Type and sites of invasive or surgical procedures

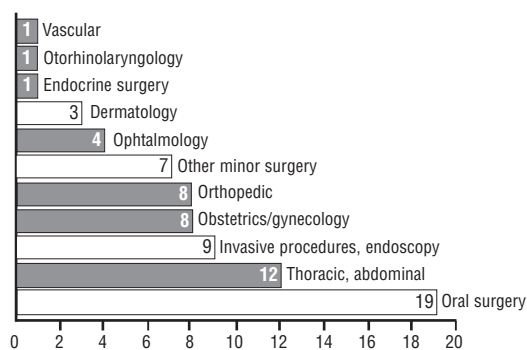


Figure 2. Types and sites of invasive procedures or surgery. Minor and major surgical procedures are indicated in white and gray horizontal bars, respectively.

patients with this disease. In this large retrospective study, we report the efficacy and safety of Haemate® P administered for bleeds, surgery and secondary long-term prophylaxis over a period of 36 months in 100 well-characterized patients with inherited VWD at ten Italian Hemophilia Centers. This is the largest retrospective survey in Italy on the clinical use of a VWF/FVIII concentrate after the introduction of the recommendations on VWD diagnosis and therapy published in the guidelines approved by the Italian Association of Hemophilia Centers (AICE).² The number of patients analyzed is also higher than that included in the Canadian study on the same VWF/FVIII concentrate, which also enrolled patients with acquired von Willebrand syndrome.¹³ Our cohort of patients included mainly cases with severe disease. There is a higher number of VWD type 2 and 3, as demonstrated by the relatively high frequency of cases with basal VWF:RCo levels <10 IU/dL. Among these, a relatively high percentage of patients with VWD type 2M VIC were enrolled in the study at three Hemophilia Centers in northern Italy. Therefore, it is not surprising that spontaneous bleeds such as hemarthroses, hematomas, epistaxis, menorrhagia and gastrointestinal bleeding

Table 3. Type of surgery and invasive procedures according to VWD types and the use of Haemate® P according to the type of intervention.

Intervention	VWD type						Total dose IU VWF:RCo	Daily dose IU VWF:RCo/kg/day	Days of hospitalization (**)	Days of treatment	Number of infusions
	Type 1	Type 2A	Type 2B	Type 2M (*)	Type 2M VIC	Type 3					
Major surgery (n=17)	3 (17.6)	1 (5.9)	1 (5.9)	3 (17.6)	3 (17.6)	6 (35.3)	57,600 (14,400-177,600)	96 (53-146)	8 (6-18)	7 (2-18)	7 (2-18)
Minor surgery (n=28)	8 (28.6)	2 (7.1)	5 (17.9)	5 (17.9)	2 (7.1)	6 (21.4)	16,800 (4,800-55,200)	71 (32-120)	1 (1-10)	3 (1-11)	3 (1-10)
Dental procedures (n=19)	8 (42.1)	4 (21.0)	1 (5.3)	3 (15.8)	2 (10.5)	1 (5.3)	7,200 (2,400-21,600)	74 (27-124)	0 (0-3)	1 (1-5)	1 (1-5)
Invasive procedures (n=9)	4 (44.5)	0	1 (11.1)	1 (11.1)	3 (33.3)	0	7,200 (3,600-28,800)	76 (47-111)	0 (0-7)	1 (1-5)	1 (1-5)
Total (n=73)	23 (31.5)	7 (9.6)	8 (11.0)	12 (16.4)	10 (17.8)	13 (13.7)	6,800 (2,400-177,600)	80 (27-146)	1 (0-18)	3 (1-18)	3 (1-18)

(*)results are expressed as No. cases (percentage) (**)results are expressed as median (min-max).

occurred relatively frequently. In the group of patients treated with Haemate® P for bleeds, we identified a group of 11/59 (19%) patients who were responsible for 179 (64%) bleeding events and for the use of 4.06×10^6 IU VWF:RCo. Excellent or good responses were recorded in 95% of these 59 VWD cases for 280 bleeding events, a result which agrees with previously reported rates.^{13,16} Age does not seem to affect the clinical response to Haemate® P, since a 95% rate of excellent/good responses was observed not only in the general population of 59 cases, but also in the subgroup of 12 patients aged under 14 years of age. Large amounts of Haemate® P were used for gastrointestinal bleeds and hemarthroses which usually require prolonged on-demand treatment. Most of the VWD patients whose episodes of gastrointestinal bleeds and hemarthroses tended to recur were allocated to secondary long-term prophylaxis (see below). The efficacy and safety of Haemate® P were also observed in 56 patients undergoing major or minor surgery or other invasive procedures. Replacement therapy with Haemate® P showed a good to excellent clinical efficacy in 97% of cases. This agrees with results of previous retrospective studies.¹³⁻¹⁶ These findings also support the safety and efficacy of the VWF/FVIII concentrate Haemate® P when administered in doses based upon VWF:RCo units. Other recent studies included a retrospective analysis of the efficacy and safety of Haemate® P in preventing bleeding during surgery or invasive procedures,¹⁴ and a prospective, multicenter, open-label, non-randomized study was conducted in the USA on the use of Haemate® P in emergency surgical procedures.¹⁶

Whereas prophylaxis in hemophilia has become widespread, this management strategy is used only

Table 4. Features and responses of VWD patients treated with Haemate® P as prophylaxis.

Prophylaxis	Gastrointestinal bleeds	Joints bleeds	Other
Number of patients	5	4	3
Sex (male/female)	2/3	2/2	2/1
Age (years)*	59 (71-56)	42 (2-87)	35 (11-71)
Weight (kg)*	70 (48-90)	68 (36-78)	50 (28-70)
Number of cycles	8	6	3
Duration (days)*	230 (92-730)	269 (30-365)	60 (36-730)
Total VWF:RCo IU	3,024,000	1,357,000	826,000
VWF:RCo IU/kg/day*	60 (24-96)	72 (69-72)	86 (72-96)
Cycles vs (infusion/week)			
Type 1	1 (2/wk)	—	—
Type 2B	1 (3/wk)	—	—
Type 2M VIC	3 (3/wk)	—	—
Type 3	1 (3-2/wk)	4 (2/wk)	1 (2/wk)
Type 3	1 (2/wk)	2 (3/wk)	2 (3/wk)
Type 3	1 (3/wk)	—	—
Clinical response			
excellent/good	100	100	100
moderate/poor	—	—	—

*Results are expressed as median (min-max).

occasionally in VWD. There has been a recent report on the results from a long-term prophylaxis experience in Sweden²⁰ in which 37 patients were treated for a median of 11 years (range 2-45). The majority of patients (n=28) had type 3 VWD. The concentrate used in the Swedish study since the mid 1980s was Haemate® P, with a mean dose of 24 units factor VIII:C/kg body weight given 1-3 times weekly. Other clinical information on secondary long-term prophylaxis in VWD has also been recently collected by a single Italian Center.²¹

In this retrospective study clinical data were collected on 17 cycles of secondary long-term prophylaxis administered to 12 patients with VWD type 3 and in two other patients mainly because of gastrointestinal bleeding and hemarthroses. As in the previous study, this approach seemed to be very promising as shown by the 100% excellent clinical responses and the reduction in days of hospitalization for blood transfusions with packed red cells.²¹ However, prospective studies aimed at evaluating the cost/benefit ratio of secondary long-term prophylaxis are required before recommending this approach in current clinical practice. A large amount of Haemate[®] P was used within 36 months, in 59 cases for bleeds (5.7×10^6 VWF:RCo IU), in 56 cases for surgery (1.97×10^6 VWF:RCo IU) and in 12 cases for secondary long-term prophylaxis (5.6×10^6 VWF:RCo IU). We observed a trend to a relatively higher consumption, measured as VWF:RCo Units/Kg body weight, compared to that in other previously reported retrospective studies. This may be explained by the high proportion of patients with severe VWD in our cohort (71%) and by the fact that Haemate[®] P and other VWF/FVIII concentrates in Italy are still labeled in FVIII activity units, and not as VWF:RCo. This might have led to the use of more concentrate than necessary. However, the expression of results in VWF:RCo IU was useful to compare our findings with those reported in the USA and Canada. This emphasizes once more the importance of dosing VWF/FVIII concentrates according to VWF:RCo units and of measuring FVIII before and after every injection to evaluate the secondary response that also includes the endogenous production of FVIII in VWD patients.

Despite the fact that some patients received more than 100 IU/kg of VWF:RCo with repeated infusions to stop bleeding, during surgery or for long-term prophylaxis, no major side effects, including thrombosis, were reported. During this study, FVIII levels after each administration during repeated infusions of Haemate[®] P, especially during surgery, were not higher than 180 UI/dL. These data certainly suggest that unnecessary higher levels of FVIII can be avoided simply by assaying FVIII before any additional repeated treatment and that the frequency of administration of Haemate[®] P should be reduced when FVIII levels are higher than 150 UI/dL.

In conclusion, our retrospective analysis provides further evidence supporting the safety and efficacy of Haemate[®] P as on-demand treatment for the management of bleeding episodes and to prevent bleeding during surgery, as well as for secondary long-term prophylaxis to prevent recurrent bleeding in VWD patients.

Authors' Contributions

ABF, GC, MF: design of the study, collection of the clinical data, analysis and discussion of the clinical data, preparation, revision and approval of the final version of the paper; MM, EZ, AC, AT, EB, MGM, GR: design of the study, collection of the clinical data, revision and approval of the final version of the paper; PMM: design of the study, collection of the clinical data, preparation of the paper, revision and approval of the final version of the paper.

Conflict of Interest

This study was organized as a retrospective survey and is based only on GMCP. There was no need to register this study because the drug has been already commercially available and has been used for the management of these patients with VWD since 1985.

Preliminary results of the study were presented as a Poster at the International Meeting of the World Federation of Hemophilia in Vancouver, Canada.

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